Multiple Myeloma

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Multiple myeloma is a neoplastic plasma cell dyscrasia (PCD) characterized by a clinical pentad: (a) anemia, (b) a monoclonal protein in the serum or urine or both, (c) abnormal bone radiographs and bone pain, (d) hypercalcemia, and (e) renal insufficiency or failure. With the exception of monoclonal gammopathy of undetermined significance (MGUS), it is the most common PCD, with an incidence of about 4.5 per 100,000 per year in the United States. Solitary plasmacytoma and plasma cell leukemia (PCL) are recognized as separate entities and are much less prevalent. The underlying pathogenesis of the plasma cell malignancies is not well understood but is an area of active investigation. At present, according to the WHO (World Health Organization) and REAL (Revised European-American Lymphoma) classification systems, there is only one category for multiple myeloma (1). Results of clinical trials are confounded by this underclassification. Emerging information about the genetic underpinning of the disease, however, will likely change this deficiency. The interactions among the plasma cells, their antibody product, the local bone and bone marrow environment, and other organs are complex. There is no cure for multiple myeloma, but there are many effective treatments that prolong and improve the quality of life of patients with the disease.

History

Earliest Diagnoses and Diagnostic Methods

Samuel Solley reported the first well-documented case of myeloma in Sarah Newbury in 1844 (mollities ossium) (2,3). Several years later, William MacIntyre described and recorded the properties of the disease we now call multiple myeloma in Thomas Alexander McBean (4). Both Drs. MacIntyre and Bence Jones noted and described some of the peculiar urine properties of this same patient. On heating, the urine was found to “abound in animal matter,” which dissolved on the addition of nitric acid but reappeared after cooling. These urinary proteins became known as Bence Jones proteins (5). MacIntyre and Dalrymple described the postmortem examination of Mr. McBean's bones (4). The former described the affected bones as softened and fragile, with their interiors replaced with a soft “gelatinform” blood-red substance. Dalrymple suggested that the disease began in the cancellous bone and extended through the periosteum. The nucleated cells, which formed the bulk of the gelatinous material, were heterogeneous in size and shape, but the majority were round to oval. Many of the larger and more irregular cells frequently contained two or three nuclei (3). The term “multiple myeloma” was coined in 1873 by von Rustizky (6), who independently described a similar patient to emphasize the multiple bone tumors that were present.

In 1889, Professor Otto Kahler (7) described a case involving a 46-year-old physician with multiple myeloma and published a major review of the disease. He described the skeletal pain, albuminuria, pallor, anemia, a precipitable urinary protein, and the findings on necroscopy and linked these findings as part of a clinical syndrome, which bears his name (multiple myeloma is also known as Kahler disease).

In 1898, Weber predicted the usefulness of roentgen x-rays in establishing the diagnosis (3,8) and later postulated that the Bence Jones protein was produced in the bone marrow

(9). Wright (10) emphasized that multiple myeloma arose specifically from plasma cells of the marrow; Jacobson (11) recognized Bence Jones proteins in the bloodstream; and Walters (12) concluded that the Bence Jones protein was probably derived from blood proteins through the action of the abnormal cells in the bone marrow. The technique of bone marrow aspiration (13) facilitated the diagnosis of multiple myeloma.

Bayne-Jones and Wilson (14) identified two similar but distinct groups of Bence Jones proteins by immunizing rabbits with Bence Jones proteins derived from patients. Precipitin tests on these Bence Jones preparations revealed two distinct groups: I and II. Using the Ouchterlony test, Korngold and Lipari showed that antisera to Bence Jones protein also reacted with myeloma proteins. The two classes of Bence Jones proteins have been designated κand λas a tribute to these two men. In 1962, Edelman and Gally (15) showed that the light chains prepared from an IgG monoclonal protein and the Bence Jones protein from the same patient's urine were identical.

Serum electrophoresis, described by Tiselius in 1937 (16), made it possible to separate serum proteins. Longsworth et al. (17) applied electrophoresis to the study of multiple myeloma and described the tall, narrow-based “church spire” peak. The use of filter paper as a support for protein electrophoresis permitted the separation of protein into distinct zones that could be stained with various dyes (18). Because this technique was simple and inexpensive, this test became universally available in clinical laboratories. Paper electrophoresis was supplanted by filter paper in 1957 and most recently by high-resolution electrophoresis on agarose gel. Immunoelectrophoresis (19) and immunofixation or direct immunoelectrophoresis (20) made it possible to detect small monoclonal light chains not recognizable by electrophoresis. The immunoglobulin free light-chain assay has been added to the diagnostic armamentarium to detect circulating free light chains in the majority of patients hencetoforth designated nonsecretory (21).

Kunkel (22) hypothesized that monoclonal proteins were the product of malignant plasma cells and were the equivalent of normal antibodies produced by normal plasma cells. Before 1960, the term “gamma globulin” was used for any protein that migrated in the gamma mobility region of the electrophoretic pattern; however, in 1959, Heremans (23) proposed the concept of a family of proteins with antibody activity. In 1961, in a Harvey Lecture (24), Waldenström distinguished between monoclonal and polyclonal hypergammaglobulinemia.

In 1928, Geschickter and Copeland (25) reported on the largest case series of multiple myeloma—13 cases—and reviewed the 412 cases reported in the literature since 1848. They documented a higher incidence in men than women and an overall survival of about 2 years. They emphasized six features: (a) involvement of the skeletal trunk, (b) pathologic rib fractures, (c) Bence Jones proteinuria in 65% of cases, (d) backache with early paraplegia, (e) anemia in 77% of cases, and (f) chronic renal disease. They did not note abnormalities of blood protein or an increased erythrocyte

sedimentation rate (3). In 1931, Magnus-Levy (26) described amyloidosis as a complication of multiple myeloma. Salmon, Durie, and Smith developed methods to quantitate the total body burden of tumor cells (27) and to stage patients (28) in 1970 and 1975, respectively.

Earliest Treatments for Multiple Myeloma

In 1947 Snapper (29) reported that stilbamidine along with a low-animal-protein diet relieved myeloma pain in 14 of 15 patients. Subsequent studies did not confirm this benefit. Urethane was believed to be effective until 1966 (30). It was first used in the treatment of multiple myeloma by Alwall in 1947 (31,32) and then by Loge and Rundles in 1949 (31,32). Their early observations were encouraging, and the use of urethane became widespread. Toxic effects included severe anorexia, nausea, and vomiting. Leukopenia, thrombocytopenia, and hepatic damage also occurred (33). In 1966, however, Holland et al. (30) published the results of a randomized controlled trial of urethane versus placebo in 83 patients with symptomatic multiple myeloma. They found that there was no difference in any objective measurement of improvement between the two groups and that the median overall survival was higher in the placebo group. Previously untreated patients had a median survival of 12 or 5 months, depending on whether they received placebo or urethane, respectively.

In 1950, Thorn et al. (34) reported the first observations on the salutary effects of adrenocorticotropic hormones on myeloma (Fig. 99.1). During that decade, it was recognized that the adrenocorticotropic hormones cortisone and prednisone were useful agents in patients with multiple myeloma. Corticosteroids decreased bone pain, improved hypercalcemia, increased hemoglobin values, and decreased abnormal serum and urine globulin concentrations (33). However, it was not until 1967 that high-dose corticosteroids were recognized as effective antineoplastic agents against multiple myeloma (35).

Blokhin et al. (36) reported benefits in three of six patients with multiple myeloma who were treated with sarcolysin (a racemic mixture of the *d*- and *l*-isomers of phenylalanine mustard). Subsequently, the *d*- and *l*-isomers were tested separately, and the antimyeloma activity was found to reside in the *l*-isomer, melphalan. Bergsagel et al. (37) reported significant improvement in 14 of 24 patients with multiple myeloma with the use of melphalan; this activity was quickly substantiated by others (38). Similar effectiveness was noted with cyclophosphamide (39). Subsequently, interferon-α, doxorubicin, carmustine, thalidomide, bortezomib, and lenalidomide (40,41,42,43,44,45) have each been reported to have activity as a single agent in myeloma (Fig. 99.1).

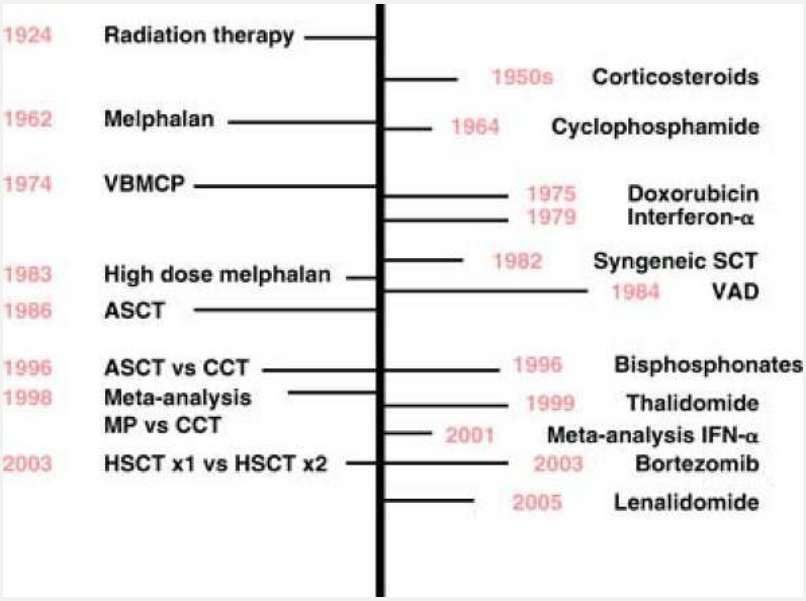

Figure 99.1. Landmark therapeutic innovations (34,37,39,41,43,233,237,245,274,319,391,432,439,466,481,710,1002,1110**).** ASCT, autologous stem cell transplant; CCT, conventional chemotherapy; VAD, vincristine, doxorubicin, dexamethasone; VBMCP, vincristine, BCNU, melphalan, cyclophosphamide, and prednisone (M-2 regimen).

Incidence and Epidemiology

Epidemiology of Myeloma

Approximately 16,570 new cases of multiple myeloma are diagnosed each year in the United States, and 11,310 deaths are recorded (46). SEER (Surveillance, Epidemiology and End Results) incidence data, age-adjusted rates from 1992 through 1998, show an overall incidence of 4.5 per 100,000 per year, with the incidence among whites being 4.2 per 100,000 per year and among blacks, 9.3 per 100,000 per year (47). Male-to-female ratio is 1.3 to 1 (46). The median age at diagnosis of myeloma is 71 years. Mortality rates are consistently higher among men than women and among blacks than whites in each age group (47). Myeloma accounts for 1% of all malignancies and 10% of all hematologic malignancies in whites and 20% in African Americans (47). International mortality data reveal that the highest rates of myeloma occur in Northern Europe, North America, Australia, and New Zealand, and the lowest rates are in Japan, Yugoslavia, and Greece (48). Geographic clusters (49) and familial clusters (50,51,52,53,54,55) of myeloma among first-degree relatives have been documented. Modest increases in multiple myeloma rates were observed when incidence data from 1973 to 1992 were calculated in nine population-based cancer registries, with further projected increases by 2007 (56). This increase is likely a result of heightened awareness of the disease.

Etiologic Factors

Radiation Exposures

Atomic Bomb Exposure

Reports of increased myeloma incidence and mortality among Japanese atomic bomb survivors have suggested an association between ionizing radiation and multiple myeloma. Evaluations of cancer incidence (57) and mortality (58) among Japanese atomic bomb survivors have demonstrated an increased risk of multiple myeloma with increasing radiation dose. However, with an additional 12 years of follow-up from previous reports, the findings of an increased myeloma risk associated with atomic bomb irradiation were not maintained (59).

Radiation-Related Occupation

An excess of myeloma deaths among U.S. radiologists was reported in the 1960s (60). Myeloma risk was considered to be two times higher among radiologists exposed to low doses of radiation than among physicians not exposed to radiation (61). However, among 27,000 Chinese diagnostic radiography workers, no excess incidence of myeloma was observed in a 30-year period (62). An analysis of 115,000 workers from the combined roster of four different nuclear plants showed a positive association between multiple myeloma and radiation exposure in older age groups (63). No increases in multiple myeloma incidence and mortality have been observed among British (64) or New Zealand (65) military men who participated in atmospheric nuclear weapons testing.

Diagnostic and Therapeutic X-rays

Diagnostic x-ray exposure has not been linked with the development of multiple myeloma in most epidemiologic studies (66,67,68,69,70,71). A large multicenter, population-based case-control study showed no evidence of excess risk of myeloma among individuals who reported exposure of 10 or more diagnostic radiographs (72). One study reported that the overall risk for multiple myeloma was not high (RR, 1.14), but that there was evidence of increasing risk with exposure to increasing numbers of radiographic procedures (73).

Of historic interest is the finding of an association between myeloma and the use of Thorotrast (67). Studies of the effects of therapeutic irradiation on myeloma risk have shown conflicting results, but a study of 180,000 women treated for cervical cancer demonstrated no overall excess risk of developing myeloma (74). Similarly, a study of 14,000 patients suffering from ankylosing spondylitis and treated with radiation revealed no significant increase in the risk of developing myeloma (75).

Workplace Exposures

Agricultural Occupations and Exposures

Several epidemiologic studies have evaluated the risk of myeloma among agricultural workers, with positive associations reported by many (76,77,78,79,80,81) but not all of the studies (82,83,84). Khuder and Mutgi (85) found a relative risk of 1.23 in a meta-analysis of several studies.

Metal Industries

Workers in various metal occupations and industries have been reported to have an increased myeloma risk (86,87,88).

Benzene

Benzene has been suggested as a possible etiologic agent for multiple myeloma (89,90,91). A comprehensive review of published literature found no evidence of a link between benzene exposure and myeloma (92). Subsequently, Sonoda and colleagues (93) conducted a meta-analysis of case-control studies and showed no excess risk for the development of multiple myeloma. A meta-analysis by Wong and Raabe (94) of more than 350,000 petroleum workers similarly showed no increased risk.

Lifestyle Factors

Cigarette Smoking and Alcohol Consumption

Multiple studies to date have found no etiologic role for cigarette smoking or alcohol consumption in the development of multiple myeloma (95,96,97,98).

Dietary Links

Tavani et al. (99) suggested a dietary link for multiple myeloma and found a higher risk among people consuming large quantities of liver (odds ratio [OR], 2.0) and butter (OR, 2.8), and a lower risk among people consuming large amounts of vegetables (OR, 0.4). Coffee and alcohol had no association with multiple myeloma. No association of multiple myeloma and consumption of red meat has been found (99). Brown and colleagues (100) looked at diet and nutrition as risk factors for multiple myeloma among blacks and whites in the United States. Elevated risks were associated with obesity in comparison to people of normal weight. Obesity was more frequent in black than in white controls. Reduced risks were associated with the frequent intake of cruciferous vegetables, fish, and vitamin C supplements. The authors concluded that the greater use of vitamin C supplements by whites and the higher frequency of obesity among blacks may explain part of the higher incidence of multiple myeloma among blacks compared with whites in the United States.

Socioeconomic Status

Some investigators have reported that there is an inverse relationship between the risk of multiple myeloma and socioeconomic status (101) and that this inverse correlation may account for a substantial amount of the black and white differential of multiple myeloma incidence (102). Earlier studies did not show a link between socioeconomic status and myeloma (103).

Hair Dyes

Personal use of hair dyes was evaluated as a risk factor for myeloma (104), including two prospective studies (105,106). Thun et al. (105) found that women using permanent hair dyes are not generally at increased risk of fatal cancer. Women with prolonged use of dark, particularly black, hair dyes may have increased risk of fatal non-Hodgkin lymphoma and multiple myeloma, but these women are a small fraction of hair-dye users. A subsequent meta-analysis by Correa et al. (107) showed no increased risk.

Precursor Medical Conditions

Monoclonal Gammopathy of Undetermined Significance

MGUS is considered a potential precursor condition for multiple myeloma. In a long-term study of prognosis in MGUS, Kyle and colleagues (108) identified 1,384 patients in southeastern Minnesota in whom MGUS was diagnosed. During 11,009 person-years of follow-up, 115 of the 1,384 MGUS patients progressed to multiple myeloma, IgM lymphoma,

primary amyloidosis, macroglobulinemia, chronic lymphocytic leukemia, or plasmacytoma. The risk of progression of MGUS to multiple myeloma-related disorders is thus ~1% per year (109). Among a group of 1,231 patients in Italy with MGUS and smoldering multiple myeloma, cumulative transformation probabilities at 10 and 15 years were 14 and 30%, respectively (110). A higher rate of MGUS in African Americans accounts for part of the increased incidence of myeloma in this population (111).

Chronic Antigenic Stimulation

Repeated or chronic antigenic stimulation of the immune system may lead to myeloma. Several case-controlled studies have suggested that myeloma risk is associated with a past history of infections, inflammatory conditions, connective tissue disorders, autoimmune illnesses, and allergy-related disorders (96,112,113). Increased risks of myeloma have been observed in patients with rheumatoid arthritis (54,114,115). Other studies of individuals with these conditions have shown no increased risk of multiple myeloma (116,117,118,119).

Viral Infections

Patients with the human immunodeficiency virus may have an increased likelihood of developing myeloma (120,121). In addition, myeloma and hepatitis C may be associated (122,123,124). The finding of human herpes virus 8 has been suggested as a possible etiologic agent (125), but this has not been confirmed (126,127,128,129).

Clinical Manifestations

The symptoms of multiple myeloma may be nonspecific and include fatigue, bone pain, easy bruisability and bleeding, recurrent infections, manifestations of anemia, hypercalcemia, lytic bone lesions, hyperviscosity, thrombocytopenia, and hypogammaglobulinemia (Fig. 99.2). Weakness, infection, bleeding, and weight loss are reported in as many as 82, 13, 13, and 24% of patients, respectively (130,131,132,133). Hypercalcemia is present in 18 to 30% of patients (130,131,132). One third to two thirds of patients present with spontaneous bone pain (130,131,132). “Tumor fever” is present in <1% of presenting patients.

Anemia

The most common clinical feature of multiple myeloma is anemia. A hemoglobin concentration of <120 g/L occurs in 40 to 73% of patients at presentation (130,131,132) and contributes to the weakness and fatigue observed in as many as 82% of patients (130,131,132). The anemia is normochromic, normocytic in most patients, but macrocytosis may be observed as well. When there are high concentrations of serum immunoglobulin, rouleau formation may be observed (Fig. 99.3). The combination of anemia and hyperproteinemia leads to a marked increase of the erythrocyte sedimentation rate in >90% of cases (134).

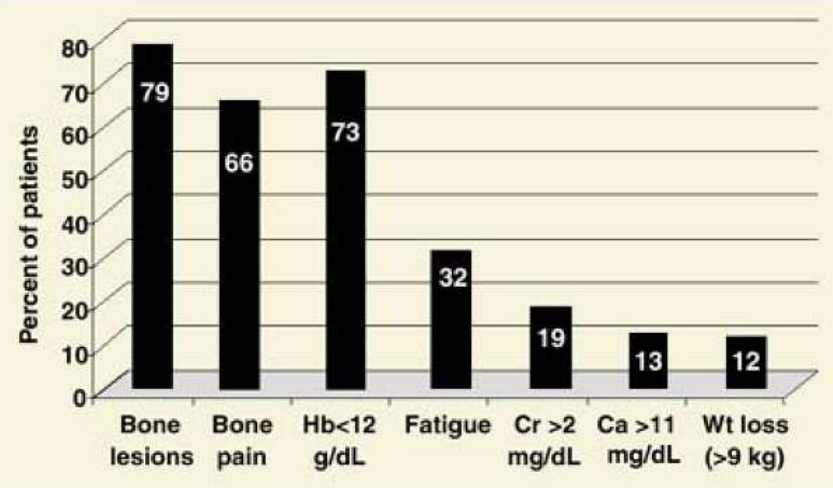

Figure 99.2. Signs and symptoms of 1,027 newly diagnosed myeloma patients seen at the Mayo Clinic from 1985 trhrough 1998.

The anemia is related partially to direct infiltration and replacement of the bone marrow. Hemoglobin concentration is also correlated directly with the percentage of myeloma cells in S phase (135), suggesting that the bone marrow cytokine milieu, permissive for myeloma cell proliferation, is not conducive to efficient erythropoiesis. Cytokines, like tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), may inhibit erythropoiesis (136). Fas ligand-mediated erythroid apoptosis is also increased in patients with myeloma (137). Finally, relative erythropoietin deficiency from myeloma-induced renal insufficiency also contributes to the observed anemia.

Monoclonal Proteins

The M protein (M component, myeloma protein, or M spike) is a hallmark of the disease; 97% of myeloma patients have either an intact immunoglobulin or a free light chain that can be detected by protein electrophoresis (Fig. 99.4), immunoelectrophoresis, or immunofixation studies of the serum or urine (130,132). Those cases without a detectable monoclonal protein have been referred to as nonsecretory myeloma, which had accounted for ~1 to 3% of myeloma cases. With the immunoglobulin free light-chain assay, small quantities of free light-chain monoclonal proteins, previously not seen by older methods, are detected in approximately two thirds of the cases we had referred to as nonsecretory(21). Historically, monoclonal proteins have had a valuable role in the fields of immunology and molecular biology, for distinguishing MGUS from myeloma and for calculating myeloma tumor burden and kinetics (27,108,138). Practically, both serum and urine M-protein concentrations are used to stage myeloma patients and to document their response to treatment.

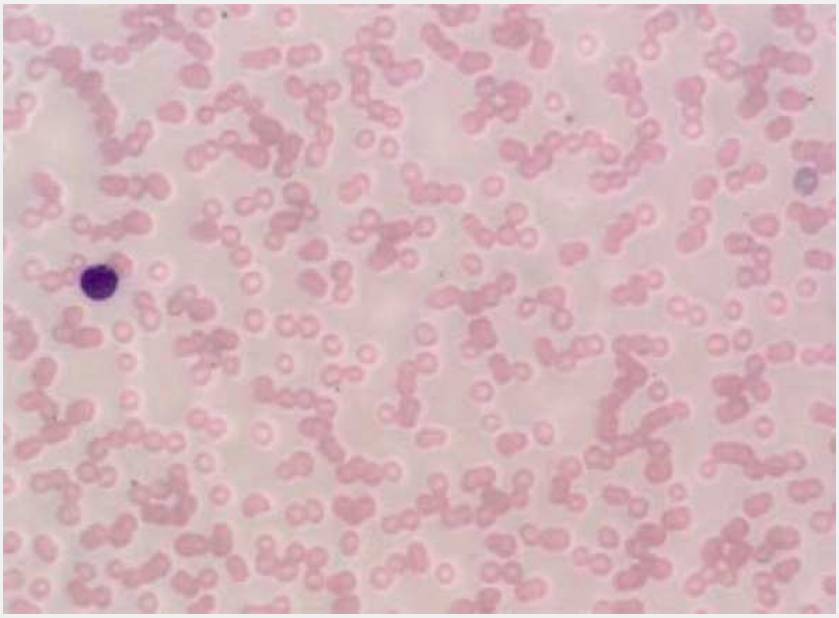

Figure 99.3. Rouleaux.

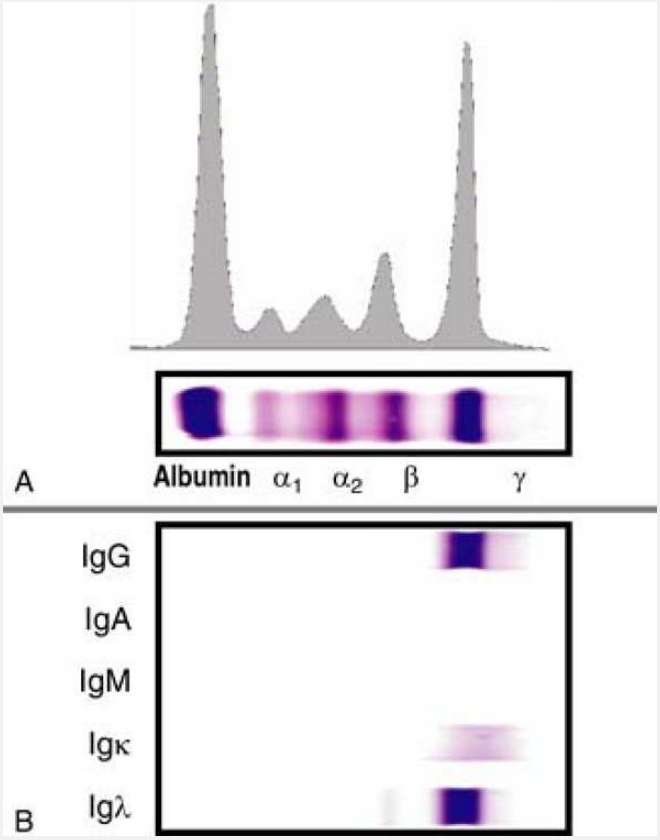

Figure 99.4. A: Serum protein electrophoresis. B: Immunofixation pattern.

An M protein represents overproduction of a homogeneous immunoglobulin or immunoglobulin fragment. In a series of 1,027 newly diagnosed cases of myeloma, the

immunoglobulin type was IgG, IgA, IgD, and free light chain only (Bence Jones myeloma) in 52, 20, 2, and 16% of cases, respectively (132). Fewer than 1% of myelomas are IgM; most IgM monoclonal proteins are associated with diagnoses of MGUS, lymphoma, Waldenström macroglobulinemia, or primary systemic amyloidosis (139). Ninety-three percent of patients have a monoclonal protein detected in their serum. About 90% of myeloma patients have reductions in at least one of their uninvolved immunoglobulins (139). About 70% have a monoclonal protein—or fragment thereof—detected in the urine.

Bone Disease

Approximately one third to two thirds of patients present with bone pain (130,131,132,133). There is an uncoupling of the tightly regulated balance between osteoclastic and osteoblastic activity seen under normal circumstances. Even before the development of bone lesions, enhanced osteoblastic recruitment with an increased generation of new osteoclasts is observed in early multiple myeloma (140). Regardless of the initiating signal, whether IL-1β, IL-6, and sIL-6R, TNF-α, MIP-1α, receptor activator of NF-κB (RANK) ligand, or parathyroid hormone–related protein (PTHrP) (141), the eventual outcome is bone destruction (142).

Myeloma bone disease is a major source of morbidity and may present as an area of persistent pain or as a vague migratory bone pain, often in the lower back and pelvis. The type, location, and duration of the pain has no characteristic features. At times, pain and tenderness may be sudden in onset, especially when associated with a pathologic fracture, and is most commonly precipitated by movement. Persistent localized pain also may be associated with a pathologic fracture.

A myelomatous lesion may extend through the cortex of a vertebral body and cause either nerve root or spinal cord compression in <2% of patients (131). Alternatively, the myeloma can disturb the mechanical integrity of a vertebral body, resulting in

compression fracture with retropulsion of either plasmacytoma or bony fragments into the spinal canal, again causing neurologic deficits.

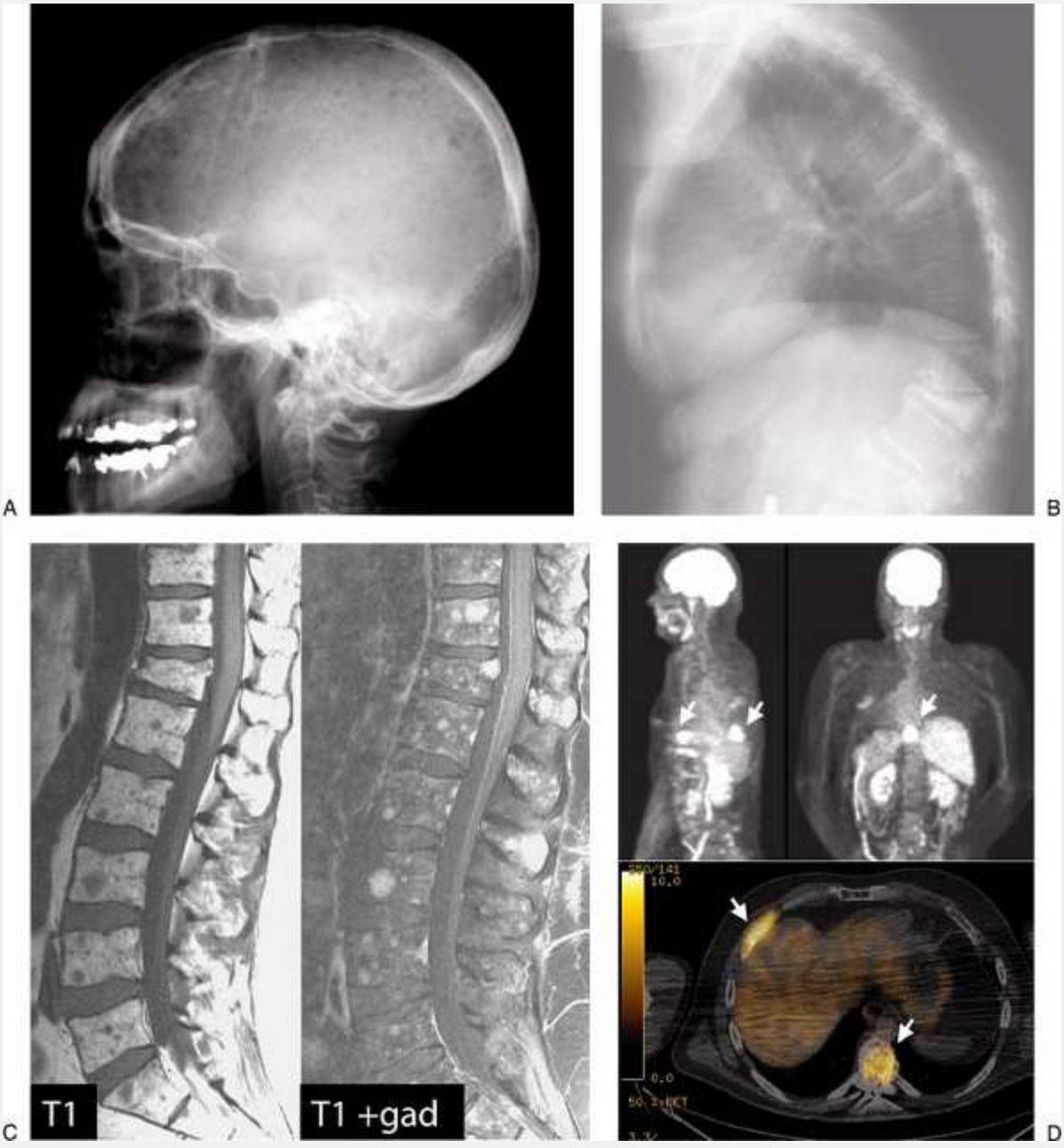

Figure 99.5. Myeloma bone disease. A: Skull. **B:** Compression fracture. **C:** Myelomatous marrow involvmement by MRI. **D:** FDG-PET/CT, spine and rib involvement.

Approximately 75% of patients have punched-out lytic lesions, osteoporosis, or fractures on conventional radiography. The vertebrae, skull, ribs, sternum, proximal humeri, and femora are involved most frequently (130,132,133) (Fig. 99.5). A small subset of patients have *de novo* osteosclerotic lesions (143), and osteosclerosis is seen in a few patients after therapy and may serve as a marker of healing.

Because myelomatous bone lesions are characteristically lytic, conventional radiography is superior to technetium-99m bone scanning (144,145). About twice as many myelomatous bone lesions are detected by radiographs as by bone scans; an exception to this general finding is at the lumbar spine and the rib cage, where the two methods are equally reliable

(145). There have been reports supporting the use of technetium-99m sestamibi scans. These scans are almost as sensitive as plain radiographs for bone disease in untreated patients with active disease (146). They may be able to distinguish active myelomatous bone lesions from inactive lesions (146) and are quite sensitive for bone marrow involvement (147,148,149). There is a high concordance between scintigraphic findings and clinical status in patients undergoing chemotherapy or autologous stem cell transplantation (150,151). Fluorodeoxyglucose positron emission tomography (FDG-PET) also shows promise in the staging of myeloma, with sensitivity and specificity rates of 84 to 92% and 83 to 100%, respectively (152).

Computed tomography (CT) and magnetic resonance imaging (MRI) are more sensitive than conventional radiography. Both reveal specific lesions in 40% of stage I myeloma patients (153). The presence of lacunae >5 mm with trabecular disruption on CT appears to be sensitive and specific for myeloma. This information may be useful in distinguishing between senile and myelomatous osteoporosis and compression fractures (154). Among asymptomatic multiple myeloma patients with normal radiographs, 50% have tumor-related abnormalities on MRI of the lower spine (155).

In patients with Durie Salmon stage I myeloma, MRI can distinguish patients at higher and lower risks of progression (156). One third of patients with an apparently solitary plasmacytoma of bone have evidence of other plasma cell tumors on MRI (157).

MRI is superior to radiographs for the detection of lesions in the pelvis and the spine, but overall it is inferior to radiographs for detecting bone involvement in multiple myeloma (79 vs. 87%, respectively) (158). On MRI, vertebral fractures due to spinal infiltration or osteoporosis are seen in 48% of patients with symptomatic myeloma, and spinal canal narrowing with impingement occurs in 20% (155). Nanni et al. (159) compared MRI to FDG-PET/CT in 28 newly diagnosed myeloma patients. In 25% of the patients, FDG-PET/CT detected more lytic bone lesions, all of which were out of the field of view of MRI; and in 25% of the patients, MRI detected an infiltrative pattern in the spine that was not discerned on FDG-PET/CT.

MRI has been said to have predictive value in patients newly diagnosed with myeloma and in patients who have received chemotherapy (160,161). Three patterns are described: focal lesions, diffuse involvement, and an inhomogeneous pattern of tiny lesions against a background of normal marrow (variegated) (161,162). Not surprisingly, there are correlations among MRI patterns of marrow involvement, bone marrow plasmacytosis (161,163,164), and the clinical stage (162,164). After treatment, resolution of marrow abnormality or persistent abnormality without enhancement corresponds to a complete response (160). In one analysis, the best independent prognosticators of survival were the MRI findings and C-reactive protein levels. Even though patients with the diffuse pattern had more bone marrow plasmacytosis, higher serum calcium values, higher β_2-microglobulin (β_2-M) values, and lower hemoglobin concentration, these factors were not significant on multivariate analysis (165). However, given the expense of MRI, it cannot be recommended for routine clinical use in all patients.

Hypercalcemia

Hypercalcemia occurs in 18 to 30% of patients. About 13% have concentrations >11 mg/dl. Rates of hypercalcemia at presentation have been decreasing in the last few decades, perhaps because of the earlier diagnosis of patients (130,131,132,133). Hypercalcemic patients may complain of fatigue, constipation, nausea, or confusion. Calcium can precipitate in the kidneys and aggravate renal insufficiency. Inorganic phosphate is rarely decreased, except in cases of acquired Fanconi syndrome (166).

Renal Insufficiency

Approximately 25% of myeloma patients have a serum creatinine value >2 mg/d*L* at diagnosis. Another 25% have mildly elevated creatinine values (130,131,132,133,167,168,169,170). Patients with Bence Jones or IgD myeloma have the highest rates of renal insufficiency (168,170). Free light-chain proteinuria is a risk factor for renal failure (171). Contributing factors to the renal insufficiency associated with myeloma kidneys include hypercalcemia, dehydration, hyperuricemia, and the use of nephrotoxic drugs (172). If the renal insufficiency reverses with therapy, as it does in more than half of cases (172,173), survival is fourfold to sevenfold higher than in those in whom it does not reverse (167,174). Factors predicting for renal function recovery include a serum creatinine of <4 mg/dl, serum calcium value >11.5 mg/dl, proteinuria <1 g per 24 hours, and adequate rehydration (167). For those patients with multiple myeloma and severe renal failure who survive the first 2 months on dialysis, 40% have an objective response to chemotherapy and a median survival of almost 2 years (175).

The pathologic lesion of myeloma kidney consists of monoclonal light chains in the tubules in the form of dense, often laminated, tubular casts. These casts contain albumin and Tamm-Horsfall protein. Light chains are normally filtered by the glomeruli and reabsorbed and catabolized in the nephron's proximal tubules. It is postulated that these systems become overwhelmed, and casts result. When other causes contributing to renal insufficiency are excluded, there is a good correlation between the extent of myeloma cast formation and the severity of renal insufficiency (176,177). Tubular atrophy and degeneration correlate well with renal dysfunction (178). The most common findings on autopsy include tubular atrophy and fibrosis (77%), tubular hyaline casts (62%), tubular epithelial giant cell reaction (48%), and nephrocalcinosis (42%). Evidence of acute and chronic pyelonephritis were observed in 20 and 23% of cases, respectively. Plasma cell infiltrates and amyloid may be observed in 10 and 5% of cases, respectively (133). Rarely, myeloma may be associated with the acquired Fanconi syndrome (166,179).

An important feature of myeloma kidney is that it is primarily a tubular rather than a glomerular disease (178). Glomerular function is preserved initially, and there is a predominance of immunoglobulin light-chain protein in the urine instead of the nonspecific protein loss observed in glomerular disease. This feature helps predict the renal lesion: nonspecific protein loss (i.e., mostly albumin) is more compatible with primary systemic amyloidosis, light-chain deposition disease of the kidney, or proteinuria unrelated to the plasma cell dyscrasia (176); a free light-chain predominance is consistent with myeloma kidney.

Infection

Patients with multiple myeloma are at high risk for bacterial infections and for dying of overwhelming bacteremia. Overall, the incidence of bacterial sepsis varies between 0.8 and

1.4 infections per patient-year (180,181,182). During the first 2 months after initiating chemotherapy the infection incidence is as high as 4.68 infections per patient-year (182) but decreases to 0.44 to 0.49 per patient-year in those reaching a plateau phase (181,182). Risk factors for infection are serum creatinine values ≥2 mg/dl (180,182) and decreased levels of polyclonal serum immunoglobulins (181,182).

Since the 1960s, Gram-negative bacilli have become more common pathogens than *Streptococcus pneumoniae* in patients with myeloma (183). At disease onset, infections with encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae* are most common (183). After diagnosis, the proportion of infections due to Gram-negative bacilli and *Staphylococcus aureus* increases markedly, and are responsible for >90% of deaths from infection (183). The mechanism of the immunodeficiency observed in these patients is not understood completely.

Hemostasis in Myeloma

Multiple myeloma can be associated with hemostatic abnormalities, more often bleeding than thrombosis. Bleeding as a complication of myeloma may be present in as many as one third of patients (184) and is related to thrombocytopenia, uremia, hyperviscosity, and interference with the function of coagulation factors.

Rarely, myeloma proteins may also interact with coagulation proteins. The immunoglobulin may interfere with fibrin monomer aggregation (184,185) or serve as a specific inhibitor of thrombin (186), von Willebrand factor, and factor VIII (184). Heparinlike anticoagulants have been observed (187). Nonspecific inhibitors may also be present, but unlike the specific inhibitors, they do not correlate with clinically observed bleeding tendencies (184). Depression of clotting factors II, V, VII, VIII, X, and fibrinogen has been described (184). The association with thrombosis is less clear because of coexisting factors such as old age and immobility, which confound the interpretation of available data; however, the risk of thrombosis may be increased in myeloma patients (184,188). Individual cases of aberrance have been reported. Monoclonal proteins have been shown to be responsible for the development of lupus anticoagulants

(189,190), acquired protein S deficiency (191,192), acquired activated protein C resistance (193), and inhibition of tissue plasminogen activator (194).

Fewer than 7% of myeloma patients have a viscosity >4 (130,132). Symptoms of hyperviscosity include bleeding, particularly from the oronasal areas, purpura, decrease in visual acuity, retinopathy, neurologic symptoms, dyspnea, expanded plasma volume, and congestive heart failure. Most patients become symptomatic when the serum viscosity is 6 or 7 centipoise (normal is ≤1.8 centipoise).

“Acute Terminal Phase of Plasma Cell Myeloma” and Cause of Death

Bergsagel and Pruzanski (195) described the “acute terminal phase” of patients with myeloma, which they observed in about one third of their preterminal patients. They defined the syndrome as rapidly progressive disease with an unexplained fever and pancytopenia and a hypercellular marrow. Extramedullary plasmacytomas are also not uncommon

preterminally (196). As the disease progresses, and at autopsy, cutaneous, visceral, and even meningeal involvement is possible (196). Besides “progressive disease,” the most frequent causes of death are infection in 24 to 52% and renal failure in ~20% (133,172,195,196). Acute leukemia, myelodysplastic syndromes, and hemorrhage are the causes of death in a minority of patients (133,195,196). In one autopsy series, 85% of patients had evidence of either bacterial or fungal infection, and myelomatous involvement was found in the spleen, liver, lymph nodes, and kidneys in 45, 28, 27, and 10% of patients, respectively. Other, less frequent areas of myelomatous involvement were the lung, pleura, adrenal glands, pancreas, and testis (133).

Histopathology

The bone marrow microenvironment is hospitable to malignant plasma cells that circulate through the blood. There is a complex interaction among the malignant clone, its surrounding stromal cells, and the remaining immune cells. The morphologic and immunologic phenotypes of myeloma cells can vary, and they often resemble normal plasma cells. Plasma cells are at least two to three times the size of peripheral lymphocytes and are round to oval, with one or more eccentrically placed nuclei (Fig. 99.6). The nucleus, which contains either diffuse or clumped chromatin, is displaced from the center by an abundance of rough-surfaced endoplasmic reticulum—the site of specialized immunoglobulin synthesis. Intranuclear and cytoplasmic inclusions are not uncommon (197). There is a perinuclear clear zone that is the site of the Golgi apparatus, the machinery used for immunoglobulin packaging and glycosylation for secretion. Derangements of immunoglobulin secretion are responsible for an assortment of cytologic aberrations, including flaming cells, Mott cells, Russell bodies, and Gaucher-like cells. Flaming cells are plasma cells that have intensely eosinophilic cytoplasm with a magenta or carmine coloring of their margins, which is due to plugging of peripheral secretory channels by precipitated immunoglobulin or immunoglobulin fragments. These cells are most commonly seen in IgA myeloma. Thesaurocytes are large flaming cells with a pyknotic nucleus that is pushed to the side. Mott cells (grape cells or morula forms) are plasma cells filled with dense spherical immunoglobulin inclusions; these inclusions are colorless, pink, or blue. Other inclusions are Russell bodies and their intranuclear counterparts (intranuclear dense bodies); these appear cherry red and can be as large as several micrometers in diameter. Gaucher-like cells are not uncommon in myeloma infiltrates; these cells are macrophages laden with sphingolipids released by the dying plasma cells (198). None of these interesting inclusions are specific for malignancy, nor do they have prognostic value.

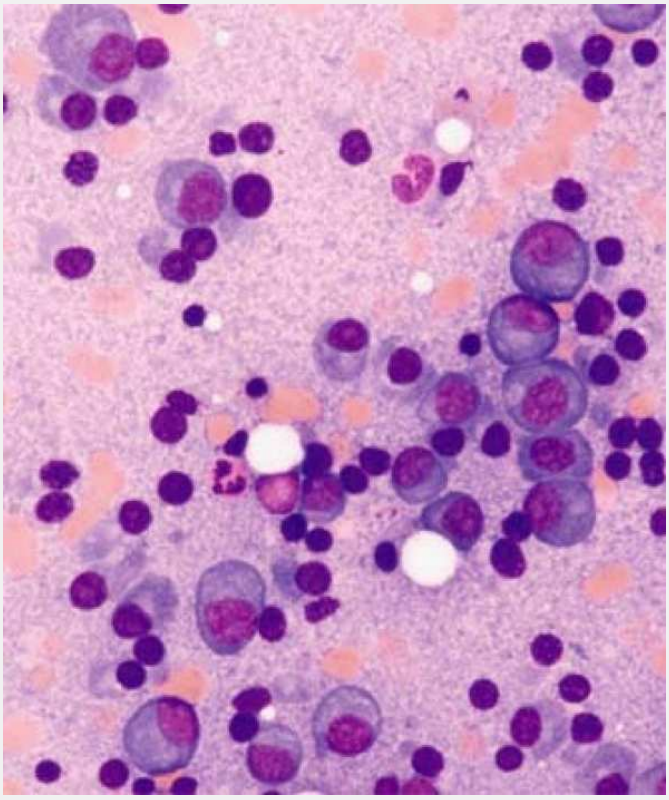

Figure 99.6. Bone marrow. Myeloma cells on aspirate specimen.

In myeloma, there is often discordance between the nucleus and cytoplasm, the former appearing immature and the latter highly differentiated. About 20% of myeloma cases have plasmablastic morphology: a diffuse chromatin pattern, nucleus >10 µm or nucleolus greater than 2 µm, relatively less abundant cytoplasm, and a concentrically placed nucleus with little or no hof (199,200). Both diffuse and nodular infiltration patterns can be observed, although the former is more common. A minority of patients have plasma cells that have a lymphoplasmacytic appearance. Myeloma cells are commonly present in cords around bone marrow microvessels. There is a high correlation between the extent of bone marrow angiogenesis, evaluated as microvessel area, and the proliferating fraction of marrow plasma cells in patients with multiple myeloma (201,202). Mild marrow fibrosis may be observed in as many as 27% of cases; extensive fibrosis is rare (203,204). Less than 1% of cases have an extensive idiopathic granulomatous reaction (197). Growth patterns may be nodular, infiltrative, or both. In cases in which the marrow involvement is focal rather than diffuse, bone marrow specimens from alternate sites may vary.

The immunophenotype of myeloma cells is complex. In general, myeloma cells are $CD45^-$, $CD38^+$ and $CD138^+$ (205,206). However, there is increasing evidence that a subset of myeloma cells is $CD45^+$ (206,207), with an increasing proportion of $CD45^+$ myeloma cells in less advanced disease (208,209). CD19 and CD20 are earlier B-cell antigens that are variably expressed on myeloma cells; surface immunoglobulin is seen in up to one third of patients. CD56 is strongly positive in about 55 to 78% of myeloma cases (206,210,211). CD56-negative myeloma cells tend to be present in more aggressive disease, such as end-stage myeloma or PCL (211,212). Other surface antigens such as CD10 (CALLA), CD28,

CD117 (c-kit), CD13, CD33, and CD20 are present on a minority of patients' myeloma cells (205,206,207,213,214). Costimulatory molecules involved in the activation of B and T lymphocytes (CD28 and CD40) are seen in 40 and 70% of patients, respectively (215,216). The labeling index of bone marrow plasma cells can be used to identify plasma cell clonality and rate of division. This assay has some value in differentiating MGUS from myeloma and indolent myeloma from active myeloma (217,218). This determination can be done by 5-bromo-2-deoxyuridine immunofluorescence staining,

thymidine labeling, or flow cytometry. In general, myeloma is a low-growth-fraction tumor with only a small percentage of cells in the S phase of the cell cycle at any given time.
No individual bone marrow finding, however, is pathognomonic for a malignant plasma cell process; the bone marrow diagnosis of myeloma relies on percentage of clonal bone marrow plasma cells, with 10% accepted as a cutoff. The clinical diagnosis, of course, is made from a synthesis of bone marrow findings and other clinical features.

Diagnosis

The diagnosis of multiple myeloma has not been subject to static norms. In 1973, the Chronic Leukemia-Myeloma Task Force (219) set forth guidelines for the diagnosis of myeloma (Table 99.1). These criteria, which by today's standards are not stringent enough, have been replaced by a more modern definition (Table 99.2) (220). In the last 3 decades, the terms and definitions of MGUS, smoldering myeloma, indolent myeloma, and symptomatic multiple myeloma (130,221,222,223) have evolved and are now to be replaced by the following designations: MGUS, inactive (smoldering) myeloma, and active (or symptomatic) multiple myeloma (220).
This internationally accepted classification schema is derived from more than 3 decades of experience of treating and studying multiple myeloma patients. Because multiple myeloma includes a spectrum of biologic features, physicians should not feel compelled to start treatment as a result of a single threshold value. The diagnosis of active myeloma is not a straightforward pathologic one; rather, it is a clinical diagnosis that requires thoughtful synthesis of multiple variables. Patients with Durie-Salmon stage I disease, who also meet the criteria for smoldering or asymptomatic myeloma, should be managed expectantly. Median progression-free survival in asymptomatic stage I patients, observed without any therapy, is 12 to >48 months (224,225,226,227); for similar stage II patients, progression-free survival is 12 months (224). No survival advantage has been demonstrated by treating asymptomatic myeloma patients (223,225,226,228).

Treatment for Multiple Myeloma

Before starting therapy for multiple myeloma, a distinction must be made between smoldering (asymptomatic) myeloma and active myeloma (Table 99.2). Approximately 20% of patients with multiple myeloma are recognized by chance without significant symptoms; such patients can be carefully monitored without instituting therapy. Weber et al. identified three risk factors for progression: serum M protein >3 g/dl (30 g/L), IgA isotype, and Bence Jones protein excretion >50 mg per day. Patients with two or more of these features required treatment at a median of 17 months, whereas the absence of any adverse variables was associated with prolonged stability (median, 95 months) ($p < .01$) (229). Cesana et al.

identified >10% bone marrow plasmacytosis, Bence Jones proteinuria, and IgA isotype as risk factors for evolution. Other risk factors for progression include circulating plasma cells (230) and myeloma cells that produce high levels of interleukin-1β (231).

Table 99.1 Chronic Leukemia-Myeloma Task Force Definition of Multiple Myeloma (1973)

If M protein present in serum or urine, one or more of the following must be present:
Marrow plasmacytosis >5% in absence of underlying reactive process
Tissue biopsy demonstrating replacement and distortion of normal tissue by plasma cells
More than 500 plasma cells/mm^3 in peripheral blood
Osteolytic lesion unexplained by other causes
If M protein absent in serum and urine, there must be radiologic evidence of osteolytic lesions or palpable tumors and one or more of the following must be present:
Marrow plasmacytosis of >20% from 2 sites in absence of a reactive process
Tissue biopsy demonstrating replacement and distortion of normal tissue by plasma cells

Data from Proposed guidelines for protocol studies. I. Introduction. II. Plasma cell myeloma. 3. Chronic lymphocytic leukemia. IV. Chronic granulocytic leukemia. Cancer Chemother Rep 1973;4:141–173.

Table 99.2 Criteria for Diagnosis of MGUS, SMM, and MM, International Working Group

Monoclonal Gammopathy of Undetermined Significance
Serum monoclonal protein (<30 g/L)
Bone marrow <10% plasma cells
No evidence of other B-cell proliferative disorders
No related organ or tissue impairment[a,b]
Smoldering Myeloma (asymptomatic)
Serum monoclonal protein (≥30 g/L) and/or
Bone marrow clonal plasma cells ≥10%
No related organ or tissue impairmenta
Multiple Myeloma (active or symptomatic)
Monoclonal protein present in serum and/or urine
Clonal bone marrow plasma cells or plasmacytoma
Related organ or tissue impairmenta

MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering multiple myeloma.
[a]The absence of CRAB (calcium elevation [>1 mg/dl above upper limit of normal], renal dysfunction [creatinine >2 g/dl], anemia [hemoglobin 2 g/dl below lower limit

of normal], bone lesions [lytic lesions or osteoporosis with compression fracture] attributable to the plasma cell disorder).
[b]The existence of immunoglobulin light-chain amyloidosis or another paraneoplastic disorder attributable to the monoclonal gammopathy, such as a peripheral neuropathy, would be termed "monoclonal gammopathy associated with—."
*Source:*Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 2003; 121:749–757

Once the decision has been made to treat for symptomatic disease, a long-term plan for managing the disease should be formulated before instituting therapy. Figure 99.7A,B outlines a possible treatment algorithm. Because high-dose therapy with hematopoietic stem cell support has been accepted as an important treatment modality for patients younger than age 65, cumulative doses of alkylator-based therapy should be avoided prior to the collection of hematopoietic stem cells in patients considered candidates for high-dose therapy.

Systemic Therapy

General Comments

Historically, bifunctional alkylating agents, such as melphalan and cyclophosphamide, have been the foundation of therapy for multiple myeloma. Myeloma cells tend to proliferate slowly, and alkylators, whose effectiveness does not rely heavily on cell division and DNA replication, are useful therapeutic agents. Prior to 1999, the bifunctional alkylators, nitrosoureas, doxorubicin, and glucocorticoids were the primary agents shown to have single-agent activity against multiple myeloma in vivo (232). These drugs, along with vincristine, either singly or in combination, had been the mainstay of chemotherapy for myeloma from the early 1960s to the present (Fig. 99.1). Until recently, the higher response rates seen with regimens that combine multiple active agents as part of initial therapy had not resulted in improved overall survival rates (233).
Interferon-α has been incorporated into induction and maintenance protocols with minimal benefit (40,234,235,236). Both autologous and allogeneic stem cell transplantation have become important therapeutic options since McElwain and Powles' description in 1983 (237) of the benefit of dose intensification of melphalan

in patients with multiple myeloma. With the recognition of thalidomide's activity against myeloma in 1999 (43) and the subsequent development of bortezomib (44) and lenalidomide (45), there is hope that the next 4 decades of myeloma treatment will be even more promising than the last.

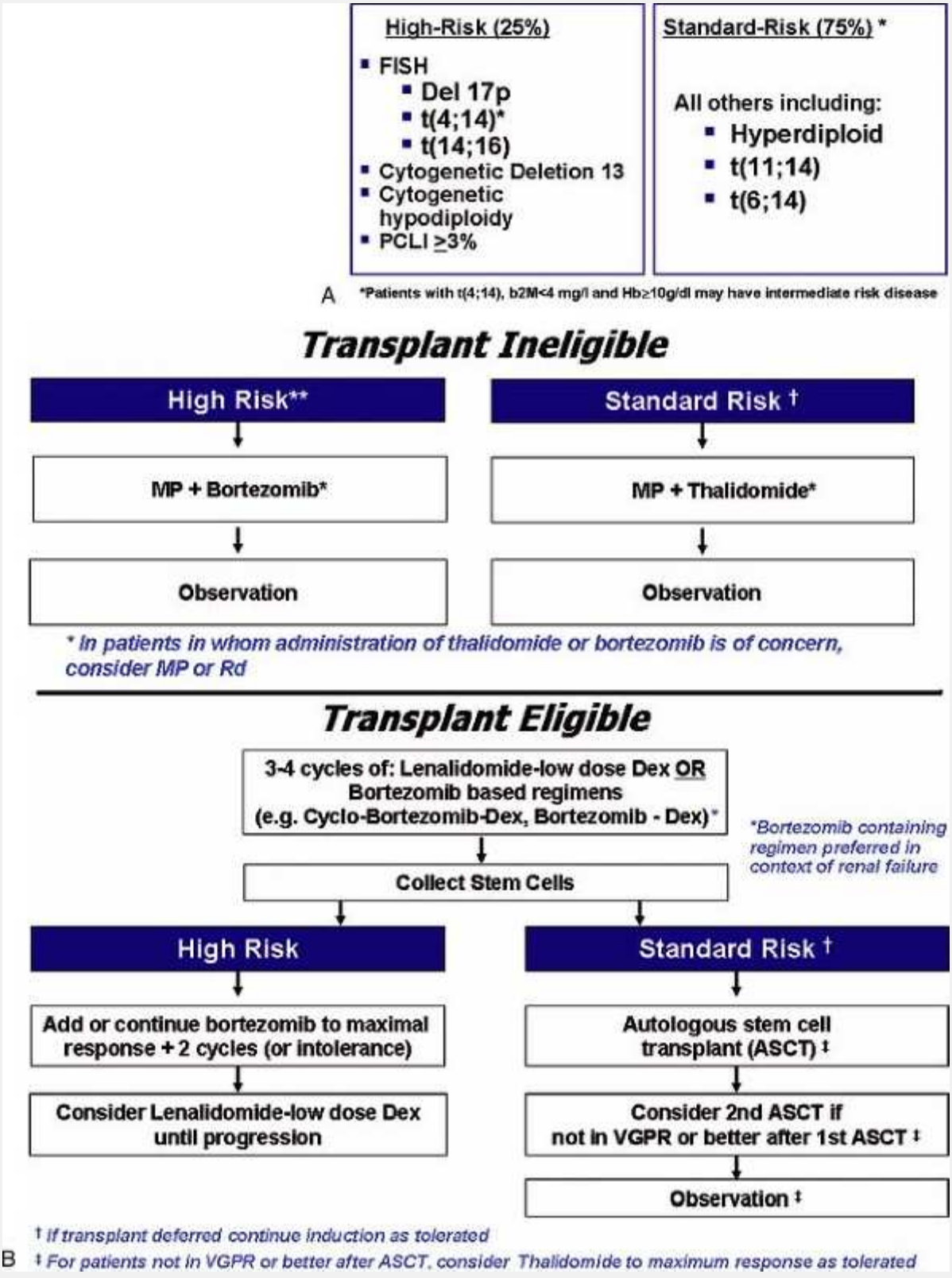

Figure 99.7. Mayo stratification for myeloma and risk-adapted therapy. A: Risk stratification. **B:** Possible treatment algorithm for patients with newly diagnosed myeloma for patients not being treated on a clinical trial. Dex, dexamethasone; HR, high risk (see text);

lenalid, lenalidomide; MP, melphalan, prednisone; PR, partial response.

Before discussing induction, transplantation, maintenance, and salvage therapies, two general concepts will be reviewed: interpretation of study response data, and the efficacy of single chemotherapeutic agents commonly used to treat myeloma. Figure 99.7 is an algorithm for treating patients with newly diagnosed myeloma. Table 99.3 serves as a reference for commonly cited regimens.

Interpreting Study Response and Survival Data

Four points are emphasized regarding the interpretation and comparisons of the myeloma treatment literature. First, definitions of response vary (Table 99.4). Second, definitions of evaluable patients may be different. Third, concurrent corticosteroid therapy, either as part of the regimen or for other indications, may confound interpretation of efficacy. Finally, patient population risk and prognosis may differ substantially. Lead-time bias and treatment of MGUS or smoldering myeloma can significantly distort survival figures, as can effective salvage regimens.

The measurement of myeloma disease burden, and therefore its response to therapy, is complex, and investigators have used different methods to define response (Table 99.4). The four most common response criteria are those of the Chronic Leukemia-Myeloma Task Force (CLMTF) (219), the Southwest Oncology Group (SWOG) (238,239), the Eastern Cooperative Oncology Group (ECOG) (240), and the Autologous Blood and Marrow Transplant Registry and International Bone Marrow Transplant Registry (IBMTR/ABMTR) (241). These response criteria are relevant from a historical prospective because they should all be supplanted by the new International Response Consensus Criteria (242). Although all partially take into account hemoglobin

calcium, bone changes, and bone marrow plasmacytosis, the main distinction among them is their consideration of the serum and urine M components. With the exception of the old SWOG criteria (238,239), a partial response (PR) has been considered to be a 50% reduction in serum M component and a >50 to 90% reduction in urine M component. In the earliest literature, response included such factors as increasing hemoglobin concentration or performance status, or decreasing blood urea nitrogen levels. Neither the CLMTF nor the SWOG criteria originally had a complete response category, because it was unusual for the M protein to disappear completely. It was not until the advent of high-dose melphalan that investigators such as Selby et al. (243) and Gore et al. began (244) to define a complete remission category. Their definition, unlike more modern definitions, only included disappearance of M protein as determined by electrophoresis, which is less sensitive than immunoelectrophoresis or immunofixation. Subsequent definitions have required immunofixation negativity to qualify as complete remission (241). Until about 1990, a SWOG objective response was defined as a 75% reduction in the *tumor mass index* (*not* serum M protein), and improvement was defined as a 50 to 74% reduction in the tumor mass index (239). A new iteration of the SWOG response criteria uses the M component (rather than the tumor mass index) as the primary measurement of the plasma cell burden. The first iteration of an international consensus definition of myeloma response were the

IBMTR/ABMTR response criteria (241). After nearly 8 years of use, several deficiencies were noted, and the International Myeloma Working Group has recently issued a new consensus definition called the International Response Criteria (IRC), which includes the Intergroupe Français du Myélome (IFM) very good partial response category (245), the ability to measure response using the serum immunoglobulin free light chain, and a new category of “stringent

complete response” that requires documentation of the absence of clonality (242).

Table 99.3 Commonly Cited Regimens and Their Dosage Schedules

Regimen	VCR	Mel	CTX	BCNU	ADR	Gluco	IMiD	Bortez
MP	—	9 mg/m^2/d, d 1–4 q 4 wk or 0.15 mg/kg/d, d 1–7b	—	—	—	P 100 mg/d, d 1–4 q 4 wk or P 60 mg/d, d 1–7b	—	—
CPa	—	—	0.25 g/m^2 per d, d 1–4 or 1 g/m^2 IV	—	—	P 100 mg/d, d 1–4 or P 50 mg, qod	—	—
ABCMc (251)	—	6 mg/m^2/d, d 1–4	100 mg/m^2/d, d 1–4	30 mg/m^2 IV, d 1	30 mg/m^2 IV, d 1	—	—	—
VBMCPd	0.03 mg/	0.25 mg/	10 mg/	0.5 mg/k	—	P 1 mg/k	—	—

(274)	kg IV, d 1	kg, d 1–7	kg IV, d 1	g IV, d 1		g, d 1–7		
VADd (391)	0.2 mg/m^2/d CI, d 1–4	—	—	—	9 mg/m^2/d CI, d1–4	D 40 mg/d, d 1–4, 9–12, 17–20	—	—
C-VAMPa (395)	0.4 mg/d CI, d 1–4	—	500 mg IV, d 1, 8, 15	—	9 mg/m^2/d CI, d 1–4	Methylpred 1 g/m^2/d, d 1— 4	—	—
Regimen	**VCR**	**Mel**	**CTX**	**Cisplatin (CDDP)**	**ADR**	**Gluco**	**IMiD**	**Bortez**
DT-PACEd (672)	—	—	400 mg/m^2/d× 4 d, CI	CI: CDDP 10 mg/m^2/d × 4 d & Etop 40 m/m^2/d × 4 d both by CI	10 mg/m^2/d × 4 d, CI	40 mg/d × 4 d	—	—
Thal-dex	—	—	—	—	—	40 mg, d	Thal	—

(441)						1–4, 9–12, 17–20 or d 1, 8, 15, 22	50–100 mg/d	
Len-dex (439)	—	—	—	—	—	As above (441)	Len 25 mg/d, d 1–21, q 28 d	—
MPT (263,451)	—	0.25 mg/kg, d 1–4 q 6 wk	—	—	—	P 2 mg/kg, d 1–4, q 6 wk	Thal 200 mg/d	—
Doxil/ Bortezа (677)	—	—	—	—	Pegylated dox 30 mg/m^2, d 4	—	—	1.3 mg/m^2, d 1, 4, 8, 11
VMPe (459)	—	9 mg/m^2, d 1–4 q	—	—	—	P 60 mg/m^2, d 1–4 q 6 wk	—	1.3 mg/m^2, d 1,

		6 wk						4, 8, 11, 22, 25, 29, & 32

IMiD, immune modulatory drug; ABCM, VBAP/VMCP without vincristine or prednisone; ADR, doxorubicin (Adriamycin); BCNU, carmustine; CDDP, cisplatin; CI, continuous infusion; CP, cyclophosphamide and prednisone; CTX, cyclophosphamide; C-VAMP, cyclophosphamide, vincristine, doxorubicin, and methylprednisolone; d, day; DT-PACE, dex, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide; gluco, corticosteroid; IV, intravenous; Mel, melphalan; MP, melphalan and prednisone; po, by mouth; MPT, MP and thalidomide; P, prednisone; q, every; qod, every other day; VAD, vincristine, doxorubicin, and dexamethasone; VAMP, vincristine, doxorubicin, and methylprednisolone; VBAP, vincristine, BCNU, doxorubicin, and prednisone; M-2, VBMCP; VCR, vincristine; VMCP, vincristine, melphalan, cyclophosphamide, and prednisone; Thal, thalidomide; Rev, lenalidomide; VMP, MP and bortezomib; wk, week.
[a]Repeated at 3-wk intervals.
[b]Repeated at 6-wk intervals.
[c]AB and CM portions of regimen are given alternately every 3 wk.
[d]Repeated every 5 wk.
[e]Repeated every 6 wk for 4 cycles, and then repeated every 5 wk, with bortezomib schedule changing to weekly administration for 4 wk followed by 1 wk rest.

Table 99.4 Response Criteria

Response	Study	% BMPC	M protein		Duration (wk)
			Serum	Urine	
Stringent CR (sCR)	IRC (242)	<5a	IF-b	IF-	0
Complete response	IRCc	≤5	IF-	IF-	6
	IBMTRc (241)	<5	IF-	IF-	6
	SWOG (239)	<1a	IF-	IF-	8

	ECOG (240)	≤3	IF-	IF-	6
	CLMTF (219)	Not defined			—
Very good partial response	IRC	—	≥90% reduction	<100 mg/24 h	—
Objective response	SWOG	—	↓≥75%c	↓≥ 0%	8
Partial Response	IRCd	—	↓≥50%	↓≥90%	6
	ECOG/IBMTR	—	↓≥50%	↓≥90% e	6
	SWOG (“Improvement”)	—	↓≥50%c	↓≥75%	8
	CLMTFf	—	↓≥50%	↓≥50%	—
Minimal response	IBMTR	—	↓≥25%	↓≥50%	—
Progression	IRC/IBMTR/SWOG	—	>25%g	>25%h	—
	ECOG	—	≥50%i	≥50%h	—

BMPC, bone marrow plasma cells; IRC, International Response Consensus; IF, immunofixation; CLMTF, Chronic Leukemia-Myeloma Task Force; CR, complete response; ECOG, Eastern Cooperative Oncology Group; IBMTR, International Blood and Bone Marrow Transplant Registry; IF, immunofixation; MR, minimum response; PR, partial response; SWOG, Southwest Oncology Group.
[a]Clonal plasma cells as measured by flow cytometry, immunohistochemistry, or immunofluorescence.

[b]Also requires normalization of serum immunoglobulin free light chain ratio.
[c]Change in synthetic index and not monoclonal protein concentration.
[d]Allows for immunoglobulin free light-chain responses in patients whose serum and urine are not measurable.
[e]Or <200 mg/24 hours.
[f]Response also takes into account reduction in size of plasmacytomas, >2 g/dl Hb rise, weight gain, correction of calcium, renal function, albumin.
[g]Absolute increase must be at least 5 g/L.
[h]Absolute increase must be >200 mg/24 hours.
[i]For ECOG, absolute increase must be at least 20 g/L.

The roving denominator also creates challenges in interpreting therapeutic studies. Often, an intent-to-treat analysis is not used to describe response rates or survival, which artificially inflates these endpoints. Definitions of evaluable patients may often include only those patients who received an “adequate” trial (3 or 6 months) of therapy, thereby excluding patients with early deaths or progression. In addition, in a steroid-responsive tumor such as myeloma, coincident use of prednisone or dexamethasone (246,247) as an antiemetic or as therapy for hypercalcemia may seriously confound the results. Finally, the striking heterogeneity of prognoses in myeloma patients cannot be excluded as a major confounding factor in interpreting both Phase II and Phase III trials. Several prognostic indicators have been identified, including stage, β2-M, labeling index, renal function, serum albumin, and chromosomal abnormalities. Unfortunately, their predictive value is limited and only skims the surface of myeloma biology and prognosis.

Efficacy of Single Chemotherapeutic Agents

Melphalan

Bergsagel et al. (37) demonstrated the benefit of melphalan in 14 of 24 patients with multiple myeloma. Others (Table 99.5) have substantiated that melphalan as a single agent results in response rates of 20 to 34% and median overall survival of 15 to 27 months (38,248,249,250,251).

Cyclophosphamide

Korst et al. were the first to report on the activity of oral cyclophosphamide. Twenty-four percent of multiple myeloma patients achieved a partial response (50% M-protein reduction), and 48% had objective improvement, that is, an improvement in the peripheral blood values, bone marrow findings, or serum blood urea nitrogen. Median survival was 24.5 months in all 207 patients and 32 months in the group that received at least 2 months of cyclophosphamide therapy. The single-agent activity of cyclophosphamide (Table 99.5) has been demonstrated in a placebo-controlled trial (249), in multiple studies of previously untreated patients (252,253), and in those who relapsed or had refractory disease (254).

Glucocorticoids

In 1950, Thorn et al. (34) reported the first observations on the beneficial effects of adrenocorticotropic hormones in myeloma. Adams and Skoog (33) observed a marked decrease in the myeloma serum protein in 18 of 26 patients treated with corticosteroids. Surprisingly, Mass (255) failed to show a difference between the survival of 55 patients randomly assigned to prednisone therapy or placebo despite clinical improvement in the former group. Subsequently, high-dose corticosteroids have been shown to produce response rates of 40 to 50%, in previously untreated patients, and 25% in refractory or relapsed patients (35,247,256,257,258,259,260,261); median survival of responding patients is 16 to 22 months (247,258,259). In reviewing their experience with single-agent dexamethasone and vincristine, adriamycin, dexamethasone (VAD), Alexanian et al. (258) noted that in patients with refractory disease, response rates with single-agent dexamethasone are comparable to those with VAD (27 vs. 32%). In contrast, in relapsed disease, response rates achieved with single-agent dexamethasone are inferior to those with VAD. These data are not randomized but rather serial observations. On occasion, patients who do not respond to high-dose dexamethasone can be salvaged with intermittent high-dose methylprednisolone (259).

Despite their contribution to quicker and more abundant responses, there are conflicting data as to whether corticosteroids prolong survival (248,250,262). As initial therapy for elderly patients, single-agent dexamethasone is responsible for both higher treatment-related morbidity and mortality compared to melphalan-containing regimens (263).

Table 99.5 Early (1969 to 1982) Randomized Trials—Untreated Myeloma

Study	Agent	Schedule	N	RR (%)	OS (mo)
Rivers and Patno, 1969 (249)	CTX	2–4 mg/kg/d	54	21	11.5a
	Placebo				3.5
Rivers and Patno, 1969 (249)	CTX	4 mg/kg/d	49	28	13
	M	0.1 mg/kg/d	54	34	15.5
Alexanian et al., 1972 (250)	M qd	0.025 mg/kg/d	35	17	18
	M intermittent	0.25 mg/kg d 1–4	69	32	18
	M alt. P	0.25 mg/kg d 1–4	28	61	24

		& 1 mg/kg MWF			
	M concurr P	0.25 mg/kg d 1–4 & 2 mg/kg d 1–4	51	65	17
MRC, 1971 (252)	CTX	150 mg/d	114	NG	28b
	M	4 mg/d	105	NG	24b
Alexanian et al., 1972 (238)	MP	M: 0.25 mg/kg & P: 2 mg/kg d 1–4	83	52a	21
	MP & procarbazine	M: 0.2 mg/kg & P: 2 mg/kg d 1–4 & Pro: 3 mg/kg d 2–10	79	41	23
Costa et al., 1973 (248)	M qd	0.15 mg/kg ×7, maintenance 0.05 kg/d	53	20	27 (30,21)c
	M qd & P	M: as above & P: 1.25 mg/kg/d with taper 8 wk	70	39	NG (53,9)
	M qd, P, & testosterone	M & P as above & testosterone: 10 g/kg/wk	56	43	NG (36,4)
MRC, 1980 (253)	MP	M: 10 mg /d d 1–7; P: 40 mg/d d 1–7 q 3 wk	174	NG	32[d,e]
	CTX IV	600 mg/m^2 q 3 wk	179		24
	MP	See above	71	NG	6[b,e]

	CMLP	C: 250 mg/m^2 po d 1–3; M: 5 mg/m^2 d 1–3; L: 50 mg/m^2 d 4; & P: 40 mg/m^2 d 1–3 q 4 wk	61	NG	6
Cornwell et al., 1982 (276)	MP	M: 0.15 mg/kg d 1–7; P: 0.8 mg/kg with taper	100	44f	27
	Carmustine-P	Carmustine: 150 mg/m^2 IV; P: 0.8 mg/kg with taper	124	34	21
	Lomustine-P	Lomustine: 100 mg/m^2 qd; P: 0.8 mg/kg with taper	137	30	21

Alt, alternating; C, cyclophosphamide; concurr., concurrently; CTX, cyclophosphamide; IV, intravenous; L, lomustine; M, melphalan; MRC, Medical Research Council Working Party on Leukaemia in Adults; NG, not given; OS, overall survival; P, prednisone; po, by mouth; qd, daily.
[a]Overall survival is significant at p=.03. No corticosteroids allowed in trial.
[b]Survival estimated from survival curves.
[c]Patients stratified for good and poor risk; median survival given as all patients (good risk, poor risk). Authors note that much quicker response observed with prednisone but worse survival with prednisone in poor-risk patients.
[d]Patients were required to have BUN≤10 mM. Difference not significant (p=.16).
[e]All patients had BUN >10 mM.
[f]Response rate between melphalan and lomustine arms significant. Median survival is not different.

The mechanism of action of this drug class is complex. Corticosteroids suppress the production of cytokines that are important in myeloma growth, such as IL-6 and IL-1β, and reduce nuclear factor κB activity, resulting in enhanced apoptosis (264,265,266,267).

Vincristine

Although vincristine has never been evaluated as a single agent in newly diagnosed myeloma, it has little activity as a single agent in refractory disease. Twenty-one patients were treated with a 0.5-mg bolus of vincristine followed by 0.25 to 0.5 mg/m^2 per day as a continuous infusion over 5 days on a 3-week schedule. Two patients had transient responses (1.2 and 2.2 months) (268). Finally, the activity credited to vincristine as a maintenance therapy is also ambiguous. Although superior survival (35 vs. 27 months, *p*

= .003) was reported in patients treated with single-agent melphalan and maintained on bimonthly vincristine (1 mg/m2) and prednisone (0.6 mg/kg for 7 days), the benefit could easily be attributed to prednisone alone (269).

Alexanian et al. (270,271) suggested that regimens that included vincristine resulted in better patient outcome than protocols that did not include this agent. The theory behind its posited utility was that after an initial kill of myeloma cells by alkylating agents, the subsequent increase in the mitotic index made myeloma cells more sensitive to vincristine (272). Reports by Lee et al., Salmon, and Case have been cited as confirmatory evidence for activity of vincristine in myeloma (273,274,275). However, several randomized controlled trials have not supported this premise (276,277,278,279) (Table 99.6). The most compelling of these is the MRC IV Trial in Myelomatosis, which randomized 530 newly diagnosed myeloma patients to monthly melphalan and prednisone, with or without monthly vincristine. Median survival in both arms was 26 months (278). Even though vincristine has not been shown to have significant single-agent in vivo activity or to improve overall survival (268,278,279,280), it is included in multiple therapeutic regimens.

Anthracyclines

Doxorubicin is the most commonly used anthracycline in the treatment of myeloma, but it has not been studied as a single agent in newly diagnosed myeloma patients. Its activity as a single agent in relapsed or refractory disease is modest, with response rates of about 10% (41,281).

A Phase II trial of mitoxantrone as a single agent (12 mg/m^2 every 3 weeks) yielded a partial response rate of 3% (1 of 35). An additional four patients showed clinical improvement lasting 4 to 7 months (282). Idarubicin is another anthracycline that has been

studied in multiple myeloma. Response rates of 0 to 27% have been observed in relapsed and refractory patients with single-agent oral regimens (30 mg/week in three divided doses given 3 of 5 weeks or 40 mg/m^2 every 3 weeks) (283,284).

Etoposide

In relapsed and refractory disease, single-agent etoposide (200 to 250 mg/m^2 over 5 days) has minimal activity; in 85 patients the response rate was <5% (285). Barlogie et al. (286) treated 14 patients with 200 mg/m^2 by continuous infusion, and 2 responded. In addition, there are 2 anecdotal reports of activity of low-dose (25 to 50 mg/day) oral etoposide (287,288).

Nitrosoureas

The nitrosoureas have single-agent activity in myeloma. In a randomized trial of 361 previously untreated patients (Table 99.5), objective response frequencies with carmustine (BCNU) (40%) and lomustine (CCNU) (42%) were lower than that of melphalan (59%), although the survival for all groups was not significantly different (276).

Table 99.6 MP versus Combination Chemotherapy as Induction: Selected Randomized Trials

Study	Regimen	N	RR (%)a	Overall Survival (mo)	P (RR)	P (OS)
SWOG 727/1972 (238)	MP	125	40[†]	28	NS	NS
	MP-Pcb	116	47	31		
SECSG 343/1984 (359)	MP	187	29	36	NS	NS
	BCP	186	37	36		
CALGB 7161/1979 (353)	MP	126	56	NG	0.047	NS
	MCBP	124	68			
NCI-C-MY1/1979 (583)	MP	125	40 b	28	NS	NS
	MCBP	239	39	31		
ECOG 4472/1982 (360)	MP	92	40	19	NS	NS
	BCP	96	50	25		
GATLA3-M-73/1980 & 198 (361,1087)	MP	67	40	38	NS	NS
	CP-MeCCNU	83	40	30		
GATLA3-M-77/1984 & 1988 (361,937)	MP	145	33	42	NS	NS
	MPCV-MeCCNU	115	44	44		
Pavia MM-75/	MP	39	41	54	NS	0.039

(1088)	Pept-VP	36	58	26		
SWOG 7704/1983 & 1986 (368,369)	MP	77	32 b	23		
	VMCP/VCAP	80	58	43	0.001	0.004 c
	VMCP/VBAP	80	49	43	0.028	
MDA7704/1984 (271)	MP	30	53 b	38	NS	NS
	VMCP/VCAP	42	55	27		
	VMCP/VBAP	34	60	28		
CALGB 7761/1986 (354)	MP (IV)	146	47	34	NS	d
	MCBP	140	56	29		
	Seq-MCBP	148	47	22		
	MCBPA	157	44	26		
IMMSG M-77/1985 (279)	MP	47	19 †	30	NS	NS
	VMCP	53	19	45		
	BC-Pept	33	3	58		
Gentofte,	MP	31	45	21	NS	NS

Denmark/1985 (277)	VMP	32	73	30		
	VBMCP	33	58	21		
ECOG 2479/1997 (373)	MP	230	51	27	<0.0001	NS
	VBMCP	235	72	29		
MRC MYEL-4/1985 (278)	MP	261	NG	26	NS	NS
	VMP	269		26		
Finnish MM80/1987 (363)	MP	66	54	41	< 0.02	NS
	MOCCA	64	75	45		
Norwegian Trial 1986 & 1988 (364,385)	MP	48	48	29	NS	NS
	VBMCP	44	54	33		
MGCS stage III/1989 (365)	MP	44	61	28	NS	NS
	VMCP/VBAP	42	52	24		
GMTG MM01/1988 & 1991 (371,384)	MP	170	33 b	60 % 4 y OS	NS	<0.02 MP
	VMCP	150	33			
MGCS stage	MP	29	69	46	NS	NS

II/1990 (370)	VMCP	25	56	33		
MGCS stage III/1990 (370)	MP	55	58	26	NS	NS
	VMCP/VBAP	53	57	24		
IMMSG M-83/1991 (366)	MP	146	64	37	0.02	NS
	VMCP/VBAP	158	77	32		
PEETHEMA 85/1993 (372)	MP	247	32	27	0.004	NS
	VMCP/VBAP	241	45	32		
Pavia 1986/1994 (225)	MP	87	24	All 24	NS	NS
	Pept-VP	83	24			
NMSG/1993 (367)	MP	74	64	31	NS	0.02
	NOP	77	60	14		
GMTG MM02/1995 (374)	MP (IV)e	99	43	~37	0.01	NS
	VBAMDe	105	64			
Meta-analysis Group (233)	MP vs. CCT	6,633	53	29	<0.00001	NS

A, doxorubicin; B, BCNU or carmustine; C, cyclophosphamide; CCT, combination chemotherapy; D, dexamethasone; IV, intravenous; M, melphalan; MeCCNU, methyl-CCNU; MOCCA, the additional C is for CCNU (lomustine); NG, not given;

NOP, mitoxantrone, vincristine, and prednisone; NS, not significant; P, prednisone; Pcb, procarbazine; Pept, peptichemo; V, vincristine.
[a]Except where stated, response is according to Myeloma Task Force criteria or modification.
[b]SWOG response criteria.
[c]Significantly superior survival in combination chemotherapy arms compared to MP in the 174 stage III patients but not in the 74 stage I or II patients.
[d]The sequential arm was significantly worse than either the MP (p=.01) or the MCBP (p=.02) and marginally worse than MCBPA (p=.09).
[e]Part of an interferon trial; stage III patients only.
Data from Anonymous. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. Myeloma Trialists' Collaborative Group. J Clin Oncol 1998;16:3832–3842.

Interferon

Despite the encouraging reports that daily human leukocyte interferon (3 to 9 MU/day) could induce responses in as many of 60% of myeloma patients (40,234) subsequent studies with recombinant interferon-α yielded rates of 10 to 20% (236,289,290,291,292). Toxicity was not inconsequential (292). In vitro activity had good predictive value for in vivo clinical response in 26 patients studied (290). However, interferon has a stimulatory effect in about one third of myeloma samples tested in vitro (290).

Thalidomide

Thalidomide is the first in the class of drugs called immune modulatory drugs (IMiDs). Recognition of the role of increased

angiogenesis in the pathogenesis and progression of myeloma (201), and evidence of thalidomide's antiangiogenic properties (293,294), led to clinical trials in multiple myeloma (43,295). The observed responses in patients without high-grade angiogenesis suggest that thalidomide may act via other mechanisms as well (296). In vitro data suggest that the drug and its metabolites may inhibit angiogenesis, but in addition may modulate adhesion molecules of myeloma cells and their surrounding stroma, modulate cytokines, and affect natural killer cells. There is evidence that thalidomide and its analogs induce apoptosis and G_1 growth arrest in myeloma cells (296).

The first published report of the utility of thalidomide in patients with relapsed myeloma was by Singhal et al. (43). Eighty-four patients with relapsed myeloma, 76 of whom had relapsed after high-dose chemotherapy with stem cell support, were treated with escalating doses of thalidomide. Patients were started on 200 mg each evening; the dose was escalated every 2 weeks if tolerated to a final maximal dose of 800 mg daily. Twenty-five percent of patients had at least a 50% reduction in their serum paraprotein. Preliminary evidence of response was apparent within 2 months in more than three quarters of the patients who did respond. Other investigators have confirmed partial response rates of 25 to 58%, with an additional 6

to 26% achieving a minimal response, median response duration of 9 to 12 months, 2-year progression-free survival of 10 to 20%, and 2-year overall survival of 48% (295,297,298,299,300,301,302,303,304,305).

When thalidomide is used as a single agent in previously untreated patients, response rates of 25% may be achieved (306,307,308).

The role of dose intensity in thalidomide effectiveness is unclear (302,309). In the original reports, the highest dose tolerated was administered (43). In high-risk patients there was a suggestion that response rates were higher and survival longer in patients receiving high doses of thalidomide (≥600 mg/day) (310). However, in some patients, responses may be seen with doses as low as 50 to 100 mg/day (309).

Toxicities associated with thalidomide include fetal malformations, constipation, weakness or fatigue, somnolence, skin problems, and sensory neuropathy in more than one third of patients. There is also an increased risk of thrombosis in patients treated with thalidomide, which appears to be exacerbated by the use of concurrent combination chemotherapy, with rates as high as 28% (311,312,313). Other life-threatening complications have included Stevens-Johnson syndrome and hepatitis (314,315).

Thalidomide is now considered a standard therapy for multiple myeloma, although U.S. Food and Drug Administration approval for this indication is pending.

Lenalidomide (CC-5013; Revlimid)

Lenalidomide is a small-molecule derivative of thalidomide and a member of the IMiD class. Lenalidomide is more potent than thalidomide in mediating direct cytokine-related and immunomodulatory effects against human multiple myeloma cell lines and patient-derived cells in vitro. It induces apoptosis of myeloma cells; overcomes cytokine and bone marrow stromal cell-mediated drug resistance; has antiangiogenic effects; and stimulates host antimyeloma T- and natural killer cell immunity (45,316). In the original Phase I study, 30% of patients responded to single-agent therapy, with a 6-month median duration of response (45). At 50 mg/day the dose-limiting toxicity was myelosuppression. In the randomized Phase II trial, two schedules were evaluated: 25 mg daily and 15 mg twice daily. In both arms, drug was given only 21 out of 28 days. Overall, ~17% of relapsed or refractory patients achieved a partial response, including a 4% complete response rate, with a median progression-free survival of 4.6 months for the patients receiving once-daily dosing (45,316). An additional 9% of patients achieved a minimal response. Aside from myelosuppression, other grade 3–4 toxicities included neuropathy and fatigue in 3 and 7% of patients, respectively. In the open-label Phase II trial of 222 patients, there was a 25% partial response rate, with a

time to progression of 5.1 months (317). Lenalidomide has never been studied as a single agent in newly diagnosed myeloma.

CC-4047 (Actimid)

CC-4047 is another IMiD with activity in MM (318); 54% of previously treated patients respond to single-agent therapy. Median progression-free survival was 9 months.

Bortezomib (Velcade)

Bortezomib is the first drug in its class of proteasome inhibitors. It is a boronic acid dipeptide that reversibly and selectively inhibits the proteasome, an intracellular complex that degrades primarily ubiquitinated proteins. The proteasome has a key role in protein degradation, cell-cycle regulation, and gene expression. Tumor cells, including multiple myeloma cells, are heavily dependent on proteasome-regulated proteins for their growth and interaction with stromal cells. Inhibition of the proteasome has emerged as an important antitumor target, and bortezomib has been shown in vitro and in vivo to cause growth arrest, to induce apoptosis, and to inhibit angiogenesis.

In myeloma patients, the same schedule (days 1, 4, 8, and 11, every 21 days) of two dose levels, 1.0 and 1.3 mg/m^2, has been studied as second-line therapy as part of a randomized Phase II study. Patients had dexamethasone added to the bortezomib either because they had progressed after two cycles or they had not achieved a partial response or better after four cycles. Though no direct comparisons were made, in the 1.3-mg/m^2 arm there was a trend toward higher single-agent response rates (38 vs. 30%), less frequent dexamethasone usage (46 vs. 57%), longer duration of response (417 days vs. 288 days), and longer time to progression (333 vs. 212 days), but higher serious adverse events. Dose reduction was necessary in a higher proportion of patients in the 1.3-mg/m^2 arm (35 vs. 11%).

Single-agent response rates in relapsed/refractory myeloma range from 28 to 38%, with a median duration of response of 8 months (319,320,321,322). In the APEX trial—the randomized trial comparing bortezomib to dexamethasone—the response rates, progression-free survival, and overall survival at 1 year were significantly superior in the bortezomib-treated patients compared to the dexamethasone-treated patients (320). Although the original studies using this drug included only eight cycles of therapy, 63 patients were treated on an extension study without significantly more serious adverse events than were seen in the parent studies of eight cycles alone (323). In previously untreated myeloma, response rates were 40% (324).

The most common adverse events associated with bortezomib are gastrointestinal disturbances, fatigue, peripheral neuropathy, and myelosuppression. Seventy-five percent of patients had serious (grade 3–4) adverse events, the most common of which were thrombocytopenia, neutropenia, anemia, gastrointestinal disturbances, fatigue, and neuropathy (320).

Arsenic Trioxide

In vitro, arsenic trioxide (ATO) induces growth inhibition and apoptosis (325). Generation of reactive oxygen species with subsequent accumulation of hydrogen peroxide enhances ATO-induced apoptosis. Because glutathione is believed to salvage free radicals, methods to reduce glutathione have been explored, the most popular of which is coadministration of ascorbic acid. In vitro, this approach has appeared to be more effective against myeloma cells of patients with refractory disease than those with newly diagnosed disease (326).

As a single agent in refractory disease, the overall partial response rate is 7.1% (327), with a total of one third achieving a 25% reduction in M protin in one study (328).

Other Agents

Barlogie et al. (286) explored the utility of cisplatin therapy for patients with myeloma. Fourteen patients were treated with 10 mg/m^2 for 7 days by continuous infusion, and two

responded. The drug has been incorporated into other regimens for relapsed disease (286,329,330) and induction therapy (331).

Cytosine arabinoside (332), teniposide (333), topotecan (334), deoxycoformycin (335,336), and paclitaxel (337,338) have been reported to produce response rates of 7, 28, 16, 0 to 15, and 15 to 29%, respectively. Topotecan induces significant toxicity, including ≥grade 3 granulocytopenia and thrombocytopenia in 93 and 53% of patients, respectively (334). Patients treated with paclitaxel were premedicated with 40 mg of dexamethasone every 21 days (337,338), bringing into question whether the observed responses were attributable to dexamethasone or paclitaxel.

Agents that do not appear to have any activity in myeloma include drugs that are interesting from a historical perspective and drugs that have known activity in other diseases. Agents in the former category include diamidines, such as stilbamidine; 1-aminocyclopentanecarboxylic acid; amsacrine (339,340), aclarubin (341), chlorozotocin (342), hexamethylmelamine (343), and azaserine (38). Other agents without activity against myeloma include methotrexate, 6-mercaptopurine, 6-thioguanine, 5-fluorouracil, fluorodeoxyuridine, hydroxyurea, mitomycin C (38), vinblastine, vindesine (247), carboplatin (344), bleomycin (281), ATRA (all-*trans*-retinoic acid), fludarabine (345), 2-chlorodeoxyadenosine (346), flavopiridol (347), and imatinib (348). Although Durie et al. (349) reported a 57% response rate with clarithromycin, subsequent reports did not corroborate this response rate, and the activity observed in the original report was attributed to concurrent corticosteroid therapy (350,351,352).

Combination Chemotherapy for Induction

A combination of multiple active agents in an effort to achieve synergy is a logical corollary. The last three decades of the 20th century were spent combining alkylators, anthracyclines, corticosteroids, and interferon. Thirty years of study indicate that though these combinations as initial therapy resulted in higher response rates, this did not translate into longer overall survival rates than standard melphalan and prednisone therapy (233) (Table 99.6) (Fig. 99.8). Although it has been suggested that patients with more advanced disease benefit from combination chemotherapy compared to melphalan (251,272,353,354,355), that hypothesis has not been proven (225,233). Now that IMiDs and proteasome inhibitors have been shown to have activity, clinical investigators have begun using these drugs in combination. For expediency, these regimens will be separated into five categories for discussion: Alkylator-based without anthracyclines, anthracycline-containing regimens, anthracycline-containing regimens with intensified doses of corticosteroids, regimens incorporating interferon, and novel therapies (Tables 99.6,99.7,99.8). As a general rule, patients who are being considered for stem cell collection and transplantation receive non–alkylator-containing induction regimens, or if alkylator-containing regimens are used, the number of cycles is restricted to four prior to stem cell mobilization. Clinical research in myeloma is moving at breakneck speed, and the current preferred induction therapies are all in the “novel” category (Tables 99.7 and 99.8). Descriptions of older regimens are provided for two reasons: to give a historical backdrop; and to familiarize the reader with these regimens. As “novel” therapies move to front-line, these older “induction” regimens will be important as salvage regimens. In time, we may be able to better ascertain biologic differences (356) between myeloma patients and direct specific types of therapy to their biology.

In the setting of induction prior to stem cell collection and transplantation, major questions revolve around “does it matter” and is “best response” necessary before proceeding to stem cell collection and transplantation. Unfortunately, no completed prospective randomized trial has yet addressed this question. Retrospective analyses have shown that patients proceeding to stem cell transplantation with deeper responses do better (357); however, does the better outcome reflect on the therapies that brought the patient to the better response? Or does it just reflect the fact that patients who

have chemotherapy-sensitive disease do better? Is biology or therapy providing the better outcomes in these retrospective analyses?

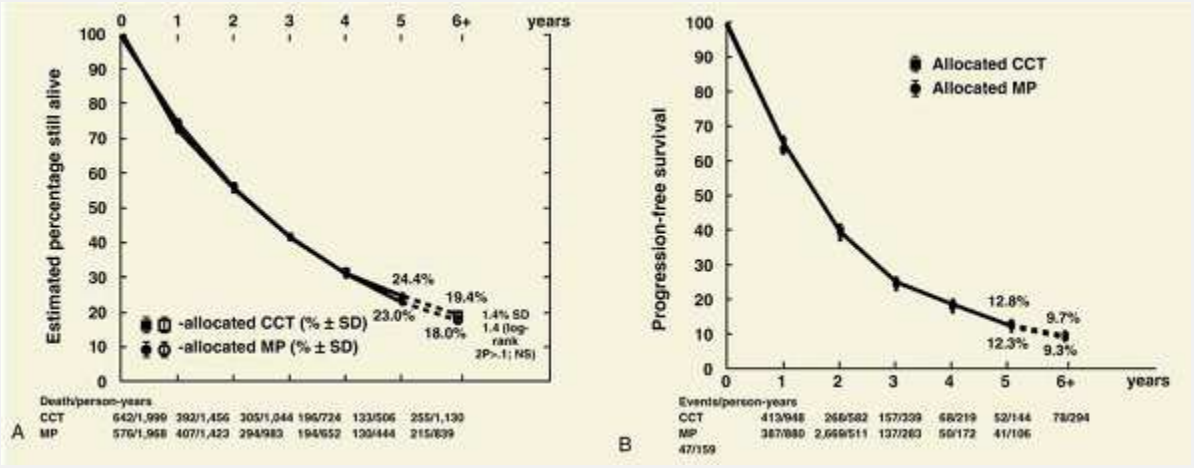

Figure 99.8. Melphalan and prednisone (MP) versus combined chemotherapy (CCT) as induction. Results from 6,633 patients from 27 randomized trials. **A:** Overall survival. **B:** Response duration. (From Anonymous. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. Myeloma Trialists' Collaborative Group. J Clin Oncol 1998;16:3832–3842. By permission of the American Society of Clinical Oncology.)

Melphalan ± Corticosteroids as Induction Therapy

Since early reports by Blokhin et al. (36) and Bergsagel et al. (37), various schedules of melphalan have been tried, including continuous daily dose, 6 to 10 mg/day for 2 to 3 weeks, followed by maintenance therapy of 0.01 to 0.03 mg/kg per day; intermittent total doses of 0.25 mg/day given for 4 days every 4 to 8 weeks; or 0.15 mg/kg per day for 7 days every 6 weeks (250,358). Several studies suggest that the intermittent schedule is superior to continuous daily dosing (250,358)

Table 99.7 Induction for Patients Who Are Not Candidates for Hematopoietic Stem Cell Transplantation, Recent Publications

Author	Regimen	Phase	N	CR (%)	VGPR (%)	PR (%)	OR (%)	PFS (mo)	OS (mo)
Facon (IFM 95-01) (263)	Dex	3	127	1	0	41	42	12.2	33
	Dex-IFN	3	121	1	0	42	43	15.2	32
	MP	3	122	1	0	40	41	21.1	34
	MD	3	118	3	0	67	70	22.9	40
Rajkumar, 2006 (446)	Dex	3	235	—	—	—	—	—	25
	Thal-dex	3	235	—	—	—	—	—	25
Klueppenlberg, 2005 (1089)	LD-Thal-Dex-Z	2	45	0	30	68	98		2 y, 68 %
Ludwig, 2005 (450)	Thal-dex	3	125/2	10	27	15	52	—	—
	MP	3	125/2	3	12	20	35	—	—
Facon (IFM 99-06) (476)	MP	3		3	5	26	34	17.5	30.3
	MPT	3	0	14	37	33	84	29.5	NR
Palumbo, 2006 (436)	MP	3	126	2	10	36	48	~14	NR

	MPT	3	129	16	21	40	76	~25	NR
Dimopoulos, 2006 (1090)	MDT	2	50	10	0	62	72	TTP 21.2 mo	28.2
Palumbo, 2006 (443)	MPR	1/2	50	10		60	70	—	—
Offidani, 2006 (453)	ThaDD	2	50	34	24	30	88	3-y EFS 57% 16 mo	3 y, 74% 16 mo
Mateos, 2006 (459)	V-MP	2	60	32	11	45	88	EFS 83%	EFS 90%
Hussein, 2006 (454)	T-DVd	2	53	36	13	34	83	28-	NR at 50 mo

CR, complete response; Dex, dexamethasone; EFS, event-free survival; IFN, interferon; LD-Thal-Dex-Z, low-dose thalidomide, dexamethasone, and zolendronic acid; MD, melphalan, dexamethasone; MDT, MD and thalidomide; mo, months; MP, melphalan, prednisone; MPR, MP and lenalidomide; **N**, number of patients; NR, not reached; OR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; T-DVd, thalidomide, pegylated doxorubicin, vincristine, and dexamethasone; thal, thalidomide; ThaDD, thalidomide, pegylated doxorubicin, and dexamethasone; TTP, time to progression; VGPR, very good partial response; **VMP, MP** and bortezomib; y, year.

The combination of melphalan and prednisone (Tables 99.5,99.6,99.7) has been studied extensively (238,248). Response rates are 40 to 60%, and anticipated median survivals are 18 to 42 months

(225,233,238,248,250,253,271,277,278,354,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374). Because of the variable gastrointestinal tract absorption of melphalan, intravenous regimens of 15 to 25 mg/m^2 every 4 weeks along with oral prednisone or dexamethasone have been tried and resulted in response rates of 50 to 82% (374,375).

Table 99.8 Induction Regimens for Hematopoietic Stem Cell Transplantation– Eligible Patients

Reference	Regimen	Phase	N	CR (%)	VGPR (%)	PR (%)	OR (%)
Rajkumar, 2003 (307)	Thal	2	29	0	0	34	34
Rajkumar, 2001 (306)	Thal	2	16	0	0	37	37
Weber, 2003 (308)	Thal	2	28	0	0	36	36
Rajkumar, 2006 (441)	Dex	3	104	0	0	41	41
	Thal-Dex	3	99	4	0	59	63
Rajkumar, 2002 (445)	Thal-Dex	2	50	0	0	64	64
Weber 2003 (308)	Thal-Dex	2	40	16	0	56	72
Sidra, 2006 (668)	CDT	2	15	0	27	60	87
Rajkumar 2005 (439)	Rev-Dex	2	34	6	32	53	91
Niesvizky, 2006 (465)	BiRD	2	40	25	18	53	95
Jagannath, 2005	Bortez	2	32	3	9	28	40

(324,1091)	Bortez +/- dex	2	32	6	19	63	88
Anderson, 2006 (457)	Bortez	2	60	10	0	28	38
Harousseau, 2005 (458)	Bortez-Dex	2		20	0	47	67
Wang, 2005 (462)	VTD	2	36	19	0	73	92
Hussain, 2002 (405)	DVD	2	33	12	0	55	67
Rifkin, 2006 (407)	VAd	3	95	0	0	41	41
	DVd	3	97	3	0	41	44
Dimopoulos, 2003 (406)	VAD	3	127	13	0	49	62
	DVD	3	132	13	0	48	61
Goldschmidt, 2005 (448)	VAD	3	406/3	3	0	60	63
	TAD	3	406/2	7	0	73	80
Hassoun, 2006 (455)	AD + TD	2	45	16	20	49	85
Zervas, 2004 (452)	T-DVD	2	39	10	0	64	74
Oakavee, 2005 (460)	PAD	2	21	24	0	71	95
Popat, 2005 (461)	LD-PAD	2	19	11	28	50	89

Badros, 2005 (463)	VDT-PACE	1/2	11	9	9	92	100
Barlogie, 2006 (1092)	TT1	2	231	12	0	51	63
	TT2 no thal	3	323	10	0	30	40
Barlogie, 2006 (594)	TT2 +thal	3	345	19	0	41	60

See Table 99.7 for abbreviations.

Not until the report by McElwain and Powles (237) on the successful use of high-dose melphalan (140 mg/m^2 intravenously) had dose intensity been studied in myeloma. In previously untreated patients, Selby et al. (243) confirmed a 78% response rate, including 27% of patients whose M component was no longer visible by protein electrophoresis. This dose intensity without stem cell salvage was associated with prolonged, severe thrombocytopenia and leukopenia (lasting a median of 24 and 28 days, respectively). Treatment-related mortality was 19%. The benefit of melphalan dose intensification was confirmed by others who used attenuated doses (50 to 70 mg/m^2) and reported response rates of 50 to 85% (376,377,378). These dose schedules are associated with 8 and 6 days of severe neutropenia and thrombocytopenia, respectively (377). Doses of 25 to 30 mg/m^2 will effect responses in ~35 to 40% of relapsed, refractory patients (379,380).

Cyclophosphamide ± Corticosteroids as Induction Therapy

Since the original report by Korst et al. (39) of the utility of cyclophosphamide in myeloma patients, several single-agent induction regimens have been studied. Despite documented equivalency for low-dose oral regimens of cyclophosphamide and melphalan (252), induction therapies of melphalan and prednisone tend to be preferred over those of cyclophosphamide and prednisone. Most commonly, cyclophosphamide has been used in multidrug combinations for induction, for therapy in relapse, and for stem cell mobilization rather than as a single agent for induction, as has melphalan. For newly diagnosed myeloma, oral daily dosing of cyclophosphamide (150 mg/day) (252,381,382) or intravenous doses of 600 mg/m^2 every 3 weeks (253), with or without prednisone, has resulted in a response rate of ~25% and median survival of 24 months.

Multidrug Combination Chemotherapy without Anthracycline for Induction

The 1970s and 1980s were a testing ground for various combinations of alkylators, corticosteroids, and doxorubicin. Melphalan/cyclophosphamide/prednisone (270), carmustine/ cyclophosphamide/prednisone (359,60), melphalan/cyclophosphamide/armustine/prednisone (MCBP) (270,353), and vincristine/melphalan/cyclophosphamide/prednisone (VMCP) (270) resulted in response rates of 47, 37 to 50, 49 to 68, and 62%, respectively. Median survivals with these regimens were 25 to 36 months (270,353,359,360). Lee and Case (274) introduced the five-drug regimen of vincristine/carmustine/melphalan/cyclophosphamide/prednisone (VBMCP or the M-2 regimen), which included the same four drugs as MCBP plus vincristine; dose intensities, however, were different in these two regimens. Response rate for VBMCP was ~85% in previously untreated patients, with a median survival of 38 months (274,383). The success of the VBMCP regimen supported the value of vincristine. However, the MRC IV trial, which randomized 530 previously untreated patients with myeloma to melphalan and prednisone versus melphalan/vincristine/prednisone, revealed no difference in either response rate or overall survival between the two arms (278). VMCP has not produced any response or survival advantage over melphalan and prednisone (371,384). Finally, the MOCCA regimen, which is essentially VBMCP with CCNU replacing BCNU, results in response rates similar to those for VBMCP (75%), but again no survival benefit in comparison to melphalan and prednisone (363)

Although subsequent randomized trials have substantiated the superior response rates of VBMCP over standard melphalan and prednisone (Table 99.6), they have not demonstrated superior

survival (277,364,373,385). In fact, the meta-analysis performed by the Myeloma Trialists' Collaborative Group (233), involving 6,633 patients in 27 randomized trials, revealed a superior response rate (60.2 vs. 53.2%, $p < .000001$, two-tailed) but no survival benefit for combination chemotherapy over standard melphalan and prednisone (Fig. 99.8). A prior meta-analysis of 18 published trials (3,814 patients) also demonstrated no benefit for combination chemotherapy in terms of survival. There might be a survival advantage in the subgroup of patients with more aggressive disease (355), but this was not substantiated in the larger meta-analysis (233).

Combination Chemotherapy with Anthracycline for Induction

The use of alkylator/doxorubicin-based combination chemotherapy was stimulated by a report on the benefits of a combination of doxorubicin and BCNU in patients who had become resistant to melphalan (386). Regimens such as MAP (melphalan/doxorubicin/prednisone), CAP (cyclophosphamide/doxorubicin /prednisone), VCAP (vincristine and CAP), and VBAP (vincristine/BCNU/ doxorubicin /prednisone) were tried; by SWOG response criteria, objective response rates were 41, 46, 64, and 61%, respectively (270,387). Median survival ranged from 30 to 32 months; subsequent analysis demonstrated a superior median survival for the VBAP arm of 37 months (388).

Enthusiasm for alternating VMCP and VBAP (or VCAP) was generated by the SWOG study of 237 patients randomized to melphalan and prednisone or the above regimens (Table 99.9) (368,369). Response rates were superior in the alternating combination chemotherapy arms compared to the melphalan arm. Survival was also superior in the combination

chemotherapy arms (43 vs. 23 months for melphalan and prednisone, $p = .004$) (387). However, a subsequent analysis with longer follow-up showed less separation of the survival curves (median survival, 25 vs. 36 months) (388). The survival benefits of this initial study were not reproducible by others (271,365,366,370,372,389,390).

The Vth MRC myelomatosis trial randomized patients to ABCM (VBAP/VMCP without the vincristine or prednisone) or melphalan as a single agent on the basis of findings emanating from the IV MRC trial, which demonstrated a lack of benefit attributable to the addition of vincristine. Median survival in the ABCM group was superior to that of the melphalan-only arm (32 vs. 24 months, $p = .0003$) (251). When corrected for adverse prognostic factors such as elevated β_2-M values, low hemoglobin values, renal insufficiency, performance status, and stage, the significance of the survival difference was $p = .003$ (280).

Table 99.9 Risk of IMiD-Associated Thromboembolism

Reference	N	Regimen	Prophylaxis	TE (%)
Zangari 2004 (437)	134	TT2	No	14
	87	TT2 + Thal	No	34
	35	TT2 + Thal	LD coumadin	31
	62	TT2	Enox	15
	68	TT2 + Thal	Enox	15
	19	DVd-T	No	58
Baz, 2005 (438)	26	DVd-T	Late ASA	15
	58	DVd-T	ASA	19
Rajkumar 2005 (439)	34	Len-Dex	ASA	0
Palumbo, 2006 (436)	65	MPT	No	17
	64	MPT	Enox	3.1
Palumbo 2006 (443)	50	MPR	ASA	2

Rajkumar 2006 (441)	102	Thal-Dex	No	17
	102	Dex	No	3
Rajkumar 2006 (440)	132	Len-Dex	No	18
	134	Len-LD-Dex	No	4
Knight 2006 (442)	87	Len-Dex +Epo	No	23
	83	Len-Dex	No	5
	67	Dex +Epo	No	7
	103	Dex	No	1

Dex, dexamethasone; Enox, enoxoparin 40 mg/d; Epo, erythropoietin; LD, low dose, TE, thromboembolism; Thal, thalidomide; TT2, total therapy 2, a complex anthracylcine containing multiagent chemotherapy regimen.

Combination Chemotherapy with Doxorubicin and Dose-Intensive Corticosteroids for Induction

The next level of combination chemotherapy includes programs that contain anthracyclines and high-dose corticosteroids. VAD-like regimens are commonly used as induction therapy before stem cell collection and transplantation. These regimens include VAP (247), VAD (391), VAMP (vincristine/doxorubicin/methylprednisolone) (260), and C-VAMP (cyclophosphamide/vincristine/doxorubicin /methylprednisolone) (260), all of which had been tried with salutary effect in relapsed disease. Subsequently, several of these regimens were applied in previously untreated patients, and response rates were 50 to 84% (392,393,394,395,396,397,398,399,400,401). The complete response rate of C-VAMP was higher than that of VAMP alone, but survival was not different (395). Several other variations have been reported in which alternative anthracyclines or corticosteroids were used (367). Median survival for patients treated initially with VAD is about 36 months (402). The response rate of single-agent high-dose dexamethasone is about 43% (257), which is only 15% lower than for VAD. This has prompted myeloma experts to use single-agent dexamethasone in lieu of VAD for induction in those patients destined for stem cell collection. Oral, noncontinuous infusional therapy has the advantage of avoidance of immediate placement of a long-term central venous catheter (257). This strategy has been

used successfully, resulting in adequate collections of peripheral blood stem cells without any apparent adverse effects on complete remission rates or progression-free survival in several single-arm studies (403,404). With the advent of other oral therapies, single-agent dexamethasone has been losing favor as induction.

In another attempt to avoid the continuous infusion required to administer VAD, several investigators have explored the use of the pegylated liposomal doxorubicin. The combination of vincristine, pegylated liposomal doxorubicin, and dexamethasone (DVD) has been studied. Response rates from single institutions suggested that DVD was more convenient and less toxic than VAD (405). Two randomized trials comparing DVD to VAD—using either standard high-dose dexamethasone (406) or attenuated doses of dexamethasone (407)—have been completed. Results were comparable between arms with regard to response rates, 42% in the attenuated-dexamethasone trial (407) and 61% in the standard-dose dexamethasone trial (406). There was more alopecia in the non–liposomal doxorubicin arms and more palmar-plantar erythrodysesthesia in the liposomal doxorubicin arms.

In a randomized trial of 151 patients comparing the NOP regimen (mitoxantrone, vincristine, and high-dose prednisone) to melphalan and prednisone, response rates were equivalent (~60%), but overall survival was inferior in the NOP arm (14 vs. 31 months, $p = .02$) (367). Response rates of 80% have also been achieved using the CAD (cyclophosphamide/doxorubicin/dexamethasone) regimen (408). The addition of etoposide to C-VAD appears to contribute only toxicity (409).

Combination Chemotherapy with Interferon for Induction

Interferon-α (INF) and dexamethasone have been combined as an induction regimen in patients with newly diagnosed myeloma and a low tumor mass. A retrospective comparison showed that the response rate of this regimen (57%) was similar to the response rate (48%) previously observed with dexamethasone alone (410). A recent randomized trial comparing MP, melphalan/dexamethasone, dexamethasone, and dexamethasone/IFN did not demonstrate any added benefit by incorporating IFN into the treatment regimen (263). Ahre et al. (411) randomized 55 patients to melphalan and prednisone

or interferon (3 to 6 MU daily); response rates in the melphalan and prednisone arm were significantly higher than in the interferon arm (44 vs. 14%, $p < .001$).

Interferon has been combined with melphalan and prednisone (412,413,414,415,416,417,418,419,420); VMCP (414,421,422,423); VMCP/VBAP (424), prednisone, cyclophosphamide, doxorubicin (Adriamycin), and carmustine (BCNU) (PCAB) (425,426); VAD (427); VBMCP (428); VBAP (429); and cyclophosphamide (430) as part of an induction regimen. Results have been mixed. Two meta-analyses have been performed in an attempt to reconcile these conflicting results (431,432). The first, reported in 2000 by Ludwig and Fritz (431), used published data and included 17 induction trials (412,413,414,415,416,417,418,419,420,422,423,424,425,426,427,429,430) with 2,333 evaluable patients; the second, reported by The Myeloma Trialists' Collaborative Group in 2001 (432), used primary data from 12 induction trials (412,413,414,415,416,417,418,419,420,422,424,425,426,428,429,430,433) involving 2,469 patients. Overall, the results were similar. In the first meta-analysis, the benefits

attributable to the addition of interferon to the induction regimen included a 6.6% higher response rate ($p < .002$) and a 4.8- and 3.1-month prolongation of relapse-free ($p < .01$) and overall survival ($p < .01$), respectively (431). In the second meta-analysis, patients receiving interferon had a slightly better response rate (57.5 vs. 53.1%, $p = .01$) and progression-free survival (30 vs. 25% at 3 years, $p < .0003$), with a superior median time to progression of about 6 months. The survival advantage of 2 months, however, was not significant ($p = .1$) (432). Figure 99.9 demonstrates progression-free survival and overall survival in patients receiving IFN as either induction or maintenance versus those who received none (432).

These meta-analyses suggest that incorporation of interferon into induction provides a modest prolongation of response and possibly of survival. The question is whether these significant differences are clinically relevant. Wisloff et al. (434) evaluated the quality of life of 583 patients randomized to either melphalan and prednisone or melphalan, prednisone, and interferon as induction. During the first year of treatment with interferon, the patients reported significantly more fever, chills, dry skin, fatigue, pain, nausea/vomiting, and appetite loss than the control patients. After the first year, however, the only symptom reported more often was dizziness. Although patients receiving interferon had a 5- to 6-month prolongation of the response and plateau phase, there was no late quality-of-life benefit observed to compensate for the early impairment. The authors questioned the clinical value of the plateau-phase prolongation and reported that only 60% of patients continued to receive interferon after 24 months, suggesting that their data might underestimate the potential toxicity of the drug. A cost-effectiveness estimation for induction was also performed. The authors concluded that interferon administration and monitoring expenses amounted to $US 41,319.28 to save a year of life of myeloma patients, assuming a dosage of 12.1 MU/week (431).

A study on patient preference also deserves mention. Ludwig et al. (435) surveyed cancer patients about “acceptable” toxicity of an unidentified drug, which had the toxicity profile of interferon, relative to its hypothetical benefit. About 50% of surveyed patients accepted the toxicity of an unidentified drug if remission or survival or both would be improved by at least 6 months. Of those patients who rejected the 6-month hypothetical benefit, 25 to 50% were willing to accept the toxicities if the benefits were ≥12 months.

Novel Therapies for Induction (Tables 99.7 **and** 99.8)

Complications Specific to Novel Therapies

These new drugs can cause the complications seen with other agents, such as fatigue, myelosuppression, fevers, infections, and gastrointestinal symptoms; however, there are several side effects particular to these new agents—the most important of which are thrombosis and peripheral neuropathy.

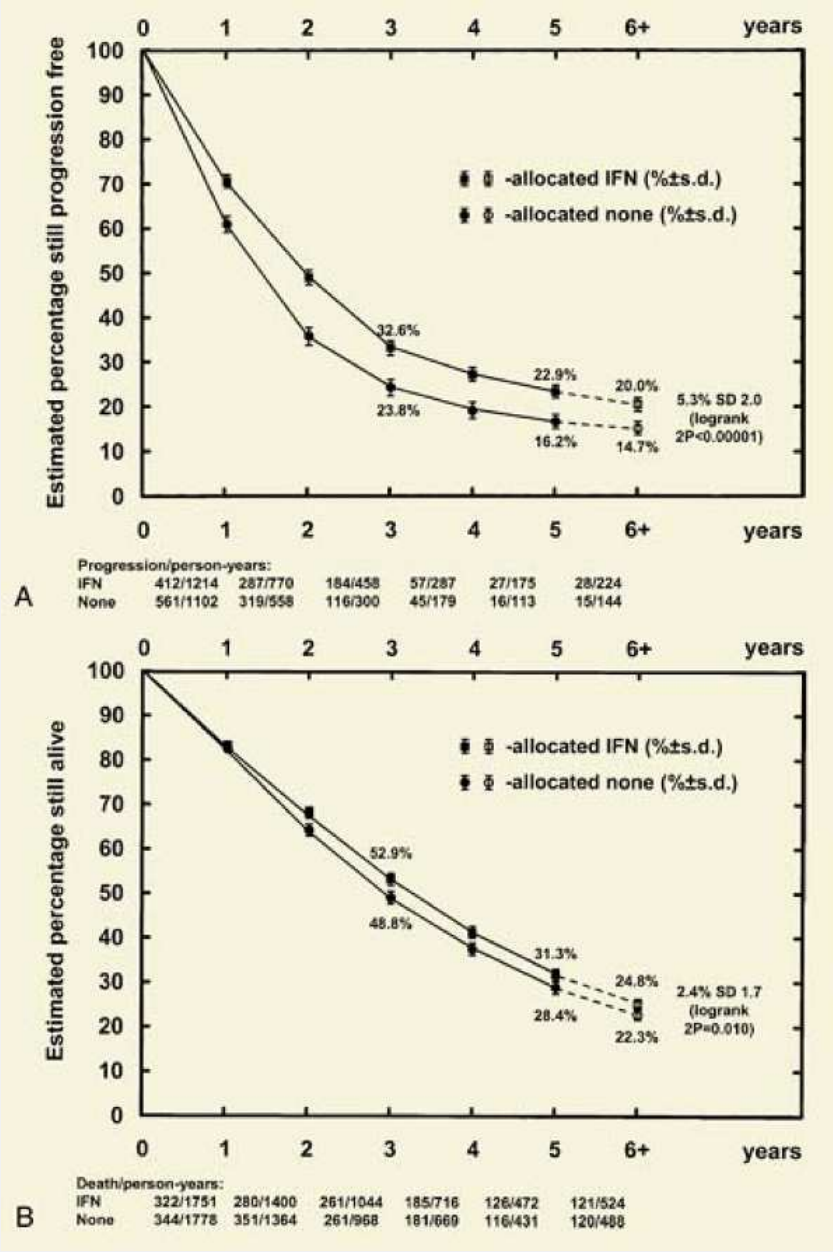

Figure 99.9. Interferon (IFN) chemotherapy as induction or maintenance therapy influences progression-free and overall survival curves from the meta-analysis by the Myeloma Trialists' Collaborative Group. Results from 24 randomized trials and 4,012 patients. Interferon curves include patients who received interferon as part of induction or of maintenance program. **A:** Progression-free survival after 23 months with interferon and after 17 months without. **B:** Overall median survival after 40 months with interferon and after 36 months without. (From Interferon as therapy for multiple myeloma: an individual patient data overview of 24 randomized trials and 4012 patients. Br J Haematol 2001;113:1020–1034. By permission of Blackwell Science.)

Thrombosis

Thrombosis is an important complication in patients undergoing treatment with IMiDs. As single agents, there does not appear to be any heightened risk; however, concomitant

chemotherapy (436)—especially anthracyclines (437,438)—high-dose corticosteroids (439,440,441), and erythropoietin (442) appear to increase the risk of thrombosis to as high as 58% (Table 99.9). Prophylactic low-molecular-weight heparin (e.g., enoxaparin 40 mg daily) (436,437)or full anticoagulation with Coumadin abrogates that risk. Low-dose Coumadin is not protective. Daily aspirin also appears to be protective (441,442,443).

Peripheral Neuropathy

Thalidomide and bortezomib are known to cause peripheral neuropathy in more than a third of patients. Patients treated with lenalidomide are also at risk for neuropathy, but because most study patients receiving lenalidomide have been previously treated, the raw rates are unknown. The neuropathy associated with thalidomide is an irreversible small-fiber peripheral neuropathy that appears to be both time- and dose-dependent.

The peripheral neuropathy associated with bortezomib has been better characterized (444). It comes in all forms: sensory, motor, and painful. In a recent review of 256 patients treated in

two Phase II studies, >80% of patients had baseline peripheral neuropathy. Treatment-emergent neuropathy was reported in 35% of patients. Grade 1 or 2, 3, and 4 neuropathy occurred in 22, 13, and 0.4% of patients, respectively. Grade 3 neuropathy was more likely to occur in patients with a baseline neuropathy. Seventy-one percent of patients with neuropathy ≥grade 3 and/or requiring discontinuation experienced resolution to baseline or improvement.

Thalidomide Combinations for Induction Therapy

As a single agent, response rates occur in about one third of patients (306,307,308). The combination of thalidomide and dexamethasone results in response rates of 63 to 72% (308,445,446). The thalidomide/dexamethasone combination has been compared to dexamethasone alone in two separate randomized trials (446). In the smaller of the two trials (n = 207), the overall response rate of thalidomide/dexamethasone was significantly higher than that of dexamethasone alone (63 vs. 41%); however, toxicity was greater using the combination, with grade 4–5 toxicity being 45 vs. 21%, $p < .001$ (441). In the second, larger trial (n = 470 patients), time to progression was significantly better in the combination arm (17.4 months, 95% CI: 8.1 months—not reached vs. 6.4 months, 95% CI: 5.6 to 7.4 months). Grade 3–4 adverse events were higher using the combination therapy: deep vein thrombosis (DVT)/pulmonary embolism (PE) 15.4 versus 4.3%; cerebral ischemia 3.4 versus 1.3%; myocardial infarction 4.7 versus 1.3%, peripheral neuropathy 3.8 versus 0.4% (446). This combination is commonly used as induction in the months before stem cell collection because of its high response rate and ease of administration, using only oral medications. The risk of thrombosis and other side effects make the combination less convenient than originally thought. Limited use of thalidomide pre–stem cell mobilization does not impair stem cell collection or engraftment, although preliminary data suggest that there may be a delay in platelet engraftment with longer continuous use (447).

Goldschmidt et al. (448) have reported preliminary results from the induction portion of the HOVON 50/GMMG-HD3-Trial, which is a Phase III study of the effect of thalidomide followed by transplant in myeloma patients up to 65 years of age. Patients were randomized to either

3 cycles of TAD (thalidomide, 200 mg for HOVON/400 mg for GMMG; Adriamycin 9 mg/m^2, days 1 to 4; dexamethasone 40 mg, days 1 to 4, 9 to 12, 17 to 21) or VAD. The first group of 406 patients (of 1,050 included) are evaluable for the comparison of VAD versus TAD. A trend for a higher toxicity was observed in the TAD arm compared with the VAD arm (dropouts: 15 vs. 8%, $p = .10$), though the overall (80 vs. 63%, $p < .001$) and complete response (7 vs. 3%, $p = .1$) rates were higher with TAD. However, preliminarily there is no difference in overall or complete response after hematopoietic stem cell transplantation (HSCT). Cavo et al. (449) performed case matching to compare patients treated with thalidomide/dexamethasone (TD) or VAD. Like the HOVON/GMMG trial, higher induction response rates were seen (76 vs. 52%). Toxicity profiles were different, with more myelosuppression in the VAD-treated patients, but DVT was more common in the TD patients. The number of patients who died and who did not make it to transplant were also comparable. Similar numbers of stem cells were collected in the TD arm compared to the VAD arm, 7.85 versus 10.5 $\times 10^6$ CD34/kg ($p = .4$). This comparison is confounded by the facts that this was only a case-match comparison (rather than a randomization) and that the TD group received thalidomide not only during induction but also during transplantation and posttransplantation.

Though thalidomide/dexamethasone results in higher response rates compared to melphalan and prednisone (450), it cannot be recommended as induction for elderly patients who are not destined for peripheral blood stem cell collection because of the high toxicity rates. Ludwig et al. randomized 350 elderly patients to either thalidomide/dexamethasone or melphalan and prednisone. Preliminary data demonstrate a higher response rate using TD (52 vs. 35%, $p < .05$), but higher rates of neuropathy (25 vs. 8%), psychological toxicity (20 vs. 8%), skin toxicity (12 vs. 3%), and thrombotic events (8 vs. 3%). The only toxicity more commonly seen in the MP arm was myelosuppression.

In contrast, combining melphalan, prednisone, and thalidomide is quite promising in elderly patients who are not HSCT candidates, and, based on the results of two randomized trials (436,451), many would consider this program to be the new standard. Palumbo et al. randomized patients to either standard-dose oral melphalan and prednisone (MP) for 6 months or to melphalan and prednisone for 6 months with concurrent thalidomide (MPT) that is continued indefinitely (436). Overall response rates were significantly higher with the MPT than the MP (76.0 vs. 47.6%), as were the near-complete or complete response rates (27.9 vs. 7.2%) and the 2-year event-free survival rates (54 vs. 27%, $p = .0006$). There was a trend toward improved 3-year overall survival in favor of MPT (80 vs. 64%). Two criticisms of this trial are that 6 months of MP is short of standard by about 6 months and that this trial addresses a maintenance question as much as an induction question.

The IFM 99-06 trial bolsters the results of the Palumbo trial, though it has not yet been published in printed form (451). In the IFM 99-06 study, 436 patients were randomized to 1 year of either MPT or MP or to two sequential mini-autologous peripheral blood stem cell transplants (MEL100). Higher response rates and longer progression-free survival (PFS) were seen for the MPT compared to either the MP or MEL100 groups, with respective PFS times of 29.5, 17.2, and 19.0 months. With a median follow-up of 32 months, there is a significant survival advantage for the patients on the MPT arm, with respective overall survival times not reached at 56, 30.3, and 38.6 months (451). So far, no data have been

provided regarding the percent of patients in the nonthalidomide arm who received thalidomide regimens as salvage therapy.

Though both MPT-versus-MP trials demonstrated higher response and survival endpoints for MPT, they also had a consistently higher toxicity profile for the three-drug combination compared to the two-drug combination. In the Palumbo study (436), the respective percentage of patients having grade 3–4 adverse events were as follows: at least 1 event, 48 versus 25% (p = .0002); thrombosis/embolism, 12 versus 2%; peripheral neuropathy, 10 versus 1%; infections, 10 versus 2%; and gastrointestinal events, 6 versus 1%. There was no significant difference in the toxic death rate between the two arms (8 vs. 5%). The authors point out that the first 65 patients received no DVT prophylaxis, while the final 64 received enoxaparin; 13 thromboembolic events occurred in the first group, but only 2 occurred in second group, and that was after discontinuing the enoxaparin.

Dimopoulos et al. have explored a different administration schedule of thalidomide along with melphalan. They treated 50 patients 75 years or older with melphalan, dexamethasone, and thalidomide. A cycle was 5 weeks in duration, and the respective doses and schedules of the three drugs were melphalan 8 mg/m^2 days 1 to 4; dexamethasone 12 mg/m^2 days 1 to 4 and 14 to 18; and thalidomide 300 mg days 1 to 4 and 14 to 18. A planned course of treatment was three cycles as above, but if patients responded, the next nine cycles were administered without the day 14–18 thalidomide and dexamethasone. Using this program, 62% of patients had a partial response to therapy and 10% had a complete response. Median time to progression was 21.2 months, deep venous thrombosis and peripheral neuropathy each occurred in 9% of patients, and overall survival was 25 months.

Palumbo et al. have treated 50 elderly patients who were not deemed candidates for HSCT with melphalan, prednisone, and lenalidomide (443). Patients received aspirin and ciprofloxacin as prophylaxis. Preliminary reports demonstrated an overall response rate of 70%, including a 10% complete response rate. Thirty-five percent of patients had grade 3–4 adverse events, including one thromboembolic event and two dermatologic events. The majority of adverse events consisted of myelosuppression.

Zervas et al. (452) treated 39 patients with thalidomide, vincristine, pegylated liposomal doxorubicin, and dexamethasone and assessed response after four cycles. Responses were seen in 74%, including 10% complete response. Grade 3–4 toxicities included neutropenia (15%), thrombosis (10%), constipation (10%), rash (5%), and peripheral neuropathy (5%). Two patients suffered early deaths secondary to infection. Forty-seven percent of patients went on to stem cell collection and transplantation.

Offidani treated 50 newly diagnosed multiple myeloma patients >65 years old with thalidomide (100 mg/day), dexamethasone (40 mg on days 1 to 4 and 9 to 12), and pegylated liposomal doxorubicin (40 mg/m^2 on day 1) every 28 days for a total of five to six cycles. The overall response rate was 88% (CR 34%, VGPR/nCR [near complete response] 24%, and PR 30%). Time to progression, event-free survival, and overall survival projected at 3 years were 60, 57, and 74%, respectively. Grade 3–4 infections and thromboembolic accidents were observed in 22 and 14% of patients, respectively (453).

Hussein et al. (454) treated 55 previously untreated patients with DVd-T (pegylated liposomal doxorubicin, vincristine, decreased-frequency dexamethasone, and thalidomide) for a maximum of eight cycles, followed by maintenance with maximum tolerated doses of thalidomide plus alternate-day oral prednisone. Though response rates were high (overall 93%, with CR of 36%), there was substantial toxicity associated with the program. Grade 3–4 toxicities included thromboembolic events in 25%, peripheral neuropathy in 22%, neutropenia in 14%, pneumonia in 12%, palmar plantar erythrodysesthesia in 8%, and thrombocytopenia in 5%. The median PFS was 28.2 months, and the overall survival (OS) was not reached at 50 months. Note that although the patients of Offidani et al. (453) were older and received lower doses of thalidomide and no vincristine, similar response rates and less toxicity were seen.

Hassoun et al. (455) treated 45 newly diagnosed myeloma patients with doxorubicin and dexamethasone for 2 or 3 months, followed by thalidomide and dexamethasone for 2 months (AD-TD regimen), with prophylactic antibiotics and daily aspirin (81 mg/day). Thirty-eight responded to therapy (84.4%), with seven complete responses (15.5%), nine near-complete responses (20.0%), and 22 partial responses (48.9%). Patients tolerated the treatment well, although five patients developed thromboembolic complications (11%).

Baz et al. (456) treated 16 patients with high-risk, newly diagnosed myeloma or relapsed/refractory disease with arsenic trioxide, ascorbic acid, thalidomide, and dexamethasone. Four patients achieved a partial response, and the PFS was 9.4 months. Nineteen percent of patients had thromboembolic events.

Bortezomib as Induction Therapy

Thirty-eight to 40% of newly diagnosed myeloma patients respond to single-agent bortezomib (324,457). The addition of dexamethasone results in an overall response rate of 67 to 88% (324,458). A number of combinations have been explored for induction.

Mateos et al. (459) reported on their Phase I/II results with VMP, bortezomib, melphalan, and prednisone, in 60 elderly patients not deemed to be HSCT candidates. Patients were treated with four 6-week cycles followed by five 5-week cycles. The final dose schedule was bortezomib (1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, and 32), melphalan (9 mg/m^2 on days 1 to 4), and prednisone (60 mg/m^2 daily on days 1 to 4). The authors excluded the three early deaths and four other early withdrawals from their response analysis and report the following response rates: overall response rate 88% (32% CR, 11% VGPR, and 45% PR). The 16-month event-free survival and overall survival were 83 and 90%, respectively. The most common adverse events were myelosuppression (>90%), infection (75%), asthenia (63%), gastrointestinal toxicity (>55%), and peripheral neuropathy (55%). The most common grade 3–4 toxicities were thrombocytopenia (51%)and neutropenia (43%), peripheral neuropathy (17%), and diarrhea (16%). Patients who were >75 years of age were more prone to the more serious nonhematologic side effects (459).

Oakervee et al. (460) have treated 21 previously untreated patients with PAD (bortezomib, doxorubicin, and dexamethasone). Patients received four 21-day cycles of bortezomib 1.3 mg/m^2 on days 1,4, 8, and 11; dexamethasone 40 mg on days 1 to 4 and 15 to 18; and doxorubicin at escalating doses of 4.5 or 9 mg/m^2/day as a continuous intravenous infusion over 4 days. Ninety-five percent of patients achieved at least a partial response, including a CR in 24% of patients. Fifteen grade 3–4 adverse events occurred in 12 patients, with the most common serious adverse events (SAE) including infections (n = 7) and shingles (n = 3).

Grade 3–4 peripheral neuropathy, postural hypotension, nausea and vomiting, atrial fibrillation, and hyperglycemia each occurred in one patient. All but one patient proceeded to stem cell collection and transplantation. Although no cardiac toxicity was observed, cardiac biomarker screening for subtle toxicities were not performed.

Popat et al. (461) treated 19 patients with previously untreated myeloma with four cycles of LD-PAD (bortezomib 1 mg/m^2 on days 1, 4, 8, and 11; doxorubicin 9 mg/m^2 by intravenous infusion on days 1–4, and dexamethasone 40 mg on days 1 to 4, 9 to 12, and 17 to 20 for cycle 1—subsequent courses only days 1 to 4). This program differs from that of Oakervee in that the dose of bortezomib was reduced by about 25%. Eighteen patients were evaluable, with an overall response rate of 89% (2 CR. 1 nCR, 4 VGPR, 9 PR). All patients successfully mobilized stem cells. Toxicity information was not provided.

Wang et al. (462) treated 36 previously untreated patients with VTD (thalidomide 50 to 200 mg/day; bortezomib 1.3 to 1.9 mg/m^2 days 1, 4, 8, and 11; and dexamethasone 20 mg on days 1 to 4, 9 to 12, and 17 to 20). All patients received full anticoagulation. Overall response rate was 92%, including a 19% CR rate. There did not appear to be any value added with bortezomib doses >1.3 mg/m^2.

In a Phase I/II trial, Badros et al. (463) combined escalating doses of bortezomib with the DT-PACE regimen (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide). Four patients had no prior therapy, and seven had one prior cycle including DT (*n* = 4) and DT-PACE (*n* = 3). Stem cells were collected at a median of 13 days (range 12 to 15 days) into the cycle, yielding a median of 20.6 × 10^6 CD 34^+ stem cells/kg (range 7.8 to 33.3 × 10^6). All 11 patients responded, with two CR/nCRs. Grade 3–4 hematologic toxicity, including neutropenic fever requiring hospitalization, was common. There were three DVTs (despite enoxaparin), significant episodes of hypotension, including syncope in two, and two patients with grade 3 diarrhea.

Lenalidomide as Induction Therapy

In previously untreated patients with active myeloma, the combination of lenalidomide and dexamethasone with and without clarithromycin yields overall response rates of 91 to 95%, with complete response/very good response rates of 32 to 38% (439,464). Rajkumar et al. (439) treated 34 patients with lenalidomide 25 mg orally on days 1 to 21 and dexamethasone 40 mg on days 1 to 4, 9 to 12, and 17 to 20, both repeated every 28 days. Aspirin was given as DVT prophylaxis. The overall response rate was 91%, with 6% achieving a complete response and 32% a very good partial response. Grade 3–4 neutropenia occurred in 12% of patients. Forty-seven percent of patients experienced grade 3 or higher nonhematologic toxicity, most commonly fatigue (15%). Six percent each had grade 3–4 muscle weakness, anxiety, pneumonitis, or rash.

Niesvizky et al. (465) treated 40 patients with clarithromycin, lenalidomide, and dexamethasone. The rationale for the clarithromycin use is that it alters the hepatic metabolism of both drugs, resulting in higher effective doses. The lenalidomide schedule was as above, but dexamethasone was administered only once weekly. Clarithromycin was given in doses of 500 mg twice daily. Aspirin was given as DVT prophylaxis. Preliminary results include a 95% response rate, including 25% CR and 18% VGPR. Forty-eight

percent of patients developed grade 3 or higher adverse events, including 15% with

thromboembolism, two of which were fatal. Four of the seven thromboembolisms occurred in patients who had discontinued aspirin.
Risk factors for thromboembolism in patients receiving IMiDs include dexamethasone intensity, erythropoietin, and other concomitant chemotherapy (440,442)

Hematopoietic Stem Cell Transplantation

Autologous Transplant

To overcome resistance of the myeloma cells to conventional-dose chemotherapy, McElwain and Powles (237) pioneered the use of high-dose melphalan to treat multiple myeloma and plasma cell leukemia. The treatment was complicated by prolonged myelosuppression. Barlogie et al. (466) subsequently used a regimen combining high-dose melphalan with total-body irradiation supported by autologous bone marrow transplantation in multiple myeloma patients refractory to VAD. Ten years later, Attal et al. published the first prospective randomized controlled trial demonstrating an improved overall survival for patients undergoing high-dose therapy with autologous stem cell support compared to conventional chemotherapy (245).
Although high-dose therapy followed by autologous stem cell transplantation (ASCT) is not curative, it improves event-free and overall survival (Table 99.10) (245,467,468) Three of the four “negative” studies (469,470,471) are largely “early” versus “delayed” transplant trials, and the fourth “negative” study excluded from randomization those patients who did not respond to induction therapy (472). Response rates with ASCT are 75% to 90%, and complete response rates are 20 to 40% (245,467,468,469,470,471,472). Antedating these randomized controlled trials, historical comparisons also showed conflicting results. For example, one historical comparison study from Spain suggested that survival in good-risk patients receiving only conventional chemotherapy was similar to that reported in selected series of patients treated with ASCT (473). In contrast, the Nordic Myeloma Study Group (474) prospectively evaluated the effect of ASCT on survival in myeloma patients younger than age 60 years and compared the survival rates of transplanted patients with those of historic controls derived from previous Nordic population-based studies of conventional-dose chemotherapy. They found that survival was prolonged with the high-dose therapy—44 months for conventional chemotherapy versus >60 months for patients treated with ASCT.

Table 99.10 Conventional Chemotherpay (CCT) versus Single Autologous Hematopoietic Stem Cell Transplantation (ASCT); Randomized Trials

	CR/VGPR (%)			ORR (%)		PFS (mo)		OS (mo)		SCT (%)	
	N	CCT	ASCT	CCT	ASCT	CCT	ASCT	CCT	ASCT	CCT	ASCT
IFM90 (245, 475)	200	13	38a	57	81a	18	28a	44	57a	9	74
MRC7 (467)	401	8	44a	46	86a	19.6	31.6a	42	54a	15	75
MAG91 (469)	190	4	6	56	59	18.7	25.3a	47.6	47.8	22	75
MAG90 (470)	185	57	20	58	78	13	39	64	65	78	98
PEETHMA (472)	164	11	30a	83	82	33	42	61	66	18	90
S9321 (471)	516	17	15	90	93	7y, 14%	7y, 17%	7y, 38%	7y, 38%	34	82
MMSGb (468)	194	6	25a	66	72	16	28a	42	58+a	39	92
HOVON-24c (477)	303	13	28a	86	90	23	24a	50	55	—	—

CR/VGPR, complete response or very good partial response; ORR, any response

greater than or equal to a partial response; PFS, progression-free survival; OS, overall survival; SCT, patients known to receive an autologous hematopoietic stem cell transplant.
[a]Significant.
[b]Transplant arm is two low-dose (melphalan 100 mg/m^2) autologous stem cell transplants.
[c]Often included in "double-transplant" tables because both arms received melphalan 70 mg/m^2 × 2 without stem cell support as induction therapy.

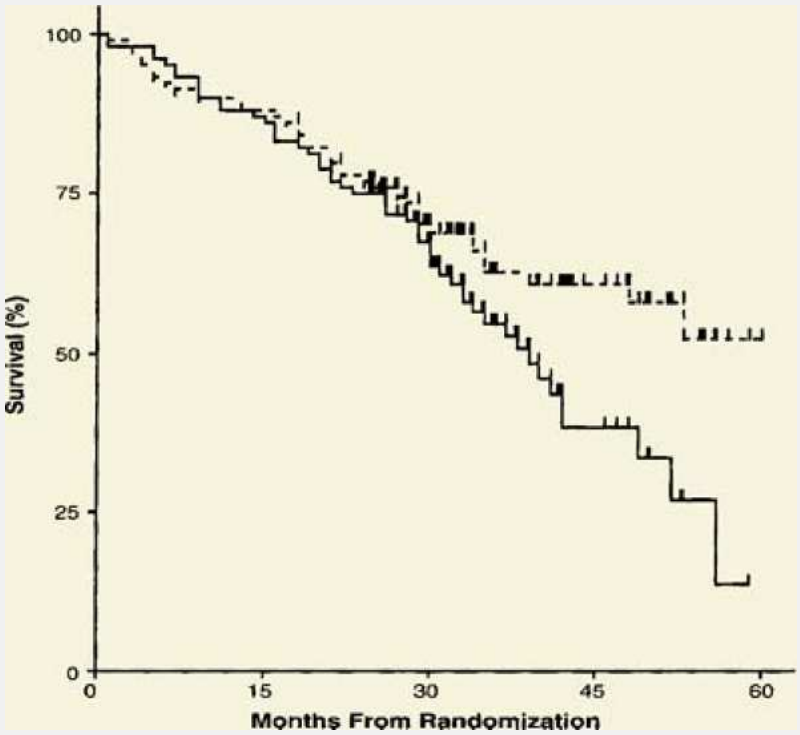

Figure 99.10. Conventional chemotherapy versus autologous hematopoietic stem cell transplantation, IFM 90 Trial. (With permission, from Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med 1996;335:91–97. Copyright © 1996 Massachusetts Medical Society. All rights reserved.)

As shown in Table 99.10, the Intergroupe Français du Myélome (245) published the first randomized trial comparing high-dose chemotherapy followed by autologous bone marrow transplantation with conventional chemotherapy (Fig. 99.10). Two hundred patients with previously untreated multiple myeloma were randomized to receive ASCT or combination chemotherapy (CCT). The 5-year event-free survival (28 vs. 10%) and overall survival rates (52 vs. 12%) were higher in the transplantation group. An updated analysis with a median

follow-up of 7 years confirmed that high-dose chemotherapy improves event-free survival (median, 28 vs. 18 months) as well as overall survival (median, 57 vs. 44 months) (475). The Medical Research Council VII trial was the second published study addressing the question of CCT versus ASCT (467). This trial included 401 randomized patients. The trial found that the complete response rates (8 vs. 44%), the median event-free survival (19 vs. 31 months), and the overall survival (42 vs. 54 months)

all significantly favored the ASCT arm, even though only 75% of the patients assigned to the transplant group actually received it and 15% of patients in CCT arm received salvage ASCT.

Three trials addressed the “early” versus “delayed” transplant strategy (469,470,471). The first was the MAG90 trial, in which Fermand et al. demonstrated that among the 185 patients randomized to either early or late ASCT, the overall survival in both groups was 64 months, and the percentages of the respective groups actually receiving ASCT were 98 and 78%, respectively (470). This trial was important because it gave patients and physicians license to opt for transplants either up-front or on a delayed basis. Most chose to transplant early, because the time without systemic therapy (TWiST) was longer in the early than the delayed ASCT group, potentially providing better quality of life for the early-transplant group. The MAG91 trial (469) randomized 190 patients under the age of 56 years to CCT or HSCT, but this trial also examined the outcomes of early versus late transplants. Only patients 55 to 65 years of age were included. Event-free survival (19 vs. 25 months), but not overall survival (47.6 vs. 47.8 months), was better in the ASCT arm. Despite the 120-month follow up, the overall survival statistics are confounded by the fact that only 75% of the “ASCT” arm received ASCT, and that 22% of the “CCT” arm received an HSCT. The intergroup trial (S9321) randomized 510 patients age 70 or younger to CCT or HSCT (471). With a 76-month follow-up, 7-year overall survival was no different between the arms; however only 82% of the “ASCT” group received an ASCT and 34% of the “CCT” group received an ASCT. Remarkably, 7 years after a myeloma diagnosis, 38% of patients were still alive.

The Spanish Cooperative Group prospective trial was dissimilar from the other randomized trials in that only those patients who responded to therapy were randomized. At enrollment, 216 patients were treated initially with four cycles of VBMCP and VBAD (vincristine, carmustine, doxorubicin, and dexamethasone) (472), and only 164 were randomized to receive eight additional courses of chemotherapy or intensification with high-dose therapy and stem cell transplantation. There was no difference between the groups with respect to complete response rates, overall response rates, progression-free survival, or overall survival. These data differ from those of other transplant trials. It is possible that patients with an excellent response to the induction therapy given do not require consolidation with ASCT; or that with longer follow-up, survival differences will emerge.

The MMSG97 trial was unique in that it randomized patients aged 50 to 70 years of age to either melphalan and prednisone or two half-dose melphalan transplants (468). Patients receiving melphalan and prednisone only had significantly worse outcomes. A significant difference between two low-dose ASCT and MP was not seen in the IFM 999-06 trial (476).

The Hovon-24 trial is commonly grouped in the “single versus double” transplant category, though it is actually an “intensified chemotherapy without transplant” versus “intensified chemotherapy followed by high-dose chemotherapy and a single ASCT” (477). The most recent analysis of this trial demonstrates a significantly higher complete response rate and event-free survival in the high-dose treatment arm. The differences in event-free survival, progression-free survival, and total time to progression were not seen until the 4-year follow up had been reached. The authors report that the lack of difference in overall survival is likely due to a “high proportion” of patients from the control arm receiving HSCT at first relapse.

Table 99.11 Single versus Double Hematopoietic Stem Cell Transplantation, Randomized Trials

Study	N	FU (mo)	Event-Free Survival (mo)			Overall Survival (%)		
			Single	Double	P	Single	Double	P
IFM, 94 (481)	403	75	25	30	.03	48	58	.01
Bologna, 96 (482)	228	~48	21	31	.001	44% at 6 y	63% at 6 y	NS
MAG, 95 (1093)	193	27	41 events	43 events	NS	27 deaths	22 deaths	NS

Single versus Double Transplantation

As the evidence was mounting that one course of dose-intensified chemotherapy with ASCT was superior to conventional chemotherapy, investigators began experimenting with two consecutive ASCTs. The concept of double or tandem transplants was promulgated by Dr. Barlogie and colleagues at the University of Arkansas (331,478,479,480). These investigators reported high complete response rates and survival (331,478,479,480). In the first report of “total therapy 1,” which included 231 patients with newly diagnosed myeloma, the overall survival with this approach was 68 months (331).

There have been preliminary data from three randomized trials that indicate increased response rates with tandem transplantation, but only two that demonstrate improvement in event-free and overall survival (481,482,483) (Table 99.11). In the largest and most mature study, that is, the IFM 94 study, there was no difference in event-free or overall survival between double and single autologous stem cell transplants after 2 years of follow-up (484); however, by 4 years and beyond, a survival benefit was detected (481). Though the response rate was not significantly different between the two groups (complete response and very good partial response 42% in the single-transplant arm vs. 50% in the double-transplant group, $p = .15$), both event-free survival (25 vs. 30 months) and overall survival (48 vs. 58 months) were improved in the double-transplant arm. The respective 7-year

overall (21 vs. 42%) and event-free survival rates (10 vs. 20%) also significantly favored the double-transplant group (Fig. 99.11). In this trial, four factors were associated with a longer survival: low β_2-microglobulin levels at diagnosis ($p < .01$), young age ($p < .05$), low lactate dehydrogenase (LDH) at diagnosis ($p < .01$), and the treatment arm to which the patient was assigned ($p < .05$). When the authors did an unplanned subgroup analysis, they found that patients who benefited most from the tandem transplant were those who did not achieve a very good partial response or better after their first transplant.

Cavo et al. (482) have made similar observations based on preliminary data, including the benefit of a second transplant being limited to those patients who do not achieve a very good partial response or better after their first transplant. Most patients under the age of 65 years should have enough stem cells collected for at least two transplants.

Timing of Transplantation

As long as stem cells are collected early, in the context of conventional chemotherapy versus as single autologous stem cell transplant, timing of transplant—either as upfront consolidation or salvage at relapse—does not influence overall survival (469,470,471).

Because the time without chemotherapy is longer in patients transplanted early in their course, many opt for early transplant. The situation is less clear when one introduces the concept of double transplants, as the relevant data are not yet available. Many physicians are acting on the reasonable premise that timing of double transplants does not matter, but all three tandem transplant trials evaluated early, “back to back” transplants. There are emerging data—but no randomized trials—regarding the role a second transplant plays as “salvage” therapy after relapse from the first. All that can be concluded from these retrospective analyses is that a second salvage ASCT is a feasible option in some patients.

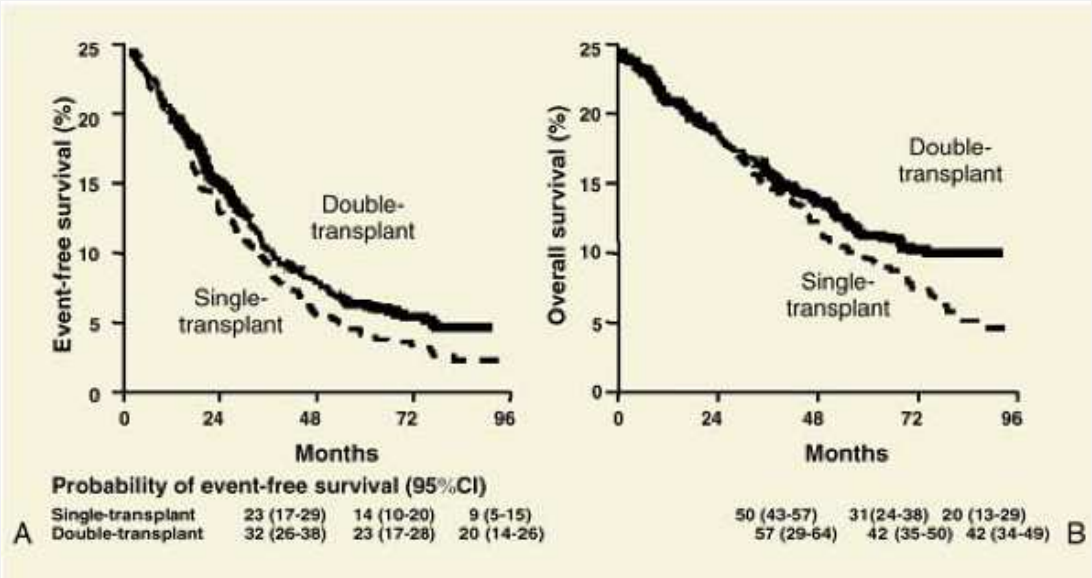

Figure 99.11. Single autologous versus double hematopoietic stem cell transplantation, IFM 94 trial. A: Event-free survival. **B:** Overall survival. (With permission, from Attal M,

Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 2003;349: 2495–2502.

The European Group for Blood and Marrow Transplantation Registry (EBMTR) analyzed "planned" and "unplanned" second transplants among 7,444 patients spanning 9 years. Though the survival was shorter after the second transplant in the group that had the "unplanned" and presumably delayed transplant, the overall survival of both groups from the time of the first transplant was similar: 60 months for the planned group and 51 months for the unplanned group (485).

Alvares et al. studied retrospectively the outcomes of 172 patients who relapsed after a single autologous ASCT (486). Eighty-three had a second ASCT at relapse, 7 died, and another 83 had alternative therapies. The median event-free survival was similar in the two groups at 1.3 years versus 0.9 years (p = .73), but there was a trend toward longer overall survival in the second transplant group (2.9 vs. 1.7 years, p = .07). The authors cautioned that the worse outcome in the latter group could potentially be accounted for by a poorer performance status in the group not receiving a second transplant. Most notable, however, was the difference in overall survival between those patients who had less than an 18-month relapse-free survival after their first transplant relative to those who had a relapse-free survival of 18 months or longer: The respective median overall survivals were <6 months in the former and nearly 3 years in the latter group (p < .00001).

Ellice et al. (487) analyzed the outcomes of 26 patients who had a second transplant upon relapse after a single transplant. From the date of relapse, the overall survival of patients undergoing second transplant was 46.9 months, whereas that of the patients receiving alternate salvage therapy was 28.3 months. The median overall survival and event-free survival calculated from the date of second ASCT were 38.1 and 14.8 months, respectively. Given the small numbers of patients, the difference between the two groups was not considered to be statistically significant.

Mehta et al. reported on 42 patients allografted for myeloma after not responding to or after having had progression following autologous stem cell transplantation (488). They compared those cases to 42 pair-matched controls that underwent salvage autologous stem cell transplantation. The 3-year event-free survival was similar for both groups (20 vs. 25%), but overall survival was significantly higher after autologous transplantation (29 vs. 54%). Although the 3-year probability of disease progression was lower after allogeneic transplantation (31 vs. 72%), the difference could be attributed to the high 1-year treatment-related mortality of 43% in the allogeneic group. Lee et al. (489) has shown that patients relapsing after two transplants may derive benefit from a third transplant as long as they have favorable prognostic factors.

Long-Term Survival in Myeloma Patients

High-dose chemotherapy with autologous stem cell transplantation has improved outcomes in patients with myeloma. Merely being eligible for transplant is itself a favorable prognostic factor. In one study, only 50% of patients who were of transplant-eligible age were actually transplanted. The reasons for not transplanting the other patients were poor medical condition (25%) and unspecified reasons (25%). Despite the caveat of selection,

unprecedented long-term survivals are being seen in populations of transplanted patients. Moreau et al. (490) reported a 10-year survival of 9% percent in patients with β_2-microglobulin of >3 mg/L, compared to 41% for patients with β_2-microglobulin of ≤3 mg/L. These same groups had median overall survivals of 31 versus 73 months. More than one third of the patients <55 years at diagnosis were alive at 10 years. In this retrospective analysis, the 10-year survival was 35% for patients who completed a second ASCT, compared to 20% for those who had only one.

Though long-term survival was the focus of the previous paper, 20 to 30% 8-year survivors have been described in other cohorts (471,491).

Transplantation for Primary Refractory Myeloma

In contrast to the experience with malignant lymphoma, stem cell transplantation appears to be effective for patients with primary resistant disease (492,493,494). Patients with multiple myeloma, in whom first-line therapy such as VAD fails, can be sensitive to high-dose chemotherapy with stem cell reconstitution. Alexanian et al. (492) reported a decrease of 75% in tumor burden in 56% of patients and a marked improvement in survival compared with matched historical controls. Kumar et al. (494) also looked at stem cell transplantation in primary refractory disease and found that though there was a lower complete response rate (20 vs. 35%) in the primary refractory patients, the 1-year progression-free survival was similar to that of patients with chemosensitive disease.

Hematopoietic Stem Cell Collection

Autologous peripheral blood stem cell transplantation has replaced autologous bone marrow transplantation because engraftment is

more rapid and there is less contamination with myeloma cells (495,496,497). Hematopoietic stem cells should be collected before the patient is exposed to alkylating agents (498,499), because prolonged melphalan exposure leads to an impaired harvest of peripheral blood stem cells when stem cells are mobilized with chemotherapy plus growth factors (500) or growth factors alone (501). Even after four to six cycles of VMCP/VBAP, which is a regimen containing low doses of melphalan, sufficient stem cells could not be collected for transplantation in ~10% of patients (245). In contrast, successful stem cell collection is achieved in 95 to 100% of multiple myeloma patients treated with VAD before mobilization with high-dose cyclophosphamide (474). The absolute number of $CD34^+$ cells/kg is the most reliable and practical method for determining the adequacy of a stem cell collection.

There are many options for mobilizing regimens, from single-agent granulocyte colony-stimulating factor (G-CSF) (501) to pegylated G-CSF (502), to an assortment of chemotherapy-plus-growth factor regimens (503,504,505,506,507). In general, chemotherapy mobilization results in higher CD34 yields (503,508,509). Chemotherapy mobilization has been associated with lower tumor contamination of the stem cell product (503,509), but no survival benefit has been demonstrated (510). The CXCR4-antagonist AMD3100 has not yet been approved by the U.S. Food and Drug Administration, but it has already shown efficacy in clinical trials (511).

Autologous Hematopoietic Stem Cell Transplantation in Special Populations

The mortality rate from autologous stem cell transplantation is currently <5%. Age >65 years alone is not a contraindication for transplantation, although there are no randomized data proving or disproving its utility in this age group. Such patients are candidates for transplantation if they have good functional status and limited comorbidities (512,513). Patients with renal failure, including dialysis patients, can successfully undergo HSCT with melphalan 140 mg/m^2, with similar response rates and progression-free survival, and a proportion will even have reversal of their renal failure. Treatment-related morbidity is higher (514), and their overall survival is inferior to that of their dialysis-independent counterparts (515,516).

Conditioning Therapy and Stem Cell Transplantation

In an effort to improve autologous stem cell transplantation, various preparative regimens have been used. There has been only one prospective randomized controlled trial comparing conditioning regimens in patients with myeloma (517). Moreau et al. (517) randomized 282 patients to receive either melphalan (140 mg/m^2) plus total-body irradiation or melphalan alone (200 mg/m^2). There was no difference in response rates or event-free survival. Survival at 45 months favored the melphalan-alone arm (65.8 vs. 45.5%, p = .05). Toxicity with melphalan alone was significantly less. Most investigators have now discontinued the use of total-body irradiation and give only melphalan (200 mg/m^2) as the preparative regimen.

Other regimens including various combinations of melphalan, busulfan, cyclophosphamide, idarubicin, etoposide, and/or thiotepa have been used (518,519,520,521,522,523), without any evidence of superiority of these regimens over melphalan 200 mg/m^2, and several with significantly more toxicity (519,520) and morbidity (518). Innovative trials supplementing melphalan with skeletal targeted radiation [samarium 153-ethylenediaminetetramethylene phosphonate (524) and holmium 166-1,4,7,10-tetraazocyclodo-decane-1,4,7, 10-tetramethylenephosphonic acid (525)] have been reported. Others have been studying bortezomib as a chemosensitizer for the melphalan (526,527,528).

Desikan et al. retrospectively compared the effect of different conditioning regimens used for the second autologous transplant (529). Outcomes of patients treated with melphalan 200 mg/m^2 were better than those conditioned with melphalan 200 mg/m^2 plus cyclophosphamide 120 mg/m^2, and melphalan 140 mg/m^2 plus total-body irradiation (1,125 cGy).

The Role of Purging

Virtually all peripheral blood cell products are contaminated with malignant cells (530,531). It is unclear whether the purging of tumor cells from the collection of hematopoietic stem cells is beneficial. Purging marrow with cyclophosphamide derivatives (532) or with monoclonal antibodies (533,534,535) is feasible although associated with prolonged myelosuppression after transplantation. CD34$^+$ selection of peripheral blood progenitor cells provided effective hematopoietic support in a group of 55 patients with advanced multiple myeloma after myeloablative chemotherapy (536). However, one large Phase III randomized trial has shown no clinical benefit to using CD34$^+$-selected autologous peripheral blood

stem cells (537). Another randomized trial showed an increased rate of infection without improvement in overall survival (538).

Early work shows that flowing hematopoietic cells through pulsed electric fields effectively purges myeloma cells without sacrificing functional stem cells (539). This finding has not yet made it into the clinic.

Allogeneic Transplant

Allogeneic transplantation eliminates the problem of stem cell contamination by tumor cells that is inevitable with autologous stem cell transplantation. Further, there is evidence of a graft-versus-myeloma effect with allografting (540). Allogeneic stem cell transplantation (allogeneic SCT) can lead to complete response rates of 22 to 67%, including molecular remissions in about one third (495,541,542), and prolonged disease-free survival in approximately one quarter to one third of patients (471,495,543) (Table 99.12). The high treatment-related mortality (10 to 63%) and significant toxicity from graft-versus-host disease have limited the role of this procedure in the treatment of myeloma (495,544,545).

Though there are no prospective randomized trials comparing conditioning regimens in patients receiving allogeneic transplants, one retrospective multicenter analysis of 139 patients undergoing myeloablative conditioning showed better outcomes in patients receiving melphalan/total-body irradiation (TBI) compared to cyclophosphamide/TBI, including higher CR rates (65 vs. 47%, $p = .085$), lower relapse rates (37 vs. 81%, $p < .0001$), and longer 5-year overall survival (44 vs. 28%, $p = .06$) (546).

A small single-center study of 37 myeloma patients who underwent myeloablative allogeneic SCT, but that had a median follow-up of 108 months, reported that the patients' 5-year overall survival, progression-free survival, and event-free survival were 40, 54, and 24%, respectively (547), despite a 50% treatment-related mortality and a median overall survival of 28 months. At 10 years, about 30% of the patients were alive. Outcomes were similar for the allogeneic treatment arm in the S9321 Intergroup study (471).

In another series, only 5 of 80 patients were alive without evidence of disease at 4 to 7 years after an allogeneic bone marrow transplant for multiple myeloma (495). It must be emphasized that the majority of these patients had chemotherapy-resistant disease before transplantation. Outcomes for allogeneic SCT have improved over time (548). Of 690 allogeneic, matched, sibling donor transplants for multiple myeloma reported to the European Group for Blood and Marrow Transplantation registry, 334 were performed between 1983 and 1993 (all with bone marrow) and 356 between 1994 and 1998. The 3-year overall survival was 35% for transplant recipients during the earlier period and 55% for recipients of bone marrow transplants during the later period. The improvement in survival since 1994 was the result of a significant reduction in transplant-related mortality, from 46 to 30% at 2 years (548).

Table 99.12 Nonrandomized Comparisons of Autologous and Allogeneic Hematopoietic Stem Cell Transplantation for Multiple Myeloma

Study	N	TRM (%)	PFS (mo)	P	OS (mo)	P
Bjorkstrand et al. (549)	189 Auto	13	~22	NS	34	.001
	189 Allo	41	~12		18	
Varterasian et al. (550)	24 Auto	12	16.7	NS	33.5	NS
	24 Allo	25	31		38.6	
Couban et al. (551)	40 Auto	5	14	—	>48	<.001
	22 Allo	27	~11		7	
Reynolds et al. (553)	Auto 35	6	2 y, 30%	NS	2 y, 42%	NS
	Allo 21	19	2 y, 60%		2 y, 60%	
Lokhorst et al. (552)	50 Autoa	6	3 y, 67%	NS	3 y, 82%	NS
	11 Allo[a,b]	18	3 y, 67%		3 y, 82%	
Alyea et al. (554)	166 Auto	13	2 y, 48%	.002	2 y, 74%	.006
			4 y, 28%	NS	4 y, 41%	NS
	66 Allo b	24	2 y, 23%		2 y, 51%	

			4 y, 18%		4 y, 39%	
Arora et al. (555)	70 Autoc	6	1 y, 67%	NS	1 y, 86%	NS
			4 y, 18%	NS	4 y, 50%	NS
	17 Allo	31	1 y, 58%		1 y, 64%	
			4 y, 32%		4 y, 64%	

MS, median survial; NS, not significant; TRM, treatment-related mortality.
[a]Chemotherapy-sensitive patients only.
[b]T-cell–depleted allogeneic stem cells.
[c]Cyclphosphamide and total-body irradiation conditioning.

Allogeneic transplants produce higher rates of complete molecular responses. In a series of 229 myeloma patients, allogeneic transplants resulted in a complete response of 38%, compared with 22% after autologous transplantation ($p < .01$) (541). Among patients achieving a clinical complete response, 50% of the allogeneic transplant group had a molecular complete response, compared with only 17% of those who had received an autologous transplant (541). The median relapse-free survival for those who had a molecular complete remission was 110 months, compared with 35 months for those who did not. Moreover, in those with a complete molecular remission, the relapse rate was only 16% in the allogeneic group and 41% in the autologous group. This is strong evidence that molecular complete responses are associated with a longer relapse-free survival.

There have been seven case-control or cohort-control studies comparing autologous to allogeneic stem cell transplants (Table 99.12) (549,550,551,552,553,554,555). The largest of these was by Bjorkstrand et al. (549). In their retrospective analysis of data compiled by the European Blood and Marrow Transplantation Group, there was inferior survival for myeloma patients treated with allogeneic bone marrow transplants compared to case-matched controls treated with autologous transplants (18 vs. 36 months) (549). The six smaller studies, which had relatively short follow-up, showed mixed results with regard to progression-free survival and overall survival; transplant-related mortality, however, was consistently higher in the allogeneic groups (19 to 25%).

Only one report favored allogeneic transplantation (555). However, patients in the allogeneic group were better-prognosis patients; they were significantly younger and less

likely to have IgA myeloma. Though not reaching statistical significance, there were more autologous patients having their transplant as salvage (37 vs. 23%). In addition, cyclophosphamide and total-body irradiation were used to condition both the autologous and allogeneic transplant patients. With follow-up times for the two groups of 24 and 43 months, respectively, the 1-year overall survival was 86 and 64%, and the 4-year OS was 50 and 64%.

Two of these studies have evaluated the role of T-cell depletion. Lokhorst et al. (552) compared autologous stem cell transplants to T-cell–depleted allogeneic stem cell transplants. Myeloma patients were eligible if they had chemotherapy-sensitive disease. Genetic randomization was used. After 44 months' median follow-up, overall survival had not yet been reached in either group (Table 99.12). Transplant-related mortality in the allogeneic group was 18%, compared with 6% in the autologous group. In their Phase successor III study (HOVON [Dutch-Belgian Hemato-Oncology Cooperative Group] 24), 53 newly diagnosed myeloma patients with an HLA-identical sibling were allocated to a partial T-cell–depleted allogeneic SCT after induction therapy (556). The overall response rate was 89%, including a 19% complete response. With a median follow-up of 38 months, 33 (62%) had died, 18 from treatment-related mortality. The median progression-free survival from the allogeneic SCT was 17 months, and median overall survival was 25 months. Only three patients are in continuing complete response. The authors conclude that their data do not support T-cell–depleted myeloablative allogeneic SCT as part of first-line therapy.

Alyea et al. also evaluated T-cell–depleted allografts, followed by donor lymphocyte infusions (Table 99.12). This approach appeared to be of limited benefit, with a high treatment-related mortality, inferior 2-year PFS and OS, but similar 4-year PFS and OS (554).

Ballen et al. reviewed the National Marrow Donor Program (NMDP) experience of myeloablative allogeneic transplants (557). There were 71 consecutive cases from July 1989 to February 2000, with a median age of 44 years (range 22 to 60 years). Median time to unrelated donor transplant was 17 months. Thirty-nine percent were T-cell–depleted. The 2-year survival rate was 27%, and at 5 years only 9% of patients were alive.

Nonmyeloablative Allogeneic Transplant

In another effort to reduce allogeneic transplant-related mortality, “nonmyeloablative,” “reduced-intensity” or “mini” stem cell transplant regimens have been studied in patients with multiple myeloma. The principle behind this approach is to harness the improved complete response rate and relapse-free mortality seen in a standard full allogeneic transplant while eliminating the high treatment-related mortality rates. The mortality rate for allogeneic

transplantation must be reduced before it can assume a major role in the treatment of multiple myeloma. Table 99.13 contains the results from the first studies employing this reduced-intensity conditioning approach. Many studies included relapsed or refractory patients, which was thought to account at least in part for the poor outcomes. It also became apparent that this approach was less useful in patients who had significant residual tumor burden at the time of the nonmyeloablative transplant, which led to the concept of a planned autologous SCT followed a couple of months later by a reduced-intensity allogeneic

stem cell transplant (RIC SCT). Preliminary results of this latter approach are summarized in Table 99.13.

Table 99.13 Reduced-Intensity Conditioning (RIC) for Allogeneic Hematopoietic Stem Cell Transplantation for Multiple Myeloma

Study	N	Diagnosis to RIC, mo RIC (range)	Sibling/ MUD Allograft	Age, y (range)	RIC regimena	Median FU, mo	CR/PR, no.	TRM, %	PFS, % (at time in mo)	OS, % (at time, in mo)
Giralt et al. (558)	22	36 (3–135)	13/9	51 (45–64)	FM	15	7/9	41	19% (24)	Med 10 mo
Badros et al. (513,568)	60	NS	49/11	52 (38–68)	Mel 100 or FM-TBI; 26 Auto → RIC	45	18/36	34	26% (60); Med 8 mo	34% (60); Med 9 mo
Gerull et al. (1095)	52	35 (8–233)	32/20	52 (36–68)	F-210 cGy	18	1/8	17	29% (18)	41% (18)
Crawle	2	19	19	5	Va	2	10	2	21	41

y et al. (560)	29	.2 (2–132)	2/37	2 (32–66)	ried	8	/53	2	% (36)	% (36)
Perez-Simon et al. (1096)	70	—	—	54 (30–66)	FM; 15 Auto → RIC	19	18/40	24	Med 32 mo	Med 10 mo
Shimazaki et al. (1097)	45	—	NS	53 (39–63)	F-based	25	9/24	9	18.8% (36)	38.5% (36)
Galimberti et al. (1098)	20	11	NS	51 (35–66)	Auto → RIC	35	NS	20	51% (24)d	58% (24)d
Maloney et al. (561)	54b	NS	54/0	52 (29–71)	Auto → RIC	22c	25/14	25	55% (24)c	78% (24)c
Kroger et al. (562,5	47	11.2 (4.	24/23	52 (3	Auto →	16	26/13	11	54% (36	70% (36

63,564)		7–57)		1–64)	RIC				)	)

ATG, antithymocyte globulin; Bu, busulfan; CR, complete response; F, fludarabine; FC, fludarabine and cyclophosphamide; FM, fludarabine and melphalan; FU, follow-up; Mel, melphalan; MM, multiple myeloma; MMF, mycophenolate; MTX, methotrexate; MUD, matched unrelated donor; RIC, reduced-intensity conditioning; NS, not stated; OS, overall survival; PFS, progression-free survival; PR, partial response; TBI, total-body irradiation; TRM, treatment-related mortality.
[a]All studies used cyclosporine as part of the graft-versus-host prophylaxis program.
[b]Forty-eight percent with relapsed or refractory disease prior to autologous transplant.
[c]Time measured from autologous stem cell transplantation.
[d]Time measured from RIC.

The first published report of a RIC series came from Giralt et al., working at the M. D. Anderson Cancer Center (Table 99.13). They treated 22 patients, who were predominantly relapsed or refractory, with a reduced-intensity program including fludarabine and melphalan. With a median follow-up of 15 months, the median overall survival was 10 months, and 19% were progression-free at 24 months (558). The same group compared salvage autologous ASCT to RIC SCT for patients failing prior ASCT. With a median follow up of 18 months for the autologous patients and 30 months for the allogeneic group, the respective PFS were 6.8 and 7.3 months and the respective OS were 29 and 13 months (559).

Investigators from the University of Arkansas reported the results of RIC SCT in 31 poor-risk myeloma patients (513). Twenty-five were HLA-compatible siblings, and 6 of the recipient-donor pairs were unrelated but matched (Table 99.13). The conditioning regimen consisted of melphalan 100 mg/m^2 for related and melphalan 100 mg/m^2 plus total-body irradiation (250 cGy) plus fludarabine for unrelated allografts. Donor lymphocyte infusions were initially given on days 21, 42, and 112 to patients with no clinical evidence of graft-versus-host disease (GVHD); however, because of high rates of lymphocyte-induced GVHD, donor lymphocyte infusions were reserved for patients who needed to attain full donor chimerism or who required eradication of residual disease. All but one patient had received one or more than two prior autologous transplants. Fifty-five percent of the patients had progressive disease at the time of the allograft. Acute GVHD developed in 18 patients. Ten patients progressed to chronic GVHD—limited in 6 and extensive in 4 patients. Two patients failed to engraft even after a second allogeneic peripheral blood stem cell infusion. At a median follow-up of 6 months, 12 patients achieved complete remission and another 7 a near-complete remission, while 3 achieved a partial remission. There were 3 treatment-related deaths during the first 100 days and another 6 after 100 days, for an overall treatment-related mortality of 28%. Three patients died of progressive myeloma. Patients who received transplants with progressive disease or who had received more than one prior

autograft had a statistically higher mortality rate. The authors also compared their nonmyeloablative transplant experience to their prior standard allogeneic experience and found that the nonmyeloablative group had a lower mortality during the first year (p = .09), most notably the subset who had received only one prior autologous transplant (*p* = .05). Crawley et al. reported the outcome of 229 patients who received an allograft for myeloma with reduced-intensity conditioning regimens from 33 centers within the European Group for Blood and Marrow Transplantation (560) (Table 99.13). Ten percent of patients had at least two prior stem cell transplants, and 26% had never received an ASCT. Seventy-eight percent of patients received matched sibling transplants. Sixteen percent had unrelated donors. Only 20% received bone marrow stem cells. Conditioning regimens were heterogeneous, but most were fludarabine-based and T-cell–depleted with antithymocyte globulin or alemtuzumab. Transplantation-related mortality at 1 year was 22%. The 3-year overall survival and progression-free survival rates were 41% and 21%, respectively. Adverse OS was associated with chemoresistant disease (relative risk, 2.9), more than one prior transplantation (relative risk, 2.0), and male patients with female donors (relative risk, 1.45). Adverse PFS was associated with chemoresistance and alemtuzumab. Grades II to IV acute GVHD occurred in 31%. Chronic GVHD was associated with better OS and PFS and were 84% and 46% for limited, 58% and 30% for extensive, and 29% and 12% in its absence, suggesting that a graft-versus-myeloma effect is important (Fig. 99.12). The authors concluded that reduced-intensity conditioning is feasible, but heavily pretreated patients and patients with progressive disease do not benefit.

Maloney and colleagues (561) reported results on 54 newly diagnosed myeloma patients who were treated with a planned tandem autologous/nonmyeloablative allogeneic stem cell transplantation (Table 99.13). After induction with four cycles of VAD chemotherapy, followed by ASCT using melphalan 200 mg/m^2

as conditioning, patients underwent a RIC SCT. The conditioning for the second transplant was with total-body irradiation (200 cGy). Matched sibling donor peripheral blood stem cells were infused immediately after the total-body irradiation. Postgrafting immunosuppression included mycophenolate and cyclosporine. Fifty-two of the 54 patients received the planned RIC SCT, with a median time between autologous and allogeneic transplants of 62 days. The granulocyte and platelet nadirs after the nonmyeloablative transplant were 760 and 95,000 cells/µl, respectively. Acute GVHD was seen in 38% of patients and was grade II in all but four cases. Forty-six percent of patients developed chronic GVHD that required therapy. All patients achieved donor engraftment. Fifty-seven percent of patients not in complete response after the first transplant achieved a complete response after the second transplant. With a median follow-up of surviving patients of 18 months, 8 patients (15%) had died of transplant-related complications, 2 of progressive myeloma, and 1 of lung cancer.

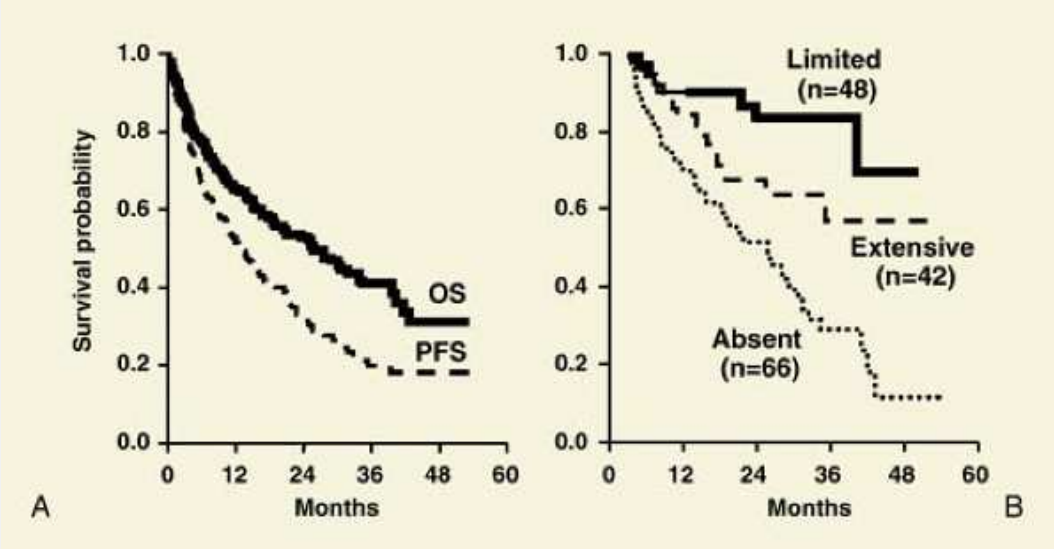

Figure 99.12. European Blood and Marrow Transplantation Registry data on the role of reduced intensity conditioning allogeneic transplantation regimens. A: Overall and progression-free survival. **B:** Overall survival relative to presence or absence of graft versus host disease. (With permission, ferom Crawley C, Lalancette M, Szydlo R, et al. Outcomes for reduced-intensity allogeneic transplantation for multiple myeloma: an analysis of prognostic factors from the Chronic Leukaemia Working Party of the EBMT. Blood 2005;105: 4532–4539. © the American Society of Hematology.)

Kroger et al. (562,563) have applied a similar strategy, including a planned standard-intensity autograft (melphalan 200 mg/m^2) followed by a dose-reduced regimen (fludarabine 180 mg/m^2, melphalan 100 mg/m^2, and antithymocyte globulin 10 mg/kg on 3 days) before allografting (Table 99.13). GVHD prophylaxis included cyclosporine and mini-methotrexate. Nine patients received allografts from related donors and 8 from unrelated donors. Acute GVHD stage II to IV occurred in 6 patients (38%). Chronic GVHD developed in 40% of the patients, but only 1 patient experienced extensive chronic GVHD requiring further immunosuppressive therapy. The 100-day mortality rate was 11%, and with a median follow-up of 17 months after autologous and 13 months after allogeneic transplantation, 13 patients (76%) are alive. The rate of complete remission with negative immunofixation increased from 18% after autografting to 73% after allografting, and 12 remain free of relapse or progression.

This same group has also reported on this approach using matched unrelated donors (564). Twenty-one patients with advanced multiple myeloma were conditioned with a reduced-intensity conditioning regimen consisting of fludarabine (150 mg/m^2), melphalan (100 to 140 mg/m^2), and antithymocyte globulin (ATG; 10 mg/kg on 3 days). All patients had received at least one prior autologous transplantation, in 9 cases as part of an autologous-allogeneic tandem protocol. Grade II to IV acute GVHD was seen in 8 patients (38%), and severe grade III/IV GVHD was observed in 4 patients (19%). Six patients (37%) developed chronic GVHD, but only 2 patients (12%) experienced extensive chronic GVHD. The estimated probability of nonrelapse mortality at 1 year was 26%. After allografting, there was an overall response rate of 90% (40% complete response and 50% partial response). After a

median follow-up of 13 months, the 2-year estimated overall and progression-free survival rates were 74% (95% CI, 54 to 94%) and 53% (95% CI, 29 to 87%), respectively. A shorter progression-free survival was seen in patients who had already experienced relapse to prior autografts (26 vs. 86%, p = .04).

Table 99.14 Prospective Randomized Trials Comparing Tandem Autologous SCT to Tandem Autologous-HLA Identical Reduced-Intensity Allogeneic SCT

Study	N	Regimen	Age, y (range)	Completed Both SCTs, %	Median FU, mo	Patients in CR, %	TRM, %	PFS, %	OS, %
Garban et al. (565,566)	219a	Automel 200/220 ± IL-6 Ab	58 (28–65)	76	24	33	5	0 at 5 y	44 at 56 mo
	65	Automel/AlloBu/Flu/ATG	54 (38–65)	71	28	43	8	0 at 5 y	33 at 5 y
Bruno et al (567)	73	Automel 200/200	53 (33–64)	75	36	16	4	41 at 3 y	62 at 3 y
	56	Automel 200/AlloTBI	54 (34–65)	100	36	46	11	75 at 3 y	84 at 3 y

FU, follow-up; OS, overall survivial; PFS, progression-free survivial; TRM, treatment-related mortality.
[a]High-risk patients as defined by the presence of deletion 13 by FISH and β_2-microglobulin of >3 mg/L.

Two randomized controlled trials compared up-front sequential autologous SCT to sequential autologous SCT, RIC allogeneic SCT (565) (Table 99.14).

The first of these was the IFM9903/9904 trial, in which high-risk patients, as defined by a β_2-microglobulin >3 mg/L and deletion 13 by FISH, were biologically randomized to either a planned ASCT followed by a RIC SCT (*n* = 65) or two dose-intensified tandem ASCTs followed by treatment with anti-IL-6 monoclonal antibodies (*n* = 219) (565,566). On an intent-to-treat analysis, outcomes of high-risk myeloma patients were no different between the groups: median survival, 35 versus 41 months; and median event-free survival, 25 versus 30 months, respectively. There was a trend toward better overall survival in the non–allogeneic SCT arm, 47.2 versus 35 month, *p* = 0.07, when only patients who completed their treatment assignment were considered.

Bruno et al. (567) have presented in abstract form their 3-year results of a prospective randomized trial of double autologous transplants versus tandem auto-RIC. Outcomes were significantly

better in the auto-RIC arm, with results far outstripping those of other auto-RIC studies.

So the question remains: Who should receive reduced-intensity conditioned SCT? The answer is not clear. Some investigators, including ourselves, have limited the application of RIC SCT to patients with very high-risk disease. However, some available data suggest that patients defined as high risk by FISH deletion 13 do not seem to do better with RIC SCT than patients receiving tandem autologous HSCT (565,566). Others have questioned whether the RIC, which contained antithymocyte globulin, was too immunosuppressive and therefore abrogated a graft-versus-myeloma effect. Data from Lee et al. show that patients with metaphase cytogenetic abnormalities, which are in part a surrogate for plasma cell proliferation, also do worse than their counterparts with normal cytogenetics (568). Patients with cytogenetic abnormalities receiving RIC SCT had a 36% likelihood of relapse at 1 year, in contrast to 5% for patients who lacked cytogenetic abnormalities going into RIC, even if they previously had cytogenetic abnormalities at an earlier date (568).

Until further refinements are made and additional confirmatory studies with longer follow-up are completed, the role of nonmyeloablative allogeneic stem cell transplantation as initial therapy in myeloma must be considered investigational. See Table 99.13 for additional preliminary data.

Donor Lymphocyte Infusions

A graft-versus-myeloma effect has been noted after the administration of donor peripheral blood mononuclear cells for relapse after allogeneic transplantation (540,569). Donor lymphocyte infusion (DLI) has been used in three ways in myeloma patients. Initially, it was used to treat relapsed or residual disease after a full myeloablative allogeneic stem cell transplant (540,569). Subsequently, it was used to supply T cells to patients who had received an allogeneic T-cell–depleted graft (570,571). Most recently, it has been used in RIC programs to treat mixed chimerism, as well as for previously established indictions (572,573,574).

In the largest DLI series for relapsed myeloma (*n* = 54) (575), 52% of patients responded to donor lymphocyte infusions, 35% with a partial response and 17% with a complete response. The most common starting T-cell dose was 1×10^7 cells/kg, with a range of 1×10^6 to 5×10^8 cells/kg. Fifty-four patients received a total of 95 DLI courses (range, 1 to 7 courses) for a

median of 20 months (range 4 to 90 months). Retreatment was prompted by a lack of response or lack of GVHD by 3 months. The majority of patients received some chemotherapy before DLI. Progression-free and overall survival were 19 and 23 months, respectively. Rates of overall acute GVHD and of grade III to IV acute GVHD were 57 and 20%, respectively. Rates of overall chronic GVHD and of extensive GVHD were 47 and 30%, respectively. Acute and chronic GVHD following DLI were the strongest predictors for response (575).

The best starting dose for DLI has not yet been established. Initial reports suggested that a T-cell dose of more than 1×10^8 cells/kg, response to reinduction therapy, and chemotherapy-sensitive disease before allogeneic transplantation (576) were predictive of best outcomes, but these data have not yet been confirmed by studies with larger sample sizes and further follow-up (573,575,577).

Von Donk et al. reviewed their experience with donor lymphocyte infusions given for relapsed (*n* = 48) or persistent (*n* = 15) myeloma following RIC SCT (574). Acute and chronic GVHD occurred in 38% and 43% of patients, respectively. There were seven treatment-related deaths. Thirty-eight percent of patients responded, with half achieving a partial response and half a complete response. With a median follow-up of 14 months, overall survival after DLI was 23.6 months (1.0 to >50.7 months): 23.6 months for nonresponders and not yet reached for responders. In responders, progression-free survival after DLI was 27.8 months (1.2 to >46.2 months). The only significant prognostic factors for response to DLI were the occurrence of acute and chronic GVHD.

Maintenance Therapy

Strategies for maintenance therapy can be divided into two broad categories: (a) continued induction therapy *ad infinitum,* and (b) addition of a novel therapy after induction therapy. The former strategy was prevalent until recognition of the risk of developing alkylator-induced myelodysplastic syndromes and leukemia (578,579,580,581,582,583). The latter strategy has mainly used immune modulators, including prednisone, interferon, cellular therapies, and, more recently, thalidomide and lenalidomide. To date, the benefits of maintenance therapy have been marginal at best, but for several of these agents, additional studies are required. No benefit has been observed with maintenance levamisole (271,369), azathioprine (584), or bacillus Calmette-Guérin (BCG) (387).

Maintenance Chemotherapy

Through the 1970s and 1980s, several randomized studies established that alkylator-based maintenance therapy does not produce a survival benefit (225,253,278,280,364,384,584,585,586). In general, patients not receiving maintenance had similar to slightly shorter remission duration than those receiving maintenance (225,364,384,584,586,587) but had higher rates of a second remission (586,587). Some studies showed a trend toward longer survival in the former group (278,280,585).

Induction therapy is commonly discontinued after plateau is reached, defined as no change in M protein of >25% for 4 to 6 months (225,278,588). With alkylator-based therapy, the ability to achieve a plateau is as important as the degree of response achieved (225,588,589,590,591,592). No benefit has been documented for treatment beyond 12 months (364), although it has been suggested—but not validated—that prolonged primary

chemotherapy may be beneficial in patients achieving less than a partial response, i.e., a minimal response or stable disease (593).

Alkylator-unmaintained remissions tend to last about 12 months (584). Patients who relapse off alkylator-based chemotherapy have response rates of 25 to 80% with resumption of the original regimen (225,387,586,587). Second response rates are lower in patients who progress or relapse during maintenance than in those who relapse without maintenance therapy in the case of alkylator-based therapy (584,587) and IMiD-based therapy (594). In a study of 115 newly diagnosed patients treated with VBMCP for ~1 year, an initial response rate of 82% was achieved, with a median duration of response of 22 months. After a first relapse, 26 of 38 patients (68%) responded again and had a median duration of response of 11 months. After a second relapse, 7 of 16 patients (44%) responded, with a duration of response of 3.5 months (595).

Corticosteroids as Maintenance Therapy

Four studies deal with corticosteroids as maintenance therapy. None justifies a recommendation of prednisone as a standard maintenance regimen for all patients.

The most recent study (SWOG 9210) compared prednisone 10 mg every other day to prednisone 50 mg every other day in patients who had responded (SWOG PR or better) to 6 to 12 months of a VAD-based program, that is, a corticosteroid-intensive program. From the time of randomization to the two different alternate-day prednisone schedules, the median progression-free survival for the higher-dose prednisone arm was 14 months, compared to 5 months for the lower dose (p = .003). Survival also was marginally better, at 37 and 26 months (p = .05) (596). Although the more dose-intensive corticosteroid maintenance strategy does provide a longer progression-free survival in corticosteroid-responsive patients, these data cannot be generalized. By comparison, after alkylator-based therapy the median unmaintained progression-free survival is 12 months in responding patients (584).

An earlier randomized study, which compared dexamethasone maintenance to interferon maintenance after induction with melphalan and dexamethasone, demonstrated equivalence to inferiority of dexamethasone compared with interferon. Patients received maintenance treatment with interferon-α (3 MU 3 times a week) or dexamethasone (20 mg/m^2 orally daily for 4 days repeated monthly) until relapse. Remission duration was identical (10 months); however, significantly more patients responded upon reinstitution of the melphalan and dexamethasone at disease relapse in the interferon group than in the dexamethasone group (82 vs. 44%, p = .001) (597).

The CALGB 7461 study addressed this issue less directly. Patients were treated initially with alkylator therapy and were randomized to observation *or* vincristine and prednisone as maintenance. Survival and response rates were significantly longer and higher in the vincristine–prednisone maintenance group who had received up-front melphalan (median, 35.3 vs. 27.0 months; p = .003) but not in patients who had received up-front BCNU or CCNU (269).

Finally, SWOG 8624, which evaluated the influence of corticosteroid dose intensity on response and survival, indirectly provided data on corticosteroid maintenance. Higher

objective response rates and median survival were observed in patients who received prolonged administration of glucocorticoids (prednisone 50 mg every other day) between chemotherapy courses. Patients given VMCP/VBAP with and without alternate-day prednisone had median overall survivals of 40 versus 31 months, respectively (p = .02). The survival advantage may have been confounded by the complexity of the study; different treatment plans were assigned after 12 months of induction therapy, determined by tumor response (402). Moreover, one could argue that the corticosteroid was a part of the induction rather than the maintenance program.

Interferon as Maintenance Therapy

After Conventional Chemotherapy

The initial positive findings by Mandelli et al. (598) in 1990 demonstrated a superior disease-free and overall survival in chemotherapy-responsive patients randomized to maintenance interferon-α. Subsequent studies have yielded divergent results. Ludwig and Fritz (431) analyzed 1,615 patients in 13 maintenance trials (374,419,422,598,599,600,601,602,603,604,605,606,607,608); the Myeloma Trialists' Collaborative Group (432) used the individual data of 1,543 patients enrolled in 12 randomized trials (374,402,419,422,426,599,601,605,609,610,611). Results were similar in that the first group found a 4.4-month prolongation of relapse-free survival (p < .01) and a 7.0-month increase in overall survival (p < .01) (431). The latter group reported a 3-year progression-free survival of 27 versus 19 months (p < .00001) in favor of the interferon maintenance group. Interferon-α prolonged the overall survival by ~7 months (p = .04) (432) (Fig. 99.10). Survival time from progression to death was significantly worse in the interferon group than in the control group (odds ratio 1.21, p = .007). No analyzed factors predicted for the interferon benefit (i.e., pretreatment hemoglobin, calcium, β_2-M, creatinine, sex, performance status, or immunoglobulin isotype). The level of response (complete response, partial response, stable disease) or interferon dose intensity (<12 vs. ≤12 MU/week) also did not predict for interferon effect (432). In 2000 the cost of the 1-year survival benefit in patients treated with interferon as maintenance was $US 18,968, assuming a dose of 11.6 MU/week (431).

In Combination with Corticosteroids

Corticosteroids have been added to maintenance interferon in an attempt to intensify the program. Small numbers of patients have been treated with standard maintenance interferon and either dexamethasone (612) or prednisone (401,612). In one small randomized study, the progression-free survival was longer in the corticosteroid-plus-interferon arm than in the interferon-only arm, although median survival was not different (401). The combination can also induce further partial remissions in more than half of responding patients so treated (612) and may also prolong the duration of a second remission (613).

Interferon after High-Dose Chemotherapy with Stem Cell Support

Fewer data are available about the utility of interferon after autologous stem cell transplantation. There is one small randomized trial of 85 patients (610) and a larger retrospective analysis of registry data by the European Group for Blood and Marrow Transplantation (614). The use of interferon in this setting cannot be recommended outside of clinical trials.

Cunningham et al. (610) randomly assigned 85 patients to interferon at 3 MU/m^2 three times weekly or to observation. The median progression-free survival in the 43 patients randomized to interferon-α was 46 months, compared with 27 months in the control patients ($p < .025$). Although there was a significant survival advantage at 54 months, at which time 12% of patients in the interferon group and 33% of patients in the no-interferon group had died ($p = .006$), this survival advantage was no longer evident at a median follow-up of 77 months.

The data from the European Group for Blood and Marrow Transplantation registry included 473 patients who had received maintenance and 419 who had not. Unfortunately, the two groups were poorly matched. The patients who did not receive interferon had significantly more prior therapy, a higher stage at diagnosis, and a longer time to transplantation. They were also significantly older, and a higher percentage had received total-body irradiation–containing conditioning regimens (614). Although these factors were "statistically corrected for" in the survival analysis, the imbalance makes interpretation of this retrospective collection of registry patients problematic. Prognostic factors such as β_2-M, C-reactive protein, cytogenetics, and PCLI were not included in the analysis. Overall survival was significantly better in the patients who received interferon (78 vs. 47 months, $p = .007$). Paradoxically, there was a more prominent survival benefit in those patients who achieved a partial response (97 vs. 46 months for interferon vs. no interferon, $p = .03$) rather than a complete response (64 vs. 51 months, $p = .1$), and the partial-response group had a better overall survival than the complete-response group.

Thalidomide as Maintenance Therapy

Several trials are evaluating the tolerability of thalidomide as maintenance (615,616,617), but very few Phase III data are evaluable at this time, and therefore thalidomide maintenance cannot be recommended as standard therapy off-study. The two completed trials that approach the question are the IFM 99-02 (618) and Total Therapy 2 studies (594). IFM 99-02 evaluates the value of maintenance thalidomide versus no thalidomide in low-risk myeloma patients who have undergone tandem ASCT. Though the 3-year event-free survival (36 vs. 52%, $p < .009$) and the 4-year overall survival (75 vs. 87%, $p = .04$) favored the thalidomide maintenance arm, there are several caveats to this trial. The first is that median follow-up is short at 39 months. The second is that only 65% of the patients on the no-maintenance arm actually received thalidomide at relapse. The third is that fewer of the no-maintenance patients received modern salvage therapy with lenalidomide or bortezomib at relapse than did the maintenance group (15 vs. 38%). With such a modest survival benefit, it is possible that this finding will not survive the test of time.

The Total Therapy 2 trial was a complex regimen in which all patients received intensive induction, tandem transplantation, and consolidative chemotherapy; patients were then randomized to receive either no thalidomide throughout or thalidomide along with all therapies and continued as maintenance. Because of the intensity of the program, it is difficult to make sweeping generalizations about the role that thalidomide played as maintenance therapy, but a few observations are worthy of note: Though response rates and event-free survival rates were significantly

better in the group receiving thalidomide, the overall survival rates were no different. This

trial also illustrates the danger of concentrating too much on event-free and progression-free endpoints in the context of maintenance trials. Finally, the question that ultimately needs to be addressed is whether salvage therapy will be as good as maintenance therapy.

Immunotherapy as Maintenance Therapy

Dendritic Cell-Based Vaccination

In an effort to prolong duration of response and, hopefully, survival, idiotype-treated dendritic cell vaccines are being explored as a therapeutic modality for myeloma patients. B-cell malignancies, including multiple myeloma, are unique in their expression of immunoglobulin (272). The immunoglobulin on malignant cells can be distinguished from that on normal B cells or plasma cells by virtue of specific idiotypic determinants. Dendritic cells are the only known natural cells that can present antigen to naive T cells (619). Antigen-pulsed dendritic cells can successfully induce both humoral and cytotoxic cellular immune responses.

Idiotypic vaccinations alone have met with limited success in human trials (620,621,622). However, vaccination with primed dendritic cells appears to be a more potent way to induce antitumor immunity than vaccination with peptide alone (623,624,625). Trials are now exploring the use of dendritic cell–based vaccinations in multiple myeloma (626).

Management of Relapsed or Refractory Disease

Relapsed and refractory myelomas have distinct biologies but are commonly grouped together in discussions of chemotherapy regimens and trials. Differentiation between relapses occurring on therapy and off therapy should be made, with the former having a poorer prognosis. Similarly, primary refractory—the condition in which the disease has not responded to initial therapy—and secondary refractory (or resistant) disease—should be distinguished from each other. Finally, with the growing list of active agents now available, the class of agents or the treatment modality to which the patient is refractory should be specified.

Before the introduction of high-dose chemotherapy with stem cell support, IMiDs, and proteosome inhibitors, treatment guidelines were more straightforward. If the relapse occurred during an unmaintained remission, resumption of the patient's original therapy was a good rule (587). Fifty to 60% of patients responded to repeat treatment if relapse occurred after unmaintained remissions (387,586,587,627), with a median survival of about 10 months (587,628). The myeloma cell doubling time and duration of response tend to decrease with each subsequent course of therapy (195,304,595). In the case of primary refractory disease or acquired resistance on therapy, the mainstays of treatment had been clinical trials—anthracycline-based, corticosteroid-based, and alkylator-based regimens.

Table 99.15 Conventional Combinations for Relapsed, Refractory Disease

Author	Regimen	N	ORR (%)	DOR (mo)	OS (mo)
de Weerdt, 2001 (637)	Continuous low-dose CTX; Pred	42	38	—	—
Trieui, 2005 (1099)	Weekly CTX; Pred	66	41	—	28.6
Lenhard, 1994 (638)	CTX IV; Pred	48	29	—	8.6
Petrucci, 1989 (379)	IV Mel 25 mg/m^2	34	34	16	8
Tsakanikas, 1991 (376)	IV Mel50-70 mg/m^2	18	50	—	11.5
Barlogie, 1984 (391)	VAD	29	59	>12	—
Dimopoulos, 1996 (657)	HyperCVAD	58	40	8	15
Finnish Leukaemia Group, 1992 (1100)	MOCCA	80	49	22	31
Lee, 2003 (672)	DT-PACE	148	32	—	—
Barlogie, 1989 (286)	EDAP	20	40	—	4.5
Bonnet, 1982 (645)	VBAP	151	25	—	7.6

CTX, cyclphosphamide; pred, predisone; mel, melphalan; DOR, duration of response; DT-PACE, dexamethasone, thalidomine, cisplatin, doxorubicin, cyclophosphamide, etoposide; EDAP, etoposide, dexamethasone, doxorubicin, cisplatin; hyperCVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; mo, months; MOCCA, melphalan, vincristine, cyclophosphamide, lomustine, doxorubicin; N, number of patients; ORR, overall response rate (partial response or better); OS, overall survival; VAD, vincristine, doxorubicin, dexamethasone; VBAP, vincristine, carmamustine, doxorubicin, prednisone.

The current landscape, however, is more complicated. New combinations incorporating the new and the old agents are being tested worldwide, leaving clinicians with an assortment of options but little guidance on how to proceed. Does one use a series of single agents, adding additional drugs as the simpler regimen fails? And if so, which agent does one use first? Or does one bet on synergy and start with a multiagent program at first relapse? So far, there are no answers to these questions, and patient and physician preference guide the decision-making process rather than data. Moreover, as we review salvage therapies, one must remember that response rates for older salvage regimens were based predominantly on alkylators and corticosteroids salvaging alkylator and corticosteroid failures. One would, for instance, expect the cyclophosphamide prednisone salvage rate to be higher for thalidomide and dexamethasone failures than melphalan and prednisone failures, although this hypothesis has not yet been examined in any formal studies.

Until myeloma is a curable disease in all patients, clinical trials will play a critical role in the treatment of these patients. They will assist in defining a better classification system for the disease, clarify which treatments offer the most value, and bring new effective agents into standard clinical practice. The subject of chemotherapy for relapsed or refractory disease will be divided into four sections: alkylator-based regimens, anthracycline-based regimens with or without dose-intensified corticosteroids, novel therapies, and other treatment modalities.

Alkylator-Based Regimens for Relapsed or Refractory Disease (Table 99.15)

There is cross-resistance among the alkylators, but this is not absolute and may be circumvented by increasing dose intensity. Without significant dose intensification, 5 to 20% of patients with melphalan-resistant disease respond to cyclophosphamide or BCNU as single agents or in combination with prednisone (628,629,630,631,632,633,634). Response rates as high as 30 to 38% can be obtained if prednisone is administered with the cyclophosphamide (635,636,637). Higher doses of cyclophosphamide (e.g., 600 mg/m^2 intravenously for 4 consecutive days) result in response rates of 29 to 43% (254,638). Both response duration and overall survival

tend to be short, ~3 and 9 months, respectively (254,638). Consolidating the chemotherapy into a 1-day schedule rather than a 4-day schedule does not improve response rates but does increase toxicity (639). Similarly, administration of 3.6 g/m^2 over 2 days with prednisone appears to produce comparable responses (640).

Dose intensification of melphalan can also be quite effective and is the basis for high-dose therapy with stem cell support (237). Selby et al. (243) reported that 66% of patients with resistant disease treated with 140 mg/m^2 without stem cell support responded, but median response duration was only 6 months, all patients relapsing within a year. Median times to leukocyte and platelet recovery were 42 and 37 days, respectively, and the regimen-related toxicity was 13%. Doses of 50 to 70 mg/m^2 result in a 50% response rate and leukocyte and platelet recovery time of 20 and 16 days, respectively (376,377). Further reducing the intensity to 30 mg/m^2 every 2 months results in response rates of 38% and a progression-free survival of 10 months (380).

VBMCP (the M-2 regimen) or MOCCA provides responses in 20 to 30% of refractory patients (246,363,641) with a median survival of about 11 months (246). Combinations of cisplatin with BCNU, cyclophosphamide, and prednisone have produced responses in heavily pretreated patients (330); however, the addition of cisplatin and bleomycin to VBAP did not appear to produce better outcomes than standard VBAP (286,329,330).

Dimopoulos et al. (642) explored a combination of high-dose cyclophosphamide (3 g/m^2) and etoposide (900 mg/m^2) followed by granulocyte-macrophage colony-stimulating factor. Of the 52 patients with advanced and refractory multiple myeloma treated, 42% responded. Median time to granulocyte recovery was 19 days, and the median duration of remission was 8 months.

Anthracycline-Based Regimens for Relapsed or Refractory Disease

Various permutations of doxorubicin-containing chemotherapy regimens—doxorubicin and cyclophosphamide (AC) (386); doxorubicin, BCNU, cyclophosphamide, and prednisone (ABC-P) (643); CAP (644); VCAP (387); VBAP (645,646); and BAP (644) have been tried in patients with relapsed and refractory disease, resulting in response rates of 7 to 28% (387,643,644,645). Response duration and survival tend to be short—<6 and 12 months, respectively. Responding patients tend to live 7 to 10 or even 22 months longer than nonresponders (644,645,646). Patients who have relapsed disease, rather than resistant or refractory disease, have higher response rates (i.e., close to 30%).

After studying high-dose cytosine arabinoside, cisplatin, and etoposide as single agents, Barlogie et al. (331) did preliminary studies with DAP (dexamethasone, cytosine arabinoside, and cisplatin) and later EDAP (etoposide and DAP). In patients with refractory disease, response rates with these treatments were 7, 14, 17, 0, and 40%, respectively. Median survival in patients treated with EDAP was 4.5 months. This regimen is myelosuppressive, with more than half of treated patients requiring platelet transfusions and 80% requiring hospitalization for neutropenic fever. In the first month, treatment-related mortality was 15%. In the complex Total Therapy 2 program, in which this regimen was used as part of induction, the respective incremental objective and complete response rates went from 55 and 9% to 65 and 15% after EDAP therapy (331).

Another approach to treating relapsed or refractory myeloma is by augmenting anthracycline and vincristine with high-dose corticosteroids. Alexanian et al. (247) described VAP (bolus vincristine 1.5 mg on day 1, doxorubicin 35 mg/m^2 on day 1, and prednisone 45 mg/m^2 for 5 days repeated every 8 days for three corticosteroid pulses); response rates according to SWOG response and improvement criteria were 47%. Barlogie et al. (391) published their experience with VAD, and numerous variants have followed. The overall response rate with VAD in 29 patients who had refractory or resistant disease was 59% according to SWOG criteria. In the 20 patients who had not received prior doxorubicin, the response rate was 70%. VAD differed from VAP in that the former included continuous-infusion vincristine and doxorubicin and a sixfold corticosteroid dose intensification (391). The activity of VAD has been substantiated by others (647,648,649). Infection is the most important complication, with 38% of patients having fever and 28%, a documented infectious agent (391). Early intravenous catheter removal may occur in ~16% of patients as a result of thrombosis or infection (258).

Variants of VAD include regimens that alter the type or dose of corticosteroid, schedule of administration, type of anthracycline used, as well as the addition of other drugs. The effectiveness of VAMP (methylprednisolone in place of dexamethasone) appears comparable to VAD, with a response rate and overall survival of 36% and 20 months, respectively, in patients with resistant disease (260). Browman et al. (650) evaluated m-VAD, in which all of the vincristine and doxorubicin was given on day 1 over 2 hours and the dexamethasone on days 1 to 4 and 15 to 18 only; the overall response rate was 27% (95% CI, 14 to 40%) with a median survival of 7.6 months. The authors expressed concern that this regimen might be less effective than standard VAD, but the confidence intervals of the response rate were large. In fact, the same bolus schedule was used by Dimopoulos et al. (albeit in newly diagnosed patients) as one arm of a randomized trial comparing bolus VAD to DVD (VAD, but with liposomal doxorubicin). Outcomes were identical between the two arms (406).

Alternative anthracyclines have been tried, including mitoxantrone (NOP or mitoxantrone, vincristine, and dexamethasone [MOD]) (651,652,653), which have resulted in response rates of 25 to 40% (651,653) epirubicin (399,654), and liposomal doxorubicin (400). In one randomized study, plateau duration was significantly longer in the VAD group than in the MOD group, but there was no difference in overall survival (653). Several investigators have added other drugs to the VAD base without measurable benefit. Concurrent interferon (427,655) adds nothing to response rate or overall survival. In single-arm studies, there does not appear to be any advantage to the addition of cyclophosphamide to VAD, VAMP, or vincristine, epirubicin, and dexamethasone (VED) to yield CVAD, hyperCVAD, C-VAMP, or VECD (257,260,399,656,657).

Novel Therapies for Relapsed or Refractory Disease

Thalidomide-Based Therapy for Relapsed or Refractory Disease

As has been mentioned, single-agent thalidomide can induce a response in 25 to 58% of relapsed/refractory patients (295,297,298,299,300,301,302,303,304).There appears to be synergy between thalidomide and dexamethasone (308,658). Response rates of 41 to 55% (658,659,660,661) have been observed in patients with resistant myeloma (Table 99.16). Doses of dexamethasone have ranged from 4 mg as a daily continuous dose (661) to 40 mg on days 1 through 4 of each month (658,660). Dimopoulos et al. (658) administered dexamethasone for an additional 8 days (days 9 to 12 and 17 to 20) in the first month only. With these combination regimens, thalidomide dose levels have ranged between 100 and 400 mg/day, without any clear dose–response effect. Patients who are resistant to dexamethasone-based (658,659) or thalidomide-based (662) regimens may respond to the combination of these two agents. Coleman et al. (663) described a 100% response rate for relapsed or refractory disease treated with clarithromycin, low-dose thalidomide, and dexamethasone. These results have yet to be substantiated by other investigators, and clarithromycin alone is not an effective treatment (350,351,352).

Investigators have combined thalidomide with alkylators either with (664,665,666,667,668,669) or without corticosteroids (670,671), achieving overall response rates as high as 79%, including complete response rates as high as 26%. Others have added thalidomide to anthracycline-based therapies (452,454,672,673).

Typically, thalidomide is administered once nightly, but Dimopoulos et al. (665) have taken a different approach by combining cyclophosphamide (150 mg/m^2 by mouth twice daily, days

1 through 5), thalidomide (400 mg PO once daily, days 1 through 5 and 14 through 18), and dexamethasone (20 mg/m^2 PO once daily, days 1 through 5 and 14 through 18). This was repeated every 28 days for three courses; and in subsequent courses drugs were administered on days 1 through 5 only. The only grade 3–4 toxicity noted was myelosuppression. Two percent of patients developed phlebitis and 4% grade 1 neuropathy. Grade 1 constipation and somnolence were each seen in about one third of patients. Median time to progression was 8.2 months, and median overall survival was 17.5 months.

Table 99.16 Novel Combinationations for Relapsed, Refractory Disease

Author	Regimen	Phase	N	CR (%)	VGPR (%)	PR (%)	OR (%)	PFS/EFS, (mo)	OS (mo)
Thalidomide-based									
Singhal, 1999 (43,310)	Thalidomide	2	169	—	—	—	30	2 y, 20%	2 y, 48%
Dimopoulos, 2001 (658)	Thal-Dex	2	44	—	—	55	55	4.2	12.6
Offidani, 2003 (670)	Mel-Thal	2	27	12	0	48	60	2-y PFS, 61%	2-y OS, 61%
Palumbo (retrospective), 2005 (1101)	Low-dose Thal-Dex	Retro	43	0	—	47	47	20	NR

Hovenga, 2005 (671)	CTX Thal	2	38	11	0	64	75	30	20
Garcia-Sanz, 2004 (664)	CDT	2	71	2	0	53	55	2-y EFS, 57%	2-y OS, 66%
Dimopoulos, 2004 (665)	CDT	2	53	5	0	55	60	TTP 8.2	17.5
Kropff, 2003 (666)	CDT	2	60	3	0	65	68	11	19
Kyriakou, 2005 (667)	Low-dose CDT	2	52	17	0	62	79	—	—
Sidra, 2006 (668)	CDT	2	47	0	19	63	83	—	—
Palumbo, 2006 (669)	MPT IV	2	24	0	13	29	42	9	—
Zervas, 2004 (452)	T-DVD	2	39	10	10	64	84	—	—
Hussein, 2006 (454)	T-DVd	2	49	20	24	31	75	15.5	39.9

Offidani, 2006 (673)	TDD	2	50	26	12	38	76	17	NR
Bortezomib-based									
Richardson (SUMMIT), 2006 (321)	Bortezomib	2	193	4	6	18	28	7	17
Jagannath, 2004 (322)	Bortez-Dex (1.0 mg/m^2)	2	27	0	19	19	37	TTP 10.9	26.7
	Bortez-Dex (1.3 mg/m^2)	2	26	0	4	46	50	TTP 7.0	NR
Richardson, (APEX) 2005 (320)	Bortezomib	3	315	6	7	25	38	6	1 y, 80 %
	Dex	3	312	1	1	16	18	—	1 y, 66 %
Kropff, 2005 (1102)	Bortez-Dex	2	15	7	—	67	74	—	—
Musto, 2006 (1103)	Bortezomib	2	21	10	0	33	43	—	—

Orlowski, 2002 (44,677)	Bortez-pegylated dox	1	22	23	14	36	72	—	—
Chanan-Khan, 2005 (1104)	Bortez-pegylated dox-thal	Pilot	6	33	—	17	50	—	—
Jakubowiak, 2005a (1105)	Bortez-pegylated dox-Dex	2	20	33	—	22	55	—	—
Berenson, 2006 (683)	Bortez-MP	1/2	34	6	9	32	47	8	—
Ciolli, 2006 (681)	Low-dose bortez-thal-dex	2	18	11	—	33	44	—	—
Zangari, 2005a (679)	Bortez-Thal-Dex	2	85	0	—	55	55	9	22
Popat, 2005a (461)	Bortez-IV Mel	2	16	—	—	75	75	—	—
Reece, 2005a* (682)	CTX-Bortez - Pred	2	16	6	—	25	31	—	—
Kropff, 2005a (1106)	CTX-Bortez - Dex	2	50	10	—	66	76	10	NR at 10 mo

Palumbo, 2005a (685)	Bortez-MP-Thal	1/2	20	10	10	35	55	—	—
Terpos, 2005a (684)	Bortez-MD-Thal	2	25	8	—	48	56	—	—
Teoh, 2006a (680)	Bortez-Thal-Dex	2	14	43	21	29	93	—	—
Lenalidomide-based									
Richardson, 2006 (316)	Lenalidomide	1	102	0	0	13	17	—	—
Dimopoulos (MM-010), 2005a (688)	Lenalidomide/dex	3	35 1/2	14		44	58	TTP 13.3	—
	Dex	3	35 1/2	4		18	22	TTP 5.1	—
Weber (MM-090), 2006a (689)	Lenalidomide/dex	3	177				59	TTP 11	—
	Dex	3	177				21	TTP 4.7	24
Richardson, 2005a (317)	Lenalidomide	2	222	0	0	25	25	TTP 5.1	>15

Richardson, 2005 (693)	Bortez-Lenalid	1	19	5	5	42	53	—	—
Gerecke, 2005a (692)	Lenalid-pegylated dox-Dex	1/2	6				100	—	—
Baz, 2005a (691)	Pegylated dox-vincristine-Dex-Lenalid	1/2	45	13	11	35	59	—	—
Other									
Munshi, 2002 (327)	ATO	2	14	0	0	7	7	—	—
Hussein, 2004 (328)	ATO	2	23	0	0	0	33[b]	—	—
Abou-Jawde, 2006 (694)	ATO-Dex-AA	2	20	—	—	—	30	10.4	—
Berenson, 2006 (696)	MAC	2	65	2	0	23	26	7	19
Wu, 2005a (695)	ATO-Dex	2	20	0	0	13	13	—	—
Berenson, 2006a (697)	ATO-Bortez-AA	1/2	22	9	0	9	18	—	—

Baz, 2006a (456)	Dex/ATO/ Thal/AA	2	16	0	0	25	25	9.4	—

AA, ascorbic acid; ATO, arsenic trioxide; Bortez, bortezomib; CDT, cyclophosphamide, dexamethasone, thalidomide (several different schedules); CR, complete response; Dex, dexamethasone; EFS, event-free survival; IFN, interferon; Lenalid, lenalidomide; MAC, melphalan, ATO, AA; MD, melphalan, dexamethasone; mo, months; MP, melphalan, prednisone; MPT IV, intravenous melphalan, prednisone, thalidomide; N, number of patients; NR, not reached; OR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; Retro, retrospective analysis; TDD, thalidomide, pegylated doxorubicin, dexamethasone; T-DVD, thalidomide, pegylated doxorubicin, vincristine, dexamethasone; T-DVd, T-DVD, but low dose dexamethasone; Thal, thalidomide; TTP, time to progression; VGPR, very good partial response; y, years.
[a]Abstract only.
[b]Minimal response.

Most programs also include corticosteroids. Two exceptions are the protocols of Hovenga et al. (671) and Offidani (670). Hovenga et al. (671) treated 38 patients with continous low-dose cyclophosphamide (100 to 150 mg) and thalidomide (maximum dose of 400 mg). Median doses of thalidomide and cyclophosphamide were 100 and 95 mg/day, respectively. Sixty-four percent of patients achieved a response (with 11% CR). With a median follow-up of 22 months, median PFS and OS were 30 and 20 months, respectively. The most common side effects were drowsiness, neurotoxicity, and constipation with grade 3–4 rates in 20, 16, and 13% of patients, respectively. One patient developed a DVT. Two patients died after grade 4 infections. One patient developed secondary acute myeloid leukemia. Offidani et al. (670) treated 27 patients with nightly thalidomide (100 to 600 mg) and melphalan 0.2 mg/kg/day for 4 days every 28 days until maximum response or toxicity. Overall response rate was 60%, including 12% complete responses. At a median follow-up of 15 months, both the 2-year PFS and OS were 61%. The main side effects were constipation (82%), somnolence (41%), fatigue (22%), sensory peripheral neuropathy (56%), deep venous thrombosis (11%), and grade 3 leukopenia (30%). However, no severe infections occurred. Moehler et al. added etoposide to thalidomide, cyclophosphamide, and dexamethasone and reported a 68% response rate in relapsed and refractory patients (674); this program was associated with a 36% rate of severe infections.

DT-PACE is a combination of five drugs (Table 99.3) and is an integral part of Total Therapy 2 and 3, piloted by Barlogie and colleagues at the University of Arkansas. Lee et al. (672) described their experience using this combination in 236 previously treated patients prior to stem cell collection. Nearly two thirds (*n* = 148) had shown progressive disease after their prior therapy. After two to four cycles of DT-PACE, of the 229 evaluable patients, 21 patients achieved a CR, 29 patients a nCR, and 44 patients a PR. Response was not affected by chemosensitivity to preceding chemotherapy. The most common grade 3–4 toxicities were myelosuppression (39%), neutropenic fever (9%), nausea and vomiting (6%),

stomatitis (4%), and thromboembolism (5%). Treatment-related mortality was 4%. Of note, before routine thrombosis prophylaxis, thromboembolic events occurred in 37% of cycles (one third of which were line-associated thromboses).

Offidani et al. (673) treated 50 previously untreated patients with ThaDD, a combination of thalidomide (100 mg daily), pegylated liposomal doxorubicin (40 mg/m^2 on day 1 every 28 days), and dexamethasone (40 mg PO on days 1 to 4 and 9 to 12). Twenty-six percent of patients achieved a complete response, 6% a near-complete response, 6% a very good partial response, and 38% a partial response, for an overall response rate of 76%. The median event-free survival was 17 months, and the median overall survival has not been reached. Grade 3 nonhematologic toxicity occurred in 12% of patients, thromboembolic disease in 12%, and severe infection in 16%.

Hussein et al. (454) treated 55 patients with DVd-T (same as Offidani, except that dexamethasone was given on only 4 days per cycle) for a maximum of eight cycles, followed by maintenance with maximum tolerated doses of thalidomide plus alternate-day oral prednisone. Though response rates were high (OR 75%, with 20% CR), there was substantial toxicity associated with the program. Grade 3–4 toxicities included thromboembolic events in 25%, peripheral neuropathy in 22%, neutropenia in 14%, pneumonia in 12%, palmar/plantar erythrodysesthesia in 8%, and thrombocytopenia in 5%. The median PFS was 15.5 months, and the OS was 39.9 months.

Bortezomib-Based

Therapies for Relapsed or Refractory Disease. Single-agent response rates in relapsed/refractory myeloma range from 28 to 38%, with a median response duration of 8 months (319,320,321,322) (Table 99.16). In vitro, there is significant synergy between bortezomib and both chemotherapy (675) and ionizing radiation (676). Clinical trials exploiting this synergy are beginning to emerge and are described in the following.

Orlowksi et al. (44,677) treated 24 patients in their Phase I trial of bortezomib plus liposomal doxorubicin. Sixty-seven percent of their patients achieved a PR or better, with a CR rate of 21%. Grade 3 or 4 adverse events seen in at least 10% of patients included thrombocytopenia (43%), lymphopenia (40%), neutropenia (17%), fatigue (14%), pneumonia (14%), peripheral neuropathy (12%), febrile neutropenia (10%), and diarrhea (10%).

Zangari et al. (678,679) have preliminarily reported their experience with bortezomib, thalidomide, and dexamethasone (VT + D). In a Phase I trial with a 2 ×2 design, they escalated bortezomib and thalidomide doses. If no partial response was seen after three cycles of VT, dexamethasone was added (20 mg the day of and after bortezomib dosing). The overall response rate was 55%; EFS and OS were 9 and 22 months, respectively. Myelosuppression was the most common grade 3–4 toxicity. Peripheral neuropathy worsened above baseline in 5 to 9% of these heavily pretreated patients. In another study presented in abstract form, addition of bortezomib to thalidomide and dexamethasone increased the complete response rate from 7.7 to 42.9% (680).

Ciolli et al. (681) explored the regimen LD-VTD (Velcade/bortezomib 1.0 mg/m^2 on days 1, 4, 8, and 11 every 28 days; dexamethasone 24 mg on days 1, 2, 4, 5, 8, 9, 11, and 12; and thalidomide 100 mg each evening) for up to eight cycles. Patients received therapeutic warfarin as DVT prophylaxis. The overall response rate was 41%, with 11% of patients achieving a CR. After a median follow-up of 11 months, 6 patients had died.

Reece et al. (682) have treated 16 patients with bortezomib, cyclophosphamide, and prednisone as part of an ongoing Phase I study. Preliminary information suggests that there is activity with this program. So far, the overall response rate is 31%, including one patient with a near-complete response.

Berenson et al. (683) have treated 35 patients with relapsed, refractory myeloma in a Phase I/II trial combining bortezomib and melphalan. Their maximum tolerated dose is a maximum of eight 28-day cycles of bortezomib 1.0 mg/m^2 on days 1, 4, 8, and 11, and melphalan 0.1 mg/kg on days 1 through 4. The overall response rate was 47%, including a combined CR/VGPR rate of 15%. The authors emphasize that five of the six patients treated had a response to therapy. The main side effects were severe myelosuppression, fatigue, and peripheral neuropathy. Patients have suffered from nausea, vomiting, diarrhea, constipation, fever, and rash.

Terpos et al. (684) have treated 31 patients with relapsed or refractory myeloma with VMDT, a combination of bortezomib (1.0 mg/m^2 on days 1, 4, 8, and 11), melphalan (0.15 mg/kg on days 1 to 4), dexamethasone (12 mg/m^2 on days 1 to 4 and 17 to 20, and thalidomide (100 mg daily). Patients were treated for up to eight 28-day cycles. In their preliminary report on 25 of these patients, 56% achieved an objective response, including 8% with a complete response. Adverse events included fatigue (56%), thrombocytopenia (12% grade 3/4), neutropenia (8% grade 3/4), anemia (8% grade 3), neuropathy (48% grade 1/2, no grade 3/4 observed), infections (36%, including two herpes zoster cases), and hyponatremia (12%). No patient experienced a DVT, while two patients died as a result of sepsis.

In a Phase I study, Palumbo et al. (685) treated 20 patients with VMPT, a combination of oral melphalan (6 mg/m^2 on days 1 to 5), prednisone (60 mg/m^2 on days 1 to 5), and thalidomide (100 mg continuously) with dose escalations of bortezomib (dose levels ranging from 1 to 1.6 mg/m^2 administered on days 1, 4, 15, and 22 of each 5-week cycle). A full course was defined as six cycles. Ten patients had a response, including two complete responses, one near-complete response, and seven partial responses. Herpes zoster was a common complication without acyclovir prophylaxis.

Other interesting combinations being explored include samarium Sm153 lexidronam (a bone-seeking radionuclide) and bortezomib (686); and the combination of bortezomib, melphalan, and pegylated doxorubicin (687).

Lenalidomide-Based Therapy for Relapsed or Refractory Disease

. Using lenalidomide as a single agent, ~18 to 25% of relapsed or refractory patients achieved a partial response, and the median duration of response for responding patients was 20 months (316,317) (Table 15). In a randomized Phase II trial of lenalidomide, the addition of dexamethasone (40 mg on days 1 to 4 and 15 to 18) for patients not responding to 2 months of lenalidomide resulted in partial response rates in an additional 22% of patients (316). The combination of lenalidomide and dexamethasone has been studied in two large Phase III trials (688,689). The results of the two trials were comparable, with 59% of patients responding to the combination, including a 14% complete response rate. This was significantly better than what was observed with single-agent dexamethasone (PR 22.5% and CR 2%). In addition, both time to progression (11 to 13 months vs. ~5 months)

and overall survival (not reached vs. 24 months) were superior in the lenalidomide/dexamethasone arm. A subgroup analysis was performed to assess the effect of prior therapy with thalidomide (690). Regardless of whether thalidomide had been used previously, the lenalidomide/dexamethasone arm outperformed dexamethasone on all metrics. However, there was a trend toward better lenalidomide/dexamethasone performance in patients who had not received prior thalidomide: CR (17.6 vs. 8.1%); and TTP (13.6 vs. 8.5 months).

Baz et al. (691) have treated 45 relapsed, refractory patients who were evaluable for response with DVd-R (standard DVd plus lenalidomide 10 mg daily) for four to six cycles, followed by lenalidomide and prednisone. Six had a CR (13%), 5 had a nCR (11%), and 16 had a PR (35%). Most common toxicities were myelosuppression, infection, and thromboembolic events. With a median follow-up of 7.3 months, 23 patients progressed and 16 died.

A number of combinations are being explored, including lenalidomide, doxorubicin, and dexamethasone (692); and lenalidomide, bortezomib, and dexamethasone (693). Both combinations are showing evidence of activity.

Arsenic Trioxide Combinations for Relapsed or Refractory Disease

As a single agent, arsenic trioxide (ATO) results in partial response rates of about 7% (327); if 25% reduction in the M-protein concentration is included as “response,” the rates are as high as 33% (328) (Table 99.15). The combination of dexamethasone, ATO, with and without ascorbic acid, resulted in response rates of 30 (694) and 13% (695), respectively. Melphalan, ATO, and ascorbic acid (MAC) provided a 26% response rate (696). Early results with other combinations are shown in Table 99.16 (456,697).

Other Agents for Relapsed or Refractory Disease

Interferon has been shown to modulate the multidrug resistance phenotype and to reinduce chemosensitivity in patients with chemoresistant multiple myeloma. In one study, nonresponding patients received the same chemotherapy to which they were resistant, preceded by a 5-day course of interferon. An objective response was achieved in 4 of 14 patients (28.6%) (698).

Several investigators have combined interferon with dexamethasone (402,699) or methylprednisolone (700) as therapy for patients with relapsed or refractory disease. With response rates of 29 to 66% (699,700) it is difficult to isolate the corticosteroid and interferon effects. There is no clear evidence that the response rate or the survival time improved compared with similar treatments without interferon (655).

Because patients with multiple myeloma refractory to alkylating agents frequently express P-glycoprotein, which is associated with the multidrug resistance phenotype, cyclosporine, a multidrug resistance reversal agent, has been combined with VAD in patients with refractory or progressive disease. No benefit was observed (701,702). As a result of the findings of a Phase I/II trial in patients with myeloma (703), PSC 833, a multidrug-resistance glycoprotein modulator, has been incorporated into a small Phase III study of VAD versus VAD and PSC 833 in the relapsed/refractory setting (704). There was no difference in response rate, progression-free survival, or overall survival in the PSC 833 arm, though there was more toxicity.

The human anti-CD20 antibody has demonstrated some effect in patients with myeloma. About 20% of patients with myeloma have CD20 expression on their plasma cells. In one study, 1 of 19 patients had a partial response to therapy; an additional 5 had stable disease (705).

Because vascular endothelial growth factor has been shown to be involved in myeloma pathogenesis (706), several investigators have evaluated different anti-VEGF therapeutic strategies. Somlo et al. (707) have explored the role of the anti-VEGF antibody rhuMAB bevacizumab versus bevacizumab and thalidomide in a randomized Phase II trial. Twelve patients have been enrolled. Median time to progression for the 6 patients treated with bevacizumab alone was 2 (range 1 to 4) months. Progression-free survival for the 5 evaluable patients treated with bevacizumab and thalidomide was 6 +, 7, 8 +, 10, and 30 + months, with 2 patients still on study and in response. Zangari et al. have evaluated SU5416, a small-molecule VEGF receptor-2 inhibitor, in 27 patients with myeloma in a multicenter Phase II study (708). Grade 3/4 toxicities were rarely observed; the most frequent was thrombocytopenia (12%). There were three thromboembolic episodes and five cases of new-onset hypertension. There were no objective responses, and overall median survival was 42 weeks (range, 3 to >92 weeks). A decrease in median VEGF plasma levels was observed in patients with stable disease (n = 7) compared to patients with progressive disease (n = 5).

The Hsp 90 chaperone inhibitor 17-AAG is showing promise in combination with bortezomib in myeloma patients. In a Phase I trial, Chanan-Khan et al. treated 20 patients (709). Of the 12 bortezomib-refractory patients, one patient had a near-complete response and another five had a 25% reduction in their serum M protein.

Radiation Therapy

As early as the mid-1920s there was recognition that external-beam radiation therapy could promote immediate relief of pain, healing of pathologic fractures, and resolution of extramedullary plasmacytomas (25,710,711). Until the 1950s, radiation therapy was the only effective treatment available for the management of plasma cell tumors. With the advent of systemic chemotherapy, indications for irradiation were primarily palliation of bone pain and solitary plasmacytomas. Concern for maintaining bone marrow reserve also constrains the use of radiation in patients with multiple myeloma. Sykes et al. (712,713) showed that radiation has long-term effects on the bone marrow; the majority of patients receiving concentrated local doses of 3,500 cGy or more showed persistent localized marrow aplasia. One must administer enough radiation to provide palliation, without jeopardizing opportunities for further systemic therapy. In a retrospective review, Norin (714) has found that objective improvement was lacking when the tumor dose was below a cumulative dose (single-dose equivalent) of 1,000 cGy. For palliation, the recommendation is therefore a cumulative dose of 1,500 cGy, corresponding to a tumor dose of 3,400 cGy, in 10 to 15 fractions (714,715). Leigh et al. (716) recommended a total cumulative dose of 1,000 cGy in these same patients. There is controversy as to whether the duration of response correlates with the radiation dose in myeloma patients (716,717).

In contrast, the conventional wisdom has been that patients with solitary plasmacytoma of bone should receive higher doses in an attempt at cure. Although the optimal dose has not been established by randomized controlled trials, 4,000 to 5,000 cGy encompassing all

disease with a margin of normal tissue is recommended by most experts (718,719,720). A recent study of 203 patients with solitary plasmacytoma of bone has brought this principle into question (721). These authors found that therapeutic doses >3,000 cGy had no bearing on local control.
P.2407

Radiation can often spare patients from undergoing surgery (722). In a recent retrospective analysis of 35 cases of patients with cervical lesions and spinal instability, it was found that 19 of the 20 patients experienced resolution of pain, 15 of whom received radiation alone. Of the 10 patients with sufficient follow-up data, none showed clinical progression of instability.

Sequential Half-Body (Hemibody) Irradiation

The first report of using whole-body irradiation to treat myeloma was by Medinger and Craver (723) in 1942. Partial or complete relief of pain was noted in the majority of patients. Once effective systemic chemotherapy came into wide use, this approach became less popular until 1971, when Bergsagel (724) postulated that sequential hemibody radiation could be a means of debulking tumor. He suggested that if a dose of ~725 cGy were given to the upper half of the body and 1,000 cGy to the lower half, a theoretical 3-log kill could be achieved and survival prolonged. After a series of retrospective studies (606,725,726,727,728,729,730,731,732) and a randomized study (390,733) evaluating its role in the earlier phases of myeloma, hemibody irradiation has once again fallen out of favor. In patients who have end-stage disease, with poor pain control, this treatment may still be important.

The majority of series involving hemibody or sequential hemibody radiation are retrospective and include patients who were either resistant to or relapsing from alkylator-based therapy. Significant relief of bone pain occurred in 80 to 90% of patients (606,725,726,727,728,729,730,731,732), and the median duration of survival was 5 to 11 months (715,727) Objective biochemical response occurred in 25 to 50% of patients (606,727,734). Pain relief typically occurred 1 to 2 days after institution of therapy, with a maximal response in 1 to 2 weeks (725). The most common side effects were moderate myelosuppression, pneumonitis, nausea, vomiting, diarrhea, and stomatitis (715,725). If an oral lead shield was not used, mucositis also occurred (715). Nadirs occurred within 3 weeks (727), and white cell count and platelet count recovery occurred by about 6 weeks (715,727). Decrements in pulmonary function occurred in about half of the treated patients (715). The most serious complication was radiation-induced pneumonitis, which was seen in 14% of patients (727). The option of sequential half-body radiation therapy must be balanced against unpredictable and varying degrees of pancytopenia and alternative treatment options (734).

Bergsagel's postulate (724) and preliminary data from several small studies (726,730,731) led two cooperative group studies (SWOG 8229 and CALGB 8003) to incorporate systemic radiation therapy as consolidation therapy (390,733). Neither study demonstrated a meaningful advantage to patients receiving adjuvant hemibody radiation (390,733), and

hemibody radiation is used only for pain palliation in end-stage chemotherapy-refractory myeloma patients.

Pathogenesis, Pathophysiology, and Prognosis

Pathogenesis and prognosis will be covered together, because in many instances there is an intimate relationship between them. To date no single molecular defect can account for the pathogenesis of multiple myeloma, though using single-nucleotide polymorphisms and gene expression profiling, several candidate genes have been identified as being different between MGUS and MM (735,736). Malignant plasma cells are long-lived cells, typically with low proliferative rates and labeling indices (199,737). A postgerminal cell of origin is indicated by their somatically hypermutated, rearranged immunoglobulin genes (738). A multitude of abnormalities has been identified in signaling pathways, apoptotic mechanisms, the bone marrow microenvironment, and the cell cycle. Factors including the level of gene expression, protein expression, and gene product phosphorylation status of cell-cycle molecules may all be relevant for the propagation of the malignant plasma cells. Extracellular signaling alterations include changes in stromal cell, osteoblast, osteoclast, vessel endothelial cell, and immune cell interactions. These changes may in turn result in activation, adhesion, and cytokine production that fuel myeloma cell proliferation and survival (Fig. 99.13).

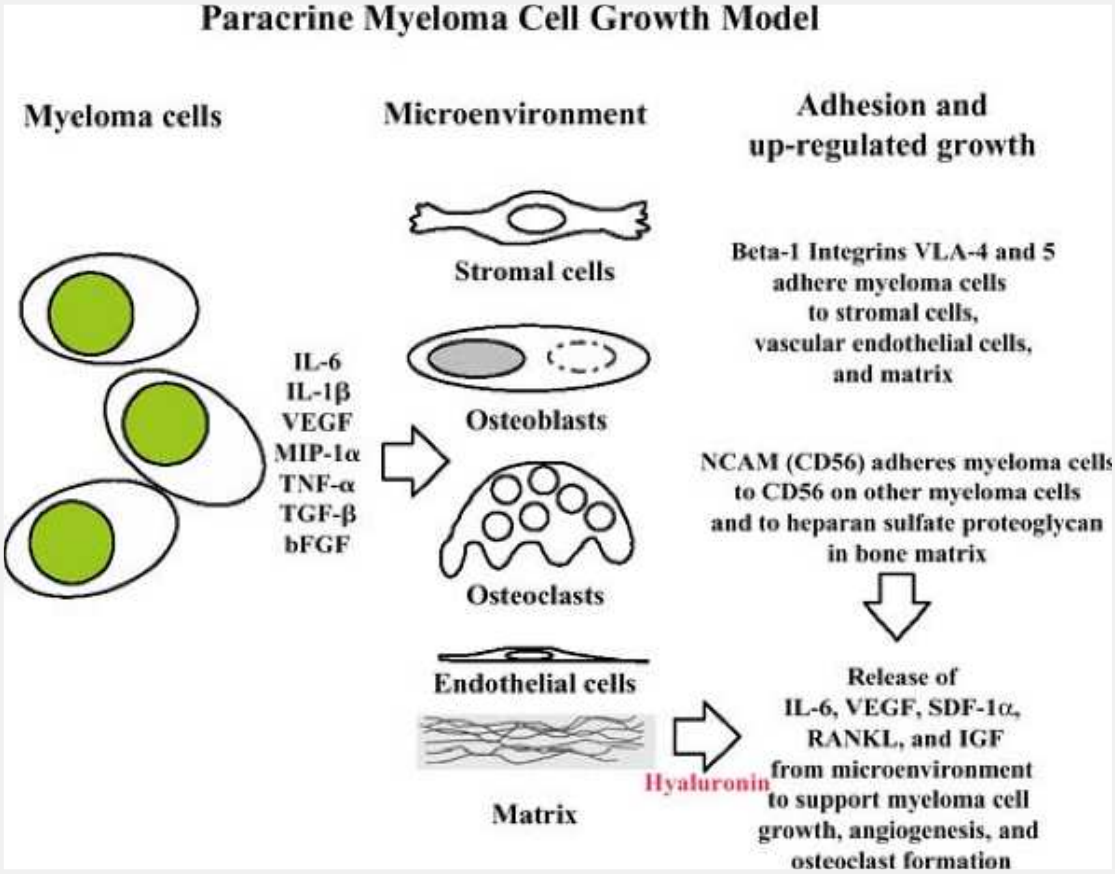

Figure 99.13. Putative pathogenic mechanisms in myeloma. IGF, insulinlike growth factor; IL, interleukin; MIP, macrophage inflammatory factor; MMP, metalloproteinase; NCAM,

neural cell adhesion molecule; TNF, tumor necrosis factor; VEGF, vascular-derived endothelial growth factor; VLA, very late antigen.

Bone Marrow Microenvironment

There is a synergistic, pathologic relationship between myeloma cells and the cells comprising the bone marrow microenvironment, including fibroblasts, osteoblasts, and osteoclasts. The stromal cells in the marrow of myeloma patients produce high levels of interleukin-6 (IL-6) in vitro (739). The IL-6 serves as a growth and survival factor for benign and malignant plasma cells, which produce IL-1β (740,741), VEGF, and macrophage inflammatory protein-1α (MIP-1α) (742,743). In turn, IL-1β and MIP-1α regulate and activate osteoclasts (740,744,745).

A cell adhesion molecule belonging to the immunoglobulin superfamily, CD56 (N-CAM), is strongly expressed in most plasma cells of myeloma patients (746) and is believed to play a role in myeloma homing and cell adhesion to the marrow. Increased levels of the adhesion molecules lymphocyte function–associated antigen (LFA)-3 (212), LFA-1 (CD11a) (747), and very late antigen-4 (VLA-4) are expressed on the myeloma cells in the majority of patients. VLA-4 may act to bind myeloma cells to fibronectin in bone marrow (748), which under appropriate conditions can significantly increase IL-6 production by stroma (749). Cell–cell contact between marrow stromal cells and myeloma cells via VCAM-1 and $\alpha_4\beta_1$-integrin enhances production of osteoclast-stimulating activity (750). Hyaluronan, a glycosaminoglycan component of the bone marrow extracellular matrix, appears to be a survival and proliferation factor for myeloma cells (751). Notch receptors are expressed in early hematopoietic stem cells, and Notch ligands are expressed on bone marrow stem cells (BMSCs). Myeloma cells expressing Notch receptors are activated by the BMSC Notch ligand, protecting the myeloma cells from drug-induced apoptosis. In addition, this interaction also activates Notch signaling in BMSCs, leading to secretion of IL-6, VEGF, and IGF-1 (752).Cell-adhesion drug resistance (CAM-DR) is a well-recognized entity (753).

The endothelial microvascular environment has also been shown to be important in multiple myeloma biology (201). There

is a high correlation between the extent of bone marrow angiogenesis, evaluated as microvessel area, and the proliferating (S-phase) fraction of marrow plasma cells in patients with multiple myeloma and in those with MGUS (201,754,755). VEGF plays an important role in angiogenesis by acting as a potent inducer of vascular permeability as well as serving as a specific endothelial cell mitogen. Plasma cells in the bone marrow from multiple myeloma patients express VEGF (756,757), which can thereby interact with the Flt-1 and KDR high-affinity VEGF receptors that are highly expressed on bone marrow myeloid and monocytic cells surrounding the tumor (754).

Investigators are beginning to understand the complex interactions between osteoclasts, osteoblasts, and myeloma cells. The receptor activator of NFκB (RANK), which is found on osteoclasts, interacts with RANK ligand (RANKL) found on osteoblasts and bone marrow stromal cells. These interactions contribute to bone destruction (758). Myeloma cells also prevent differentiation of osteoblasts through secretion of the Wnt-signal antagonist DKK1

(759). MIP-1a is produced by myeloma cells and serves as an inducer of osteoclast formation (760). In turn, osteoclasts produce a number of factors that stimulate myeloma cells, including IL-6 (141).

Cytokines and Cell Signaling

The search for a growth factor for myeloma cells culminated in the identification of IL-6, formerly known as B-cell growth factor or hybridoma growth factor (761). IL-6 is among the most important proliferation and survival factors in myeloma (762). Predominantly produced by bone marrow stromal cells—macrophages, fibroblasts, osteoblasts, osteoclasts, and monocytes (Fig. 99.13) (763)—it serves as a growth factor and as an antiapoptotic factor (764,765,766,767). In the majority of cases, myeloma cells and cell lines are capable of producing IL-6 and the IL-6 receptor, resulting in autocrine stimulation (764,765,766,767). IL-6 transmits messages intracellularly through the signal-transducing protein gp130, which can activate two pathways: the JAK-STAT pathway (768) and the Ras-MAP kinase pathway (769). Through the former pathway, which includes JAK-2 and STAT3, the antiapoptotic proteins Mcl-1 (768) and Bcl-X_L (770) are up-regulated; through the latter pathway, transcription factors such as ELK-1, AP-1, and NF-IL-6 (768) are up-regulated. NF-κB (771) and IL-6 (772,773) may also mediate the observed increase in the antiapoptotic proteins Bcl-2 (774,775), Mcl-1 (772), and Bcl-X_L (772,773,776,777). The overall effect of these pathways is prevention of apoptosis and enhancement of multiple myeloma proliferation. In addition, the constitutive activation of STAT3 may also be important in the pathogenesis of multiple myeloma, independent of IL-6 (778). Moreover, CD40 activation of myeloma cells can alter the cell surface phenotype, triggering autocrine IL-6 secretion regulating myeloma cell cycle in a p53-dependent fashion (779).

Other cytokines and growth factors produced by myeloma and stromal cells that maintain myeloma growth (780) include IL-1β (781,782,783), VEGF, insulinlike growth factor (IGF) (784,785,786,787,788,789), and tumor necrosis factor-α (790,791). Aberrant expression of IL-1β may be a critical step in the transition of MGUS to multiple myeloma (740,783). IL-1β up-regulates production of IL-6, changes expression of cell adhesion molecules, and has been shown to have osteoclast-activating factor activity. Although IL-1β does not stimulate myeloma cell proliferation directly, by virtue of its effect on stromal cells in the marrow it induces production of IL-6 (741) and IL-8 (792). Myeloma cells are capable of expressing and secreting VEGF and responding to the cytokine in an autocrine fashion (742,743). Moreover, stromal and microvascular endothelial cell exposure to VEGF induces an increase in IL-6 secretion (742), which then further stimulates myeloma cells. The precise role that basic fibroblast growth factor (bFGF), another potent angiogenic factor, plays in the growth of myeloma cells is under active investigation (793). Higher bFGF levels have been found in more advanced stages of multiple myeloma (793). IGF, which is believed to signal through the phosphatidylinositol-3′-kinase (PI-3K) pathway (784), is capable of directly stimulating myeloma cell growth and enhancing myeloma cell responsiveness to IL-6 through mitogen-activated protein kinase (787) and also inhibiting apoptosis by increasing expression of BAD (784).

Cell Cycle

Regulatory signals underlying proliferation of myeloma cells include increased cyclin D1 expression, hypermethylation of the cyclin-dependent kinase (CDK) pathway regulatory

gene p16 (794), mutations of the *ras* oncogene (795,796), loss of *p*53 (795,796), and possibly overexpression of c-*myc* in progressive disease (797).

Approximately one–third of myeloma patients have up-regulation of cyclin D1 by immunohistochemistry; the plasma cells of these same patients tend to have higher proliferative rates (798). The t(11;14) (q13;q32) translocation, which juxtaposes the immunoglobulin heavy-chain promoter and the cyclin D1 gene, is seen in ~25% of multiple myeloma patients (799,800,801,802,803). Bergsagel et al. have postulated that activation of one of the three cyclin D genes is an initiating event in myeloma (804).

Both p15 and p16 are important cell cycle inhibitors that suppress cell proliferation through inhibition of CDK4 or CDK6 or both, thereby preventing the phosphorylation of the retinoblastoma gene (*RB*). Although large deletions of p15 and p16 are rare in myeloma (0 to 12% of cases) (805,806,807), selective methylation of these genes, a form of transcriptional inactivation, occurs in as many as 67 and 75% of cases, respectively (808,809,810). Most data, including our own (811,812) suggest that hypermethylation of p16 or p15 is associated with disease progression (811,812).

K- and N-*ras* mutations have been described in 25 to 100% of newly diagnosed multiple myeloma patients (796,813,814), depending on the technique used for detection. A *p*53 tumor-suppressor gene deletion is present in less than one third of plasma cells from newly diagnosed myeloma patients (815), and mutations are even less common (816,817,818,819). The c-*myc* protein and c-*myc* RNA are overexpressed in ~25% of multiple myeloma patients (820,821). Rearrangements of c-*myc* gene are present in ~15% of patients with multiple myeloma or primary PCL (822). Dysregulation of c-*myc* appears to be caused principally by complex genomic rearrangements that occur during late stages of multiple myeloma progression (797).

Prognosis and Staging

Survival of multiple myeloma patients varies from months to more than a decade (589,823). There are no precise methods of identifying the subset of newly diagnosed patients who are best served by standard-intensity therapies, by maintenance therapies, by novel therapies, or by more intensive regimens such as hematopoietic stem cell transplantation. Prognostic factors are needed for patient counseling, therapeutic decision making, and clinical trial stratification.

Staging is one form of prognostic modeling. The Durie-Salmon system (Table 99.17), which until recently was the most widely accepted multiple myeloma staging system, separates patients predominantly by tumor burden and renal function (28). As the biology of myeloma is better understood, novel markers reflecting myeloma cell kinetics, signaling, genetic aberrations, and apoptosis have eclipsed the prognostic significance of tumor burden as a predictor of survival.

Although the Durie-Salmon system has some prognostic utility (28), other biologic variables appear to be more valuable (388,824,825,826,827,828,829,830). At the time of its inception, the Durie-Salmon staging system was an elegant system that incorporated information about immunoglobulin production and half-life, hemoglobin, calcium, creatinine, and extent of bone disease to derive

mathematically the total myeloma cell burden (28). Quantification of bone lesions used in this staging system, however, is not always reliable as a prognostic factor (827) in that patients classified as stage III solely on the basis of bone lesion criteria do not have a poorer prognosis.

Table 99.17 Durie-Salmon Staging System

Criterion	Measured Myeloma Cell Mass (cells× $10^{12}/m^2$)
Stage I	
All of the following: Hemoglobin >100 g/L Serum calcium <12 mg/dl On radiograph, normal bone structure (scale 0)a or solitary bone plasmacytoma only Low M-component production rates IgG <50 g/L IgA <30 g/L Urine light-chain M component on electrophoresis <4 g/24 hours	<0.6 (low)
Stage II	
Fitting neither stage I nor III	0.6–1.2 (intermediate)
Stage III	
One or more of the following: Hemoglobin <85 g/L Serum calcium >12 mg/dl Advanced lytic bone lesions High M-component rates High M-component rates IgG >70 g/L IgA >50 g/L Urine light-chain M component on electrophoresis >12 g/24 h	>1.2 (high)
Subclassification	

A: Serum creatinine <2 mg/dl B: Serum creatinine ≥2 mg/dl	

[a]Scale of bone lesions: normal bones, 0; osteoporosis, 1; lytic bone lesions, 2; and extensive skeletal destruction and major fractures, 3.
From Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975;36:842–854.By permission of the American Cancer Society.

Other variables, including patient age, performance status, serum albumin, immunoglobulin isotype, and bone marrow plasma cell infiltration, have long been recognized to predict survival (831,832), and subsequent models have incorporated these factors (253,589,830,833) (Table 99.18). Myeloma biology is better addressed by increased concentrations of serum β_2-M, C-reactive protein, circulating plasma cells by peripheral blood labeling index, other serum markers, bone marrow PCLI, and chromosomal abnormalities (388,824,825,828,829,830). When designing a new staging system, one must choose between readily available, inexpensive markers, which frequently describe the host more than the intrinsic properties of the myeloma, or more esoteric, expensive markers, which reflect the intrinsic biology of the individual patient's myeloma cells. Each of these systems has value, but the goal is to reach a consensus and to standardize discussions and comparisons among clinical trials and outcomes. An international consensus panel has addressed this issue and developed the International Staging System (ISS) for multiple myeloma; it incorporates serum albumin levels and β_2-microglobulin (491). Though this staging system satisfies the former condition—it is inexpensive and readily available—it does not get to the heart of myeloma cell biology as genetic changes do. Investigators in the myeloma community have preferred several genetic classification systems; the next step will be to arrive at a consensus system for this as well. With these basic concepts in mind, various prognostic markers will be discussed independently, and Tables 99.18 and 99.19 summarize several investigators' efforts to introduce more meaningful staging systems.

Individual Prognostic Markers

β_2-Microglobulin

β_2-M concentration is the strongest and most reliable prognostic factor for multiple myeloma that is routinely available (Table 99.18). It depends not only on tumor burden but also on renal function. Elevated β_2-M values predict early death (825,828,834). Formulas to correct the β_2-M concentrations for the effects of renal insufficiency have not improved its predictive value (835); the β_2-M value is still prognostic in myeloma patients with normal renal function (824). β_2-M value also predicts high-dose therapy outcome (i.e., event-free and overall survival) (245,837,838,839,840,841). However, the British Medical Research

Council has shown that after 2 years of survival, the initial β_2-M concentration loses its prognostic value (836).

C-Reactive Protein

French investigators first showed that C-reactive protein was useful as a univariate and multivariate (828) prognostic marker in multiple myeloma (Table 99.18). These findings were substantiated in groups of patients from the Mayo Clinic (825). C-reactive protein values also predict high-dose therapy outcome (803). However, C-reactive protein concentration does not appear to be useful as a marker of disease status (842).

Lactate Dehydrogenase

Increased lactate dehydrogenase values identify a group of patients with poor prognosis and aggressive disease, sometimes a lymphomalike disease characterized by tumor masses and retroperitoneal adenopathy with a short clinical course (843,844,845). Only 7 to 11% of patients with newly diagnosed myeloma have an increased concentration of LDH (132,845).

Bone Marrow Plasma Cell Number and Morphology

The quantity, growth patterns, and morphologic features of bone marrow plasma cells have been evaluated as prognosticators for patients with myeloma with variable results (833,846,847,848,849). Although the estimation of percent bone marrow plasmacytosis is not always reproducible (846,847), investigators have reported prognostic significance (833,849). Bartl et al. (833) constructed an intricate study of bone marrow characteristics of myeloma patients (Table 99.18). The architectural pattern of growth—including interstitial, interstitial/sheets, interstitial/nodular, nodular, and packed—correlates with survival (833,849), as does the plasma cell morphology (833). According to Bartl et al. (833), myeloma cell histologic features can be classified into six types: (a) Marschalko type—predominantly normal-appearing plasma cells with a mean size of 21 µm; (b) small cell type—small, round, and lymphoplasmacytoid with a mean size of 13 µm; (c) cleaved type—notched, cleaved, or even convoluted nuclei of variable size; (d) polymorphous type—marked cellular polymorphism and multinuclearity, with interspersed giant plasma cells and cytoplasmic inclusions; (e) asynchronous type—marked asynchronous maturation of the nucleus and cytoplasm, large eccentric nuclei, frequent nucleoli, and a pronounced perinuclear “hof”; and (f) blastic type—plasmablasts with large nuclei, prominent centrally located nucleoli with a moderate rim of basophilic cytoplasm, and a faint perinuclear hof (Table 99.18). Neither of these morphologic features—architecture or plasma cell phenotype—has been applied widely.

Other investigators have demonstrated the powerful prognostic significance of immature or plasmablastic plasma cells (199,200,826,845,850,851,852,853,854). Plasmablastic morphology is associated with a high PCLI, a higher level of sIL-6R, and *ras* mutations (826).

Electron microscopy confirms that immature nuclear morphology and nuclear cytoplasmic asynchrony correlate with one another and with poor prognosis (855). Nuclear immaturity and three cytoplasmic abnormalities—scattered patterns of mitochondria, single-sac looplike structures, and numerous intramitochondrial granules—have been associated with poor outcome.

Table 99.18 Noncytogenetic Prognostic and Staging Systems in Newly Diagnosed Multiple Myeloma Patients (Standard-Intensity Chemotherapy Unless Stated Otherwise)

Study	No. of Patients	Risk or Stage	Patients (%)	Features	OS (mo)
Durie and Salmon, 1980 (28,1107)	150	IA IIA & IIB IIIA IIIB	11 27 50 13	Defined in Table 4.17	61 54 30 15
MRC, 1980 (253)	485	Low	22	BUN ≤8 mM and Hb >100 g/L	>48
		Intermediate	56	Not meeting other criteria	~34
		High	22	BUN >10 mM and Hb ≤75 g/L	~24
Bartl et al., 1987 (833)	674	Low grade	71	Marschalko and small PCa	40
		Intermediate grade	28	Cleaved, polymorphous asynchronous PC	20
		High grade	2	Plasmablastic PC	8
Greipp et al., 1988 (824)	100	Low	30	PCLI <0.4% and β_2-M <4 mg/L	48
		Intermediate	25	PCLI ≥0.4% or β_2-M ≥4 mg/L	29
		High	45	PCLI ≥0.4% and β_2-M ≥4 mg/L	12

Bataille et al., 1992 (828)	162	Low	50	β_2-M and CRP <6 mg/L	54
		Intermediate	35	β_2-M or CRP ≥6 mg/L	27
		High	15	β_2-M and CRP ≥6 mg/L	6
Greipp et al., 1993 (825)	107	Low	14	PCLI <1% and β_2-M <2.7 mg/L	71
		Intermediate	54	PCLI ≥1% or β_2-M ≥2.7 mg/L	40
		High	32	PCLI ≥1% and β_2-M ≥2.7 mg/L	17
San Miguel et al., 1995 (830)	120	Ib	26	REb <6 or SM: ((a–d)=0	>80
		II	52	6 ≤ RE ≤ 8.5 or SM: 0 > ((a–d)≤ 3	36
		III	22	RE >8.5 or SM: ((a–d) ≥4	9
Finnish Leukaemia Group, 1999 (589)	324	I	61	Hb ≥100 g/L and BMPC <70%	57
		II	25	Hb <100 g/L or BMPC ≥70%	45
		III	14	Hb <100 g/L and BMPC ≥70%	25

Crowley et al., 2001 (388)	1,026	I	13	β_2-M <2.5 mg/L	53
		II	43	β_2-M ≥2.5 but <5.5 mg/L	41
		III	33	β_2-M ≥5.5 mg/L and alb >3 g/dl	24
		IV	11	β_2-M ≥5.5 mg/L and alb <3 g/dl	16
International Staging System (491)	8,056	I	29	β_2-M <3.5 mg/L and alb ≥3.5 g/dl	62
		II	38	Not stage I or III	45
		III	33	β_2-M ≥3.5 mg/L	29

Alb, albumin; β_2-M, β_2-microglobulin; BMPC, bone marrow palsma cells; BUN, blood urea nitrogen; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; MRC, Medical Research Council Working Party on Leukaemia in Adults; OS, overall survival; PC, plasma cells; PCLI, plasma cell labeling index; SWOG, Southwest Oncology Group.

[a]See text for details. The Bartl staging system is a plasma cell (PC) morphology–based staging system.

[b]From risk equation (RE) and simplified model (SM): RE: (2.2 * %S phase PC) +(0.8 (β_2-M) +(1.2 * ECOG) + (0.9 * age). SM: (a) S phase ≥ 3% (+2); (b) β_2-M ≥ 6 µg/ml (+1); (c) ECOG ≥ 3 (+1); (d) age ≥ 69 (+1); absence of each (+0).

Plasma Cell Labeling Index

The PCLI of bone marrow plasma cells is a reproducible and powerful prognostic factor in multiple myeloma (824,825,830,856) (Table 99.18). The PCLI is determined from an immunofluorescence slide-based assay (199). Cells in DNA S phase of the cell cycle incorporate bromodeoxyuridine, which can be recognized by using a monoclonal antibody. S-phase cells are then marked with a second antibody, and plasma cells are recognized by morphology and reactivity with antihuman immunoglobulin κ and λ light chains. An increased PCLI predicts a short remission and survival but does not predict response to therapy. All large studies published to date have confirmed the independent prognostic value of the PCLI for survival after treatment with conventional chemotherapy (824,826,851,857) or high-dose therapy (838). Other methods for determining proliferation include Ki67

immunohistochemical staining (858,859), and determination of S phase by flow cytometry (830,860,861). Witzig et al. (862,863) have also demonstrated the prognostic value of the peripheral blood labeling index.

Immunophenotype of Myeloma Cells

As discussed previously, the phenotype of malignant plasma cells is diverse (205,206,207,210,211,213,214) and potentially dynamic (864,865). Investigators have demonstrated that surface expression of CD45, CD56, and CD117 portends a better prognosis (207,209) and expression of CD28 and CD44, a worse prognosis (207,866). Patients with the t(11;14) translocation are more likely to have surface expression of CD56, and CD117. Patients with nonhyperdiploid myeloma have increased expression of both CD20 and CD28 in the absence of reactivity for CD56 and CD117—all poor prognostic findings (207).

Cytogenetics, Fluorescence in Situ Hybridization, and Other Genetic Abnormalities

The first cytogenetic abnormalities in myeloma were documented nearly 30 years ago (Fig. 99.14). In the past decade it has become increasing apparent that cytogenetic testing is an integral element of establishing prognosis and a treatment plan for all newly diagnosed myeloma patients. Nearly all myeloma patients have abnormal chromosomes by fluorescence *in situ* hybridization (FISH), including deletions, aneuploidy, and translocations (867,868), although abnormal karyotypes are seen in only 18 to 30% of cases. This apparent discrepancy is explained by the generally low proliferative rate of myeloma cells and the requirement of obtaining plasma cells (and not just the rapidly dividing normal myeloid

precursors) in metaphase to generate conventional cytogenetics (869,870,871). Therefore, any abnormality in conventional cytogenetics identifies a group with a higher proliferative rate (872) and a particularly poor prognosis. There is an excellent correlation between abnormal conventional cytogenetics and a high plasma cell proliferative rate (873,874). With interphase FISH, several chromosomal abnormalities, such as immunoglobulin heavy-chain translocations and deletion of chromosome 13, are observed at equal frequencies among the spectrum of plasma proliferative disorders from MGUS to multiple myeloma to PCL (875,876).

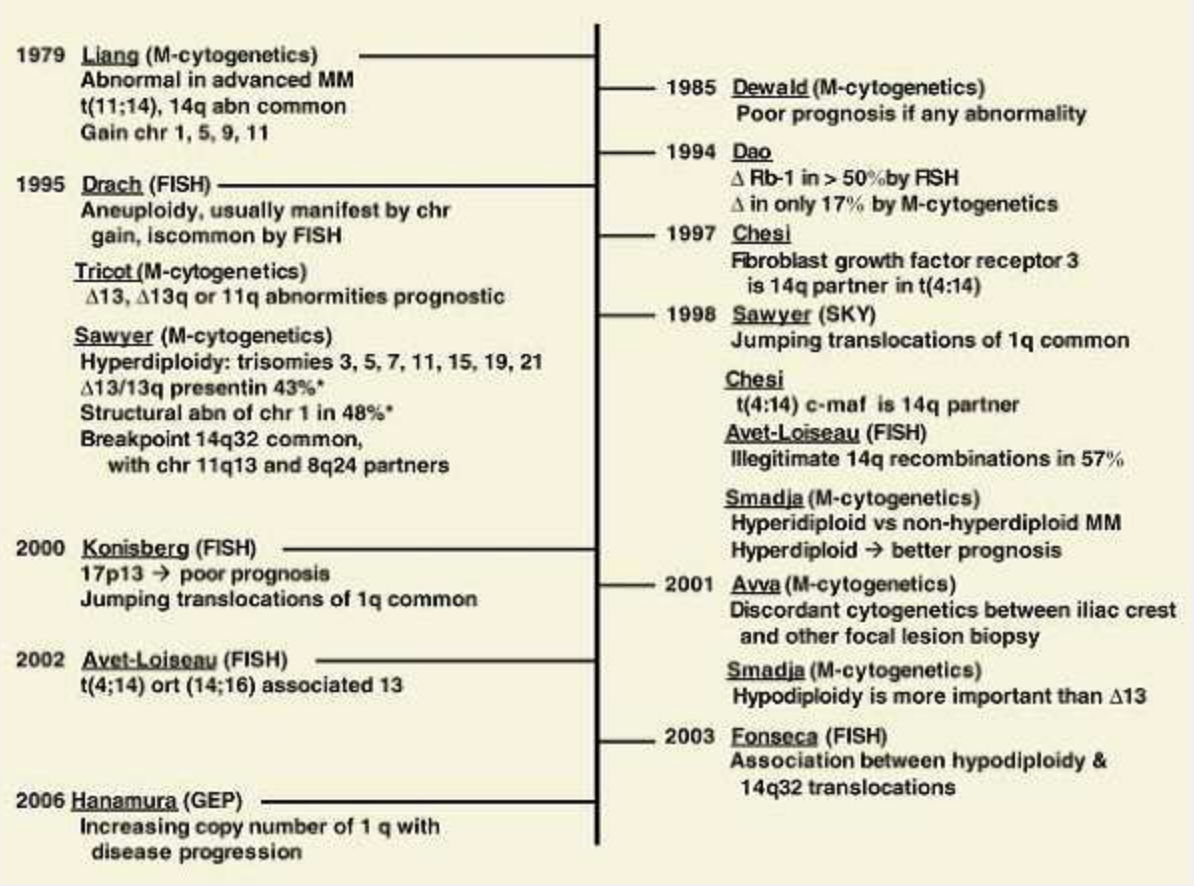

Figure 99.14. History of cytogenetic discovery.

Several “molecular classification” systems have been proposed based on gene expression profiling (877,878,879,880); however, though these systems may unravel the pathogenesis of myeloma, they are not ready for general clinical application. In contrast, cytogenetic classification systems are easily applied in the clinic at present. There is dispute as to which genetic tests should be done. Metaphase cytogenetic and FISH testing each has its own advantages and disadvantages. The added value of metaphase cytogenetics is additional negative prognostic information provided by the ability to generate a plasma cell karyotype—i.e., it captures proliferation in addition to information about ploidy status and specific structural abnormalities. The disadvantage is that certain interstitial abnormalities and translocations may be missed. In contrast, a standard myeloma FISH panel will contain probes for the common translocations and structural abnormalities and will detect them regardless of the proliferative rate of the plasma cells; ploidy status can also be estimated by the trisomy index. FISH, however, provides no information on the proliferative index of the myeloma cells. Ideally, both metaphase cytogenetics and FISH should be done for all newly diagnosed patients, but if the cost is prohibitive, the test that is more readily available should be performed.

Monoallelic loss of chromosome 13 (del 13) or its long arm (del 13q), when determined by metaphase cytogenetics, is a powerful adverse prognostic factor in patients treated with standard chemotherapy (356,829,881) or with high-dose chemotherapy and hematopoietic

stem cell transplantation (331,480,803,882,883) (Table 99.18). Approximately 50% of newly diagnosed multiple myeloma patients have del 13 or del 13q by FISH (874,876,884). Our group has shown that del 13q is associated with specific biologic features, including a higher frequency of λ-type multiple myeloma, slight female predominance, higher PCLI, and a higher frequency of a serum M component of <10 g/L (356). Patients with the deletion by FISH have worse overall survival with standard chemotherapy (356,829,874), high-dose therapy (884,885), and interferon treatment (356). The absence of abnormalities of chromosome 13 and 11 by conventional cytogenetics is associated with longer complete-response duration, event-free survival, and overall survival in patients treated with high-dose therapy (331). The prognostic significance of del 13q by FISH is less than that for del 13 by conventional cytogenetics, because the latter test incorporates both the chromosomal abnormality and a high rate of plasma cell proliferation, whereas the former captures only the chromosomal abnormality.

Hypodiploid myeloma has a worse prognosis than diploid or hyperdiploid myeloma. This has been demonstrated by flow cytometric methods (881,886,887) and metaphase cytogenetics (883,888,889,890,891). Controversy exists about whether the deletion 13q adds any additional prognostic information to a hypodiploid karyotype (888,891,892).

Up to 75% of patients with multiple myeloma have translocations involving the heavy-chain gene on chromosome 14. These translocations include illegitimate switch recombinations of the variable regions of the immunoglobulin heavy-chain gene at 14q32. Partners of the translocations into the IgH switch region on chromosome 14 include chromosomes 11, 4, 6, and 16 (893). The most common translocation in multiple myeloma is t(11;14) (q13;q32) (870,892), which increases expression of cyclin D1 (802), a protein involved in cell-cycle progression. The prevalence of t(11;14) (q13;q32) is 20% in multiple myeloma (870,892,894). Previous publications had suggested that this translocation was associated with an adverse outcome in multiple myeloma (803,829), but more recent data refute this hypothesis (894). The t(6;14) (p21;q32) is also associated with a neutral prognosis (895). The t(4;14) (p16.3;q32) is present in 15% of multiple myeloma patients (896,897,898,899,900). This translocation results in the up-regulation of fibroblast growth factor receptor 3 (FGFR3) and in the hybrid transcript IgH/MMSET (896,897). The t(14;16) (q32;q23) is also seen in a small subset (~5%) of patients with multiple myeloma (892,897). Both convey a very poor prognosis. In one study there was a tight association of del 13 abnormalities and high β_2-M values with the unfavorable t(4;14) and t(14;16) abnormalities (822).

The frequency of high β_2-M or del 13 was one half that in patients with the t(11;14) abnormality. This suggests that the poor prognosis associated with del 13 may be because of other nonrandom, associated chromosomal abnormalities. Fonseca et al. (901) have recently demonstrated that three distinct staging groups can be defined by the presence of t(14;16) (q32;q23), t(4;14) (p16.3;q32), deletion 17p13, and del 13q by FISH (Table 99.19).

Table 99.19 Genetic-Based Prognostic and Staging Systems in Newly Diagnosed Multiple Myeloma Patients (Patients Treated with Standard-Intensity Chemotherapy Unless Stated Otherwise)

Study	N	Risk or Stage	Patients (%)	Features	OS (mo)
Konigsberg et al., 2000 (829)	88	Low	36	No F-Δ 13q and β_2-M ≤4 mg/L	102
		Intermediate	40	F-Δ13q or β_2-M >4 mg/L	46
		High	24	F-Δ13q and β_2-M >4 mg/L	11
Fonseca, 2003 (901)	275	Low	39	Absence of F-Δ13q, t(4;14), t(14;16), and F-Δ 17p13	50
		Intermediate	37	F-Δ 13q	42
		High	24	t(4;14), t(14;16), or Δ 17p13	25
Smadja et al., 2001a (888)	159	Low	35	β_2-M ≤3 mg/L and nonhypodiploidb	52
		Intermediate	42	β_2-M >3 mg/L or hypodiploidb	30
		High	23	β_2-M >3 mg/L and hypodiploidb	11
Tricot, 1995c (803)	155	Low	76	Absence of M-Δ13q, and M-Δ11qb	>48
		Intermediate	17	M-Δ13q OR M-Δ 11qb	>50
		High	3	M-Δ13q AND M-	12

				Δ11qb	
Facon et al., 2001d (884)	110	Low	20	No FISH del 13q and β_2-M <2.5 mg/L	>111
		Intermediate	50	F-Δ13q or β_2-M ≥2.5 mg/L	47
		High	30	F-Δ13q and β_2-M ≥2.5 mg/L	25
Fassas 2002c (1108)	1,475	Low	67	No karyotypic abnormality	51
		Intermediate	16	Not hypodiploid, but karyotypic abn other than M-Δ13q	36
		High	17	Hypodiploid or M-Δ13q	19
Chieccio 2006a(1109)	470	Low	53	no F-Δ13q	NR
		Intermediate	26	F-Δ13q only	29
		High	18	F-Δ13q + poor IgHt OR F-Δ p53	20
		Very high	3	F-Δ13q + poor IgHt AND F-Δ p53	13

β_2-M, β_2-microglobulin; F-Δ, fluorescence in situ hybridization deletion; IgHt, poor prognosis IgH translocation; M-Δ, metaphase cytogenetic deletion; NR, not reached; OS, overall survival.

[a]Patients received either standard chemotherapy or high-dose chemotherapy with

transplant.
[b]Metaphase cytogenetics.
[c]Tandem transplant study, rather than conventional chemotherapy.
[d]High-dose melphalan, single transplant, or tandem transplant.

Another new cytogenetic prognostic marker is the gain of 1q21 in myeloma. Abnormalities of both the short and long arms of chromosome 1 have been noted since the first cytogenetic studies of myeloma (869,903) (Fig. 99.14). More recently, Hanamura et al. demonstrated that the frequency of 1q21 amplifications increases from monoclonal gammopathy of undetermined significance (0%), to overt multiple myeloma (43%), and finally to relapse (72%). Amplifications of 1q21 are concurrent with dysregulated expression of c-MAF, MMSET/FGFR3, or deletion 13 (902). Candidate genes for the molecular mechanism of prognosis imparted by the 1q21 amplication include CDS1B, BCL-9, or RAB25, but this has not been confirmed by others (736).

Trisomy is common by FISH and includes chromosomes 3, 6, 9, 11, and 15 (904). In another study, trisomy of 3, 7, and 11 accounted for >50% of the hyperdiploid cases (905). Trisomies of chromosomes 6, 9, and 17 were associated with prolonged survival (906).

Mutations of *ras* have been noted in 30 to 50% of MM patients, with increasing prevalence in the advanced stages of the disease (795,813) and shorter survival (K-*ras*) (796). Mutations of *ras* were first observed in fulminant disease (907) but have also been observed in 27 to 39% of newly diagnosed cases (795,796). Patients with *ras* mutations had a median survival of 2.1 years, versus 4 years for patients with wild-type *ras* (796).

The inactivating mutation of *p53*, locus 17p13, is rare in freshly explanted myeloma cells but is common in human myeloma cell lines and in patients with a terminal phase of myeloma (907). Such mutations have been observed in ~5% of cases of early multiple myeloma, versus 20 to 40% of cases of PCL (816,817,818,819). Deletions of *p53* as detected by FISH are present in 9 to 33% of patients with newly diagnosed myeloma (815,908) and confer a poorer median survival (15.9 vs. >38 months) (815).

Epigenetic phenomena, such as methylation of the *p16* (Met-*p16*) promoter region, have been associated with progression in the plasma cell dyscrasias (794,909,910,911). Met-*p16* is uncommon in MGUS/smoldering multiple myeloma, increases in frequency with advancing stages of the disease (811,911), and is common in extramedullary multiple myeloma, including PCL.

Zhan et al. (735,912) studied the gene expression of 74 myeloma patients by using high-density oligonucleotide microarrays interrogating about 6,800 genes. On hierarchical clustering analysis, four distinct subgroups of myeloma (MM1, MM2, MM3, and MM4) were

identified. The expression pattern of MM1 was similar to normal PCs and MGUS, whereas MM4 was similar to MM cell lines. Clinical variables linked to poor prognosis, including abnormal karyotype and high serum β_2-M levels, were most prevalent in MM4. Overexpression of genes involved in DNA metabolism and cell-cycle control were observed in MM4. Novel candidate MM disease genes have been identified.

Angiogenesis

Several studies have demonstrated the prognostic significance of increased microvessel density (i.e., angiogenesis) in multiple myeloma (201). The first description was a comprehensive study of multiple myeloma and MGUS that showed a strong association with diagnosis and with an increased S-phase fraction of plasma cells measured by the PCLI (201). This finding was corroborated in a prospective clinical trial (913). Median survivals were 4.4 and 2 years in patients with low, intermediate, and high microvessel density, respectively. However, in this study of only 74 patients there was no independent prognostic significance for angiogenesis in a model that included PCLI, β_2-M, and the percentage of marrow plasma cells (913). In another study, angiogenesis failed to predict survival (771). It is not known whether levels of angiogenic

cytokines such as VEGF, bFGF, or hepatocyte growth factor are associated with poor survival, although concentrations are reduced during effective chemotherapy (793).

Lymphocyte Subsets

Low numbers of CD4 (helper T) cells at diagnosis are associated with worse prognosis (914,915); the prognostic importance of CD4 T cells is present throughout the course of disease, including after the completion of chemotherapy and at relapse (916).
In the posttransplantation setting, the number of circulating lymphocytes appears to be an important prognostic factor. Porrata et al. (917) demonstrated lower relapse rates and prolonged survival for patients with higher absolute lymphocyte counts after autologous stem cell transplantation, suggesting an early graft-versus-tumor effect. The median overall survival and progression-free survival for myeloma patients were significantly longer in patients with an absolute lymphocyte count of ≥500 cells/μl on day 15 than for patients with an absolute lymphocyte count <500 cells/μl (33 vs. 12 months; 16 vs. 8 months). Researchers at the University of Arkansas made a similar observation. In a trial designed to evaluate the role of more intense conditioning, lymphocyte recovery, evaluated as a surrogate for immune recovery, was inferior in more intensively treated patients. Despite identical complete remission rates, event-free survival and overall survival were significantly decreased among patients receiving more intensive conditioning (529).

Other Prognostic Factors

Other factors that have adverse prognostic value include decreased staining of bone marrow plasma cells for acid phosphatase (918), increased circulating plasma cells as measured by the peripheral blood labeling index (863), apoptotic index (218), increased sIL-6R (826,919), serum neopterin (366), α_1-antitrypsin (920), C-terminal telopeptide of type I collagen (921,922), serum bone sialoprotein (923), B_{12}-binding protein (924), soluble CD56 (925), soluble Fc receptor (CD16) (926), soluble syndecan or CD138 (927), and serum IL-6 levels (920,928,929). Although IL-6 is known to have a major role in myeloma pathogenesis,

C-reactive protein levels correlate well with this more expensive and less readily available prognostic test. There are mixed results on the prognostic value of serum thymidine kinase (930,931).

Drug Resistance

One form of drug resistance is marked by multidrug resistance-1 expression on plasma cells as demonstrated by immunocytochemistry (932). The presence of this P-glycoprotein in the cell membrane of plasma cells of patients with multiple myeloma is associated with a poor prognosis. Drug resistance measured by immunocytochemical detection of lung resistance protein is highly correlated with failure of response to melphalan and poor subsequent survival (933).

Significance of the Extent of Response after Therapy

Significance of Response after Standard-Intensity Chemotherapy

Response is often used as a measure of efficacy, and it is often assumed that complete remissions are a prerequisite for cure. Indeed, patients treated with standard-intensity chemotherapy with responsive disease tend to live a median of 18 months longer than do patients with resistant disease (38,238,591). However, tumor response may speak more to a patient's tumor biology than it does to the therapy in question. Most standard-intensity chemotherapy studies suggest that the degree of response does not correlate with survival (591,593,934,935,936). Rather, the ability to achieve a plateau of at least 6 months' duration is as important, if not more important, than the degree of response to therapy (588,589,590). The data from only three (251,368,369) of 27 (233,277,354,359,362,363,366,385,937) randomized induction trials suggest that the observed higher response rate translates into longer overall survival (Table 99.6).

The importance of response kinetics is also a controversial topic. Some data support the premise that those with the most rapid responses to alkylator-based therapy have a shorter remission duration and survival (586), whereas other data contradict this assumption (591).

Significance of a Complete Response after High-Dose Therapy

It is unclear whether the achievement of a complete response as defined by the disappearance of the M protein by immunofixation of the serum and urine after high-dose therapy with hematopoietic stem cell support is of prognostic value. Multiple studies have produced inconsistent results (245,479,544,938,939,940,941). Several of these studies (245,544,939) did not use the more stringent definition of “complete response”; they relied on the absence of an M protein on an electrophoretic pattern rather than immunofixation negativity. These studies should be interpreted with caution because they do not include several of the most powerful determinants of prognosis—PCLI and cytogenetics (331,803,824,825,830).

One of these is a retrospective study of 344 patients with multiple myeloma treated with high-dose chemotherapy followed by autologous stem cell transplantation. Patients were not treated uniformly. The 5-year overall survival was 48% in those who had no M protein on immunofixation and 21% in those with a persistent M protein (940). In another study, Rawston et al. reported better overall survival in patients achieving a complete response either by immunofixation or by flow cytometry (942). In yet another study, Davies and colleagues (941) reported a series of 96 patients who received high-dose therapy and were

assessed for the effect of response on survival. Although there was a trend toward improved progression-free survival among patients with an immunofixation-negative complete response compared with patients with a partial response (49.4 vs. 41.1 months, *p* = .26), there was no improvement in overall survival. Alexanian et al. (943) reported on a series of 68 patients treated with dexamethasone-based induction therapy followed by early high-dose therapy; results were compared to those of 50 patients who were unable to receive high-dose therapy because of socioeconomic reasons. Patients who achieved an immunofixation-negative complete response by either means (i.e., high-dose or standard chemotherapy) had superior overall survival compared to patients who achieved a partial response or less. The implication of these data is that a complete response may be an important surrogate marker of long survival and less aggressive myeloma biology. In yet another study, Rajkumar et al. (944) reported a complete response in 33% of 126 multiple myeloma patients who underwent stem cell transplantation. There was no difference in the overall survival or progression-free survival between patients who achieved a complete response and those who did not; rather, overall survival was significantly influenced by the level of the PCLI (493).

Special Cases of Myeloma

Nonsecretory Multiple Myeloma

Nonsecretory multiple myeloma accounts for 1 to 5% of myeloma cases (130,945,946,947,948,949). With more sensitive testing such as immunofixation (950) and free light-chain assays (21), a majority of these “nonsecretory” patients are found to be low secretors or oligosecretory. Immunoperoxidase or immunofluorescence studies should be performed for all patients in whom nonsecretory myeloma is suspected. More than 85% of cases have a cytoplasmic monoclonal protein; in the remainder, no monoclonal protein can be detected in the cytoplasm (948,949,951). Individuals in this latter group are referred to as “nonproducers.” From a clinical standpoint, both are termed “nonsecretory.”
At presentation, hypercalcemia and anemia may be present. A reduction in background immunoglobulins is common (948,949). There is minimal to no risk of myeloma kidney (946,948). Lytic bone disease is present in most patients (945,946,947,948). Median

survival of these patients is at least as good as for those with secretory myeloma (945,947,948). Response is difficult to document, but with the new serum assays, quantitation of free light chains is possible in about two thirds of these patients (21).

Immunoglobulin D Myeloma

IgD myeloma accounts for about 2% of all cases of myeloma (952). The presence of a monoclonal IgD in the serum usually indicates myeloma, but three cases of IgD MGUS have been documented (946). Patients with IgD myeloma generally present with a small band or no evident M spike on serum protein electrophoresis. Their clinical presentation is similar to that of patients with Bence Jones myeloma (light-chain myeloma) in that both have a higher incidence of renal insufficiency and coincident amyloidosis as well as a higher degree of proteinuria than in IgG or IgA myeloma (952). IgD myeloma patients, however, appear to have a higher frequency of monoclonal λlight chains than κlight chains (952). With an incidence of 19 to 27%, extramedullary involvement is more prevalent in patients with IgD

myeloma (953,954,955). Survival with IgD myeloma has been reported to be inferior to that with other forms of myeloma, with a median of 12 to 17 months (953,954,955). In the Mayo Clinic series, however, median survival was 31 months in patients diagnosed after 1980 (946,956).

Immunoglobulin E Myeloma

IgE myeloma is a rare form of myeloma. A disproportionate number of cases are PCL, although the sample size is small, with only about 40 cases of IgE myeloma reported in the literature (957,958).

Plasma Cell Leukemia

PCL is a rare form of plasma cell dyscrasia. Between 2 and 4% (904,959,960) of malignant plasma cell dyscrasia cases are PCL. By definition, there are >20% plasma cells in the peripheral blood, with an absolute plasma cell count of >2 × 10^9/L. Some authors accept the diagnosis with only one of these criteria (946). The presentation may be primary, *de novo,* or secondary, evolving from an existing case of myeloma as part of the terminal phase of the disease. About 60 to 70% of cases are primary (959).

Although there is overlap, the phenotype of plasma cells from patients with primary PCL is different from those of myeloma patients. PCL plasma cells more frequently express the CD20 antigen (904) than those of multiple myeloma (50 vs. 17%), and they often lack CD56 antigen (210,904), which is present on the majority of myeloma cells (904). CD56 is considered important in anchoring plasma cells to bone marrow stroma, and its absence is associated with a poor prognosis (211,212). CD28 is more frequently expressed on malignant plasma cells in secondary than in primary PCL, which is consistent with an observation made in myeloma, i.e., that acquisition of the CD28 antigen on plasma cells appears to correlate with an increased proliferative rate and disease progression (961).

PCL plasma cells have higher proliferative rates (904)and more complex karyotypes than myeloma plasma cells (960). By comparative genomic hybridization and by FISH techniques, losses on 13q (962,963) and monosomy 13 (904) exist in >80% of PCL patients (962,963). Losses on chromosome 16 also occur in ~80% of cases (963). Gains in 1q are present in about half of the patients by FISH (904), but in all by comparative genomic hybridization (963). In addition, PCL patients have unique losses of 2q and 6p (963). Overexpression of PRAD1/cyclin D1, which plays an important role in control of the cell cycle, has also been observed in PCL (964).

The clinical presentation of primary PCL is more aggressive than that of multiple myeloma, with a higher presenting tumor burden and higher frequencies of extramedullary involvement, anemia, thrombocytopenia, hypercalcemia, renal impairment (904,959,960,965), increased levels of serum lactate dehydrogenase and β_2-M, and plasma cell proliferative activity (904). The incidence of lytic bone lesions is slightly lower than that usually observed in multiple myeloma (904,966).

Though the clinical and laboratory features of primary and secondary PCL are similar (966,967), the response to therapy and overall survival in primary and secondary PCL go from poor to worse (959,960,966,967). Higher response rates can be achieved with multiagent chemotherapy rather than single-alkylator programs (47 to 66% vs. 8 to 13%) (904,959,960,966). Regimens such as VMCP/VBAP, VAD, and combination cyclophosphamide and etoposide have resulted in median survivals of 18 to 20 months,

compared with 2 to 6 months when single-agent therapy is used (904,959,960,966). Response and survival rates with secondary PCL remain low (966,967). When thalidomide and dexamethasone are used, responses are possible (968,969) (personal observation), which is not surprising given the high response rates observed in patients with high PCLIs in our thalidomide trial (970). There are anecdotal reports of activity of bortezomib in these patients (971,972,973). Some patients derive excellent responses and 2- to 3-year disease-free survivals after autologous stem cell transplantation (974,975,976,977,978). Saccaro et al. (979) reported on the cumulative outcomes of PCL patients undergoing hematopoietic stem cell transplantation reported in the literature. Median survival post–autologous HSCT was 36 months, whereas it was only 12 months after allogenic HSCT. Two authors have independently noted the presence of an increased number of circulating large granular lymphocytes after stem cell transplantation (974,980); disappearance of these cells in one patient coincided with relapse (974). The significance and implication of these observations are yet to be determined.

Osteosclerotic Myeloma (POEMS Syndrome)

Osteosclerotic myeloma is a rare variant of myeloma (≤3.3% of cases) (981). There is a straight osteosclerotic variant that is similar to multiple myeloma in that anemia, significant bone marrow plasmacytosis, hypercalcemia, and renal insufficiency occur (143). Survival in these patients is comparable to that of classic multiple myeloma patients. There is, however, a more interesting form, which is known as Crow-Fukase syndrome, PEP (plasma cell dyscrasia, endocrinopathy, polyneuropathy) syndrome, Takatsuki syndrome, and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) (982,983,984,985). This variant is associated with multiple paraneoplastic phenomena, and its natural history is not similar to that of classic multiple myeloma. The acronym POEMS captures several of the dominant features of the syndrome, but it omits the sclerotic bone lesions, Castleman disease, papilledema, peripheral edema, ascites, polycythemia, thrombocytosis, fatigue, and clubbing commonly observed in the disorder. Not all features are required to make the diagnosis; at a minimum, however, a patient must have: (a) peripheral neuropathy, (b) osteosclerotic myeloma (i.e., a clonal plasma cell dyscrasia and at least one sclerotic bone lesion) or Castleman disease, and (c) at least one of the other previously mentioned features (985). The peak incidence of POEMS syndrome is in the fifth and sixth decades of life, and there is a male predominance (983,985,986).

Although the precise mechanism of POEMS syndrome is unknown, VEGF appears to be a driving factor in this disorder (987,988,989). Despite the presence of osteosclerotic bone lesions, which microscopically contain clonal plasma cell infiltrates, bone marrow aspirate and biopsy of the iliac crest typically yield only ~5% monoclonal lambda plasma cells (982,985,987).

Treatment for this disorder is far from standardized. Most agree that for an isolated plasmacytoma, irradiation is the preferred treatment (990,991,992,993). Radiation therapy produces substantial improvement of the neuropathy in more than half of the patients

who have a single lesion or multiple lesions in a limited area. If there are widespread lesions, chemotherapy and, potentially, peripheral blood stem cell transplantation should be considered (994). Responses of systemic symptoms and skin changes tend to precede those

of the neuropathy, with the former beginning to respond within a month and the latter within 3 to 6 months.
The most common causes of death are cardiorespiratory failure, progressive inanition, infection, capillary leak–like syndrome, and renal failure (982,985). The neuropathy may be unrelenting and contribute to progressive inanition and eventual cardiorespiratory failure and pneumonia. Stroke and myocardial infarction, which may or may not be related to the POEMS syndrome (985), are also observed causes of death. Patients do not die of classic myeloma (i.e., progressive bone marrow failure or hypercalcemia).

Treatment of Complications and Supportive Care

Pharmacologic Therapy of Myeloma Bone Disease

Myeloma bone disease is a significant contributor to morbidity, and there is expanding information about the relationships between bone turnover and plasma cell growth and survival (142,758,995,996,997). Locally acting osteoclastogenic and resorptive factors by both osteoblasts and stromal cells are dependent on a number of interactions between them and the myeloma cells. This neoplastic unit releases inflammatory and erosive cytokines, such as IL-1β, IL-3, IL-6, IL-11, TNF-α, and a parathyroid hormone-related protein, hepatocyte growth factor, basic fibroblast growth factor, metalloproteases, and macrophage inflammatory protein-1α (142,997).
The standard method of following patients is with periodic (every 6 to 12 months) skeletal radiographs; the use of more sophisticated imaging modalities has been described in a previous section. Cross-linked N-telopeptides of type I collagen, which can be measured in the serum or urine, appear to be a sensitive indicator of bone turnover (922,998), and urinary levels show a strong positive correlation with the dynamic histomorphometric indices of bone resorption (999). Serum levels of bone metabolism markers such as osteocalcin, MIP-1α, RANKL, and osteopetegrin have been studied and shown to be aberrantly expressed in patients with active myeloma (142). Despite careful monitoring, patients are at risk for skeletal events. Besides treating the underlying disease with chemotherapy, bisphosphonates have been the mainstay of pharmacologic therapy of myelomatous bone disease. Other drugs, such as bone-seeking radionuclides (524,686,1000) and inhibitors of the receptor activator of nuclear factor κB (RANK) signaling known as osteoprotegerin (1001), are being tested.
Monthly intravenous administration of pamidronate has been shown to reduce the likelihood of a skeletal event by almost 50% in patients with multiple myeloma (1002).
Bisphosphonates inhibit dissolution of the hydroxyapatite crystals and down-regulate the major osteoclast functions. After internalization, the nitrogen-containing bisphosphonates interfere with the biosynthetic mevalonate pathway by inhibiting farnesyl diphosphonate synthase, with the resulting inability of osteoclasts to form the ruffled borders of their membrane needed to activate bone resorption. In this study, 392 patients with stage III myeloma and at least one lytic lesion received either placebo or pamidronate, 90 mg intravenously administered as a 4-hour infusion monthly for 21 cycles (Fig. 99.15B). Skeletal events (pathologic fracture, radiation or surgery, and spinal cord compression) and hypercalcemia were assessed monthly. At 12 months, there were fewer skeletal-related events in the pamidronate group than in placebo-treated patients (28 vs. 44%; $p < .001$) (1002,1003). With longer follow-up of 21 months, the difference between groups persisted

but narrowed slightly, to 28% in the pamidronate group versus 51% in the placebo group ($p < .015$) (1004). This prospective study subsequently led the U.S. Food and Drug Administration (FDA) to approve the use of the drug in this setting.

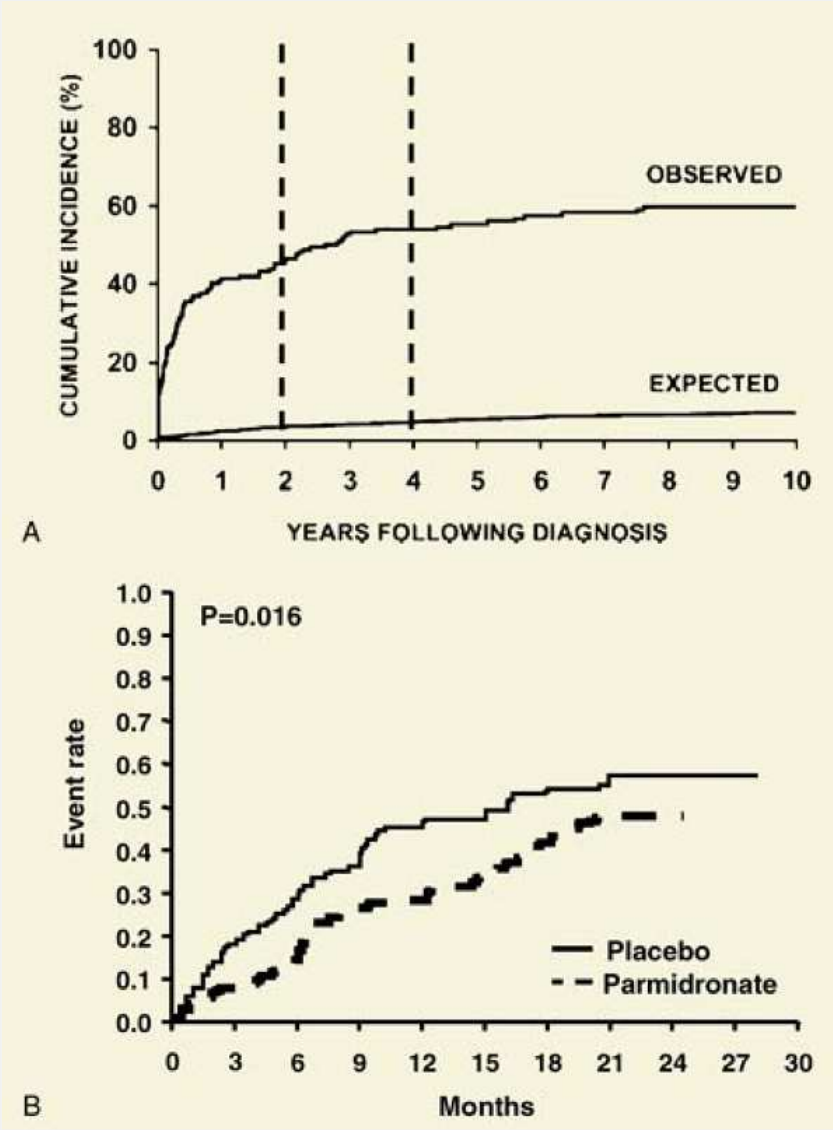

Figure 99.15. Bone risk in multiple myeloma. A: Natural history of bone events in patients with newly diagnosed myeloma (1945 to 2001) without bisphosphonate support. (With permission, from Melton LJ 3rd, Kyle RA, Achenbach SJ, et al. Fracture risk with multiple myeloma: a population-based study. J Bone Miner Res 2005;20:487–493.) **B:** Pamidronate versus placebo in newly diagnosed myeloma patients. (With permission, from Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. J Clin Oncol 1998;16:593–602.)

Equivalency of pamidronate and zoledronic acid has been demonstrated in two randomized clinical trials, a randomized Phase II trial (1004) and a randomized Phase III trial (1005). In the Phase III trial, patients with multiple myeloma or breast cancer, who had lytic disease, were treated with zoledronic acid (4 or 8 mg per dose) or pamidronate (90 mg) every 3 to 4

weeks. The infusion time for zoledronic acid was increased from 5 to 15 minutes during the trial because of an increase in creatinine occurring more frequently among patients receiving the rapid infusion. Renal problems continued to occur more often among patients randomized to 8 mg zoledronic acidum, and their dose was subsequently reduced to 4 mg. The sample size was based on showing noninferiority of zoledronic acid to pamidronate. A total of 1,648 patients were enrolled; 510 had multiple myeloma and the remainder had metastatic breast cancer. The portion of patients with any SRE after 13 months did not differ among the three treatments and did not differ between the breast cancer and multiple myeloma patients. In February 2002, the FDA approved an expanded indication for zoledronic acid for the treatment of patients with bone metastases that included its use in multiple myeloma.

Despite the fact that the longest follow-up of patient in these studies was 24 months, the recommendation of the American Society of Clinical Oncology was to continue these agents indefinitely at monthly intervals (1006). The rationale for practice was not data-driven, but based on several theoretical benefits. The first was that patients have continued bone disease throughout the course of their disease. The second was predicated on the in vitro and in vivo (murine) data that bisphosphonates exert antitumor activity (995).

In the short term, the drugs were well tolerated—occasional episodes of mild pyrexia, renal function impairment, myalgias, and hypocalcemia occurred. However, by 2003, avascular osteonecrosis of the jaw (ONJ) had been described as a new complication associated with their use (1007,1008,1009,1010,1011,1012,1013,1014,1015,1016,1017,1018). Bisphosphonate-associated ONJ has been described in various malignancies, including multiple myeloma, breast cancer, and prostate cancer. A management algorithm for ONJ has recently been published (1019). It has been seen in both the mandible and the maxilla but is more frequent in the former. The etiology of ONJ is unclear, but it is likely multifactorial in origin. Although most patients who develop ONJ have had recent dental or oral surgical procedures (70%), the remainder develop spontaneous ONJ (1012). Proposed mechanisms include that inhibition of osteoclast activity reduces bone turnover and remodeling and that bisphosphonates prevent release of bone-specific factors that promote bone formation (1020). In addition, bisphosphonates, particularly zoledronic acid, may have antiangiogenic effects, and impaired blood supply has been implicated in the development of ONJ. Finally, healing of an open bony oral wound is challenged by bacterial insult from oral microflora.

Table 99.20 Mayo Clinic Consensus Statement for Bisphosphonate Use in Patients with Multiple Myeloma

Clinical Scenario	Guideline
MM and lytic disease evident on plain radiographs	Intravenous bisphosphonates should be administered monthly.
No lytic disease evident on plain radiographs, but osteopenia or osteoporosis on bone mineral density studies	It is reasonable to start intravenous bisphosphonates in these patients.
Smoldering MM	Not recommended outside context of a clinical trial.
Duration of bisphosphonate	Patients should receive infusions of bisphosphonates monthly for 2 y. After 2 y: If the patient has achieved remission and is in stable plateau phase off treatment, the bisphosphonates can be discontinued. If the MM still requires active treatment, the frequency of bisphosphonate infusions can be decreased to every 3 mo.
Choice of bisphosphonate	In patients with newly diagnosed MM, we favor use of pamidronate over zoledronic acid.
Dental evaluation and follow-up of patients taking bisphosphonates	Encourage patients to have comprehensive dental evaluation before receiving any bisphosphonate treatment. Undergo invasive dental procedures before starting bisphosphonate treatment. See a dentist at least annually and maximize preventive care; report oral/dental symptoms promptly. Manage new dental problems conservatively and avoid dental extractions unless absolutely necessary. See an oral and maxillofacial surgeon if surgery is required. Practice good dental hygiene. Encourage physicians to Withhold bisphosphonate treatment for at least 1 mo before the procedure and do not

	resume until the patient has recovered from invasive dental procedures.

Source: Lacy MQ, Dispenzieri A, Gertz MA, et al. Mayo clinic consensus statement for the use of bisphosphonates in multiple myeloma. Mayo Clin Proc 2006;81:1047–1053.

The true incidence of this complication is hard to estimate. Durie and colleagues (1015) performed a Web-based survey of 1,203 patients with myeloma and breast cancer and found an incidence of 6.8% in patients with MM and 4.4% in patients with breast cancer. The data also suggested that the incidence was higher in patients treated with zoledronic acid than in those treated with pamidronate (1015).

In another study, Bamias et al. estimated incidence rates in myeloma patients of 9.9% (1014), and found that the time of exposure was strongly associated with development of ONJ, and that rates were higher in zoledronic acid–treated patients. Patients who developed ONJ received a median number of 35 infusions (range, 13 to 68), compared to 15 infusions (range, 6 to 74) for patients with no ONJ. Median time of exposure to bisphosphonates was 39.3 months for patients with ONJ (range, 11 to 86 months), compared with 19 months (4 to 84.7) for patients with no osteonecrosis. The likelihood of developing ONJ was 1% in the first year of treatment, increasing to 21% at 3 years of treatment for zoledronic acid–treated patients, whereas in the non-zoledronic acid–treated patients the rates were 0 the first 2 years and 7% after 4 years of treatment.

These observations prompted the Mayo Clinic Myeloma Group to proffer a Consensus Guideline Statement (Table 99.20) (1020). The recommendation is of 2 years of monthly therapy for patients with myelomatous bone disease, followed by either cessation of therapy in patients who are off active treatment for their myeloma, or continuation of bisphosphonate therapy every 3 months for those who are receiving ongoing therapy for their myeloma. These recommendations are bolstered by two recent observations. The first is the natural history of myeloma bone

disease in the days before bisphosphonate use; the period with the highest rates of bone disease is the first 2 years (1021). The second is a report by the IFM group that pamidronate use after tandem transplant for low-risk patients does not provide any significant reduction in skeletal events (618).

Nonpharmacologic Treatment of Myeloma Bone Disease

When lytic lesions are discovered in long bones, the risk of fracture has been demonstrated to be very high if pain is aggravated by functional use of that limb or if the lesion occupies

more than two thirds of the diameter of that bone. Such lesions should be stabilized by internal fixation (1022). Endosteal resorption of one half the cortical width of the femur weakens the bone by 70%. Surgical treatment should be considered for these lesions as well (1023). Once a bone has fractured, healing can occur, especially if proper internal fixation is performed and if patients have an anticipated survival of >6 months. Much of the data regarding malignant bone disease are derived from patients with carcinoma rather than multiple myeloma. In patients with carcinoma metastatic to bone, modest postoperative radiation doses (≤3,000 cGy) as adjuvant therapy are associated with better healing (1024), but the role of adjuvant radiation therapy in multiple myeloma patients is less clear. Multiple myeloma is often chemotherapy-sensitive; adjuvant systemic chemotherapy in multiple myeloma patients may be more appropriate than adjuvant radiation therapy. In general, radiation therapy should be used for pain relief in chemotherapy-refractory disease, because it relieves pain in 80 to 90% of patients with bony metastases (1025), long-term in 55 to 70% (1026).

Percutaneous vertebroplasty is occasionally an option for patients with vertebral body compression fracture. Pain relief is generally apparent within 1 to 2 days after injection and persists for at least several months and up to several years (1027). Complications are relatively rare, although some studies reported a high incidence of clinically insignificant leakage of bone cement into the paravertebral tissues. Compression of spinal nerve roots or neuralgia as a result of the leakage of polymer and pulmonary embolism have also been reported. Percutaneous kyphoplasty is also an option (1028). To date, there are no randomized trials to inform clinicians as to which procedure is more effective.

Spinal Cord Compression

In a paper published in 1979, it was estimated that nearly 10% of patients with myeloma either present with spinal cord compression or that it develops during the course of the disease (1029); with higher awareness of myeloma and better imaging technology, the incidence is likely lower now. Cord compression, however, remains an important and emergent subject. The usual standard treatment is high-dose corticosteroids and radiation therapy (1030,1031,1032,1033). On rare occasions, surgical decompression may be considered. Because most myelomatous lesions arise from the vertebral body, an anterior surgical approach is generally used, which may contribute additional morbidity. One small randomized trial addressing the question of radiation versus laminectomy and radiation showed no benefit attributable to laminectomy (1031); similarly, a larger retrospective series found no benefit (1030). If the deficit is a result of compression by the plasma cell tumor (rather than a bone fragment retropulsed by a pathologic compression fracture), outcomes with radiation therapy are probably equal (or superior) to surgical intervention in a radiosensitive tumor such as myeloma (1030,1031).

High-dose corticosteroids may provide immediate pain relief and improvement in neurologic function (1032,1033). The optimal corticosteroid dose has not been established, but common dose schedules for metastatic disease include dexamethasone in an initial bolus of 10 mg intravenously or 100 mg intravenously followed by 4 mg orally 4 times daily (1034); or a 100-mg intravenous bolus followed by 96 mg in 4 divided doses for 3 days followed by tapering doses (1032,1033).

Hypercalcemia

Patients with multiple myeloma are at risk of severe hypercalcemia that can precipitate acute renal failure, hypertension, nausea, vomiting, pancreatitis, cardiac arrhythmia, coma, and death. The extracellular volume depletion associated with hypercalcemia should be corrected by vigorous hydration (727,1035) followed by an antiresorptive agent such as intravenous bisphosphonate. Serum calcium values usually decline rapidly, reaching the normal range within 2 to 3 days in >80% of cases. It occasionally goes below normal at the nadir. Corticosteroids can also reduce serum calcium concentration in ~60% of patients with hypercalcemia (1036).

Gallium nitrate, mithramycin, and calcitonin are interesting from a historical perspective. Since the advent of bisphosphonates, they are not often used. Gallium nitrate therapy had been shown to be superior to maximally approved doses of calcitonin for acute control of cancer-related hypercalcemia (1037).

Hematologic Complications Including Anemia, Secondary Leukemia, Hyperviscosity, and Cryoglobulinemia

Anemia

The anemia of multiple myeloma can result from many factors. When the anemia is due solely to myelomatous bone marrow infiltration, chemotherapy remedies the problem. Other patients have a relative erythropoietin deficiency related to renal injury due to the myeloma or to age-related changes. In these patients, as in any patient with renal insufficiency, modest doses of recombinant erythropoietin are effective. For patients with chemotherapy-induced anemia, recombinant erythropoietin may be effective at higher doses (150 to 300 IU/kg three times weekly or 40,000 IU weekly). Two placebo-controlled trials in myeloma patients demonstrate significantly improved hemoglobin levels and a reduced number of red cell transfusions in patients receiving erythropoietin (1038,1039). An inappropriately low endogenous erythropoietin concentration is the most important factor predicting response (1040)

Secondary Myelodysplasia and Acute Leukemia

The most ominous cause of anemia in the setting of previously treated multiple myeloma is a secondary myelodysplastic syndrome or acute leukemia. Kyle et al. (578) were among the first to recognize that cytotoxic agents can induce myelodysplasia and acute myeloid leukemia (578,579,580,581). The risk of a secondary myelodysplastic syndrome or acute leukemia is ~3% at 5 years and 10% at 8 to 9 years (1041,1042), with estimates as high as 25% at 10 years (1043), with multiple other estimates somewhere in between (373,582,583). Some authors have suggested that higher cumulative doses of melphalan are implicated as a risk for acute leukemia (1041). Others have shown no difference in incidence based on the number of courses of chemotherapy or the cumulative melphalan dose between patients who did and did not develop acute leukemia (1042). In the Finnish study, the mean number of chemotherapy cycles was 19.7 and 18.5 in patients with and without secondary leukemia; mean cumulative melphalan doses were 1,440 and 1,400 mg, respectively (1042). Although cyclophosphamide has been shown to be leukemogenic, data suggest that it is less so than melphalan (1041,1044,1045). After secondary leukemia is diagnosed, median survival tends to be short—about 2 months (1042).

The occurrence of concurrent acute leukemia in multiple myeloma suggests that there may be a proclivity for acute leukemia to develop in patients with myeloma (1046,1047). After stem cell transplantation for myeloma, the risk of myelodysplastic syndrome appears to be related to prior chemotherapy rather than to the transplant itself, at least in one retrospective series (1048).

Cryoglobulinemia

Approximately 5% of myeloma gammaglobulins exhibit reversible precipitation in the cold, so-called cryoglobulins, forming either a flocculent precipitate or a gel-like coagulum when the serum is cooled (1049).

Hyperviscosity

Plasmapheresis relieves the symptoms of hyperviscosity, but the benefit of this treatment in the absence of concurrent chemotherapy is short-lived (1050).

Renal Failure

Normal creatinine values are present in ~50% of multiple myeloma patients at diagnosis (130,131,132,133,167,168,169,170), and only 15 to 25% have a creatinine value >2 mg/dl (132,173). Patients in whom the renal failure is reversed have better overall survival than those without improvement (171,174). Factors that increase renal tubular cast formation include dehydration, infection, and hypercalcemia. Maintaining a 24-hour fluid intake of at least 3 L can improve renal function (171).

Because light chains with the lowest isoelectric points tend to be more nephrotoxic in animal models, avoidance of a low or acidic urinary pH is recommended. Oral or intravenous bicarbonate is useful in the setting of acute renal failure (1051). The MRC 3rd Myelomatosis Trial randomized multiple myeloma patients with significant renal failure to oral sodium bicarbonate to neutralize urine pH (or not), with a trend toward better survival in the bicarbonate recipients (171).

The use of plasmapheresis in the setting of renal failure remains controversial. There are three randomized trials addressing this question, with conflicting results. One small randomized study of patients with active myeloma and progressive renal failure suggested benefit in a subset of patients (1052). Twenty-one patients were randomized to receive either forced diuresis and chemotherapy (10 patients) or forced diuresis, chemotherapy, and plasmapheresis (11 patients). There was a trend toward better outcome in the plasmapheresis group, but the difference was not statistically significant. It is unclear whether the lack of significance is due to the small sample size or to an equivalence of the two therapeutic strategies. The study did demonstrate that the severity of myeloma cast formation correlated directly with lack of improvement, regardless of treatment strategy.

Another randomized study in myeloma patients with severe renal compromise compared plasma exchange (and hemodialysis when needed) with peritoneal dialysis (1053). All patients received chemotherapy and corticosteroids. Of the 29 patients in the study, 24 received dialysis and 5 maintained serum creatinine concentrations of >5 mg/dl without dialysis. Thirteen of the 15 patients in the plasmapheresis (hemodialysis group recovered renal function, reaching serum creatinine values of ≤2.5 mg/dl in most cases, whereas only 2 patients in the peritoneal dialysis group had enough improvement to stop dialysis. The 1-

year survival rates were 66 and 28%, respectively ($p < .01$). The study's design was flawed in that one group received peritoneal dialysis and the other hemodialysis; the question about the role of plasmapheresis is not adequately settled.

The largest and most recent trial was a negative study (1054). One hundred and four patients with newly diagnosed myeloma and a creatinine of 2.3 mg/dl were randomized to conventional chemotherapy with or without 5 to 7 sessions of plasma exchange over 10 days. The primary outcome was a composite measure of death, dialysis dependence, or glomerular filtration rate of <30 ml/min/1.73 m^2. At 6 months the endpoint was reached in 58% of the plasma exchange group and 69% of the control group. At 6 months, 7 of the 39 control patients (18%) and 5 of 58 plasma exchange patients (9%) were on dialysis. At 6 months, 33% of each group had died. Criticisms of this study included the patient selection, including the absence of renal biopsy, the use of relatively ineffective conventional chemotherapy, and small sample size. Patients were eligible if the serum creatinine level was at least 2.3 mg/dl with an increase >0.6 mg/dl in the preceding 2 weeks despite correction of hypercalcemia, hypovolemia, and metabolic acidosis. This implies that institution of plasma exchange was delayed and that there could have been other underlying pathologic renal lesions other than cast nephropathy, which would not be responsive to plasma exchange. More than twice as many patients on the plasma exchange group had melphalan and prednisone as in the control group, which could have confounded the results because both overall response rates are lower and time to response is longer with melphalan and prednisone than with VAD.

Infection Management

Infections are a major cause of morbidity in myeloma patients (1055,1056). Pneumonias and urinary tract infections caused by *Streptococcus pneumoniae, Haemophilus influenzae,* and *Escherichia coli* are most frequent (183,1057,1058,1059). The susceptibility to infection varies with the phase of illness (182,1060). In one prospective study, the overall serious infection rate was 0.92 infection per patient-year and was four times higher during periods of active disease (1.90) than in plateau-phase myeloma (0.49) (181). In a retrospective study evaluating the sequential incidence of infection, the first 2 months of initial chemotherapy emerged as a particularly high-risk period, with nearly half of the patients experiencing at least one clinically significant infection (182). Infections late in the course of multiple myeloma may be an inevitable result of long-standing immunosuppression and overwhelming tumor burden. Prevention of infection is a critical goal for improving survival. Prevention of infections by use of vaccines is an attractive strategy. Unfortunately, responses to vaccines are poor among myeloma patients (191,1061,1062,1063). Patients with myeloma were investigated to assess whether immunologic risk factors predisposing to serious infection could be identified (181). Specific antibody titers to pneumococcal capsular polysaccharides and tetanus and diphtheria toxoids were significantly reduced compared with the control population. Low antipneumococcal and anti-*Escherichia coli* titers correlated with risk of serious infection. In addition, among 41 immunized patients, responses to pneumococcus vaccine and tetanus and diphtheria toxoids were poor. IgG subclass levels were significantly reduced, and a poor IgG response to pneumococcus vaccine immunization was associated with an increased risk of septicemia. The predominant

site of infection was the respiratory tract. Decreased concentrations of the uninvolved immunoglobulins were significantly associated with at least one serious infection (181). The two most common prevention strategies consist of prophylaxis with antibiotics (1064) or intravenous immunoglobulin (IVIg) (1064). A randomized, placebo-controlled trial of trimethoprim-sulfamethoxazole (TMP-SMX) demonstrated a significant decrease in severe infections among newly diagnosed myeloma patients randomized to TMP-SMX compared with controls (1065). Fifty-seven patients about to begin chemotherapy for multiple myeloma were randomly assigned to prophylaxis for 2 months or to no prophylaxis (control). Antibiotic prophylaxis consisted of TMP-SMX (160/800 mg orally every 12 hours) administered for the first 2 months of initial chemotherapy. Bacterial infection occurred in

11 control patients but in only 2 patients assigned to receive TMP-SMX (p = .004). Eight severe infections occurred in controls, compared with one in a TMP-SMX patient (p = .010). Severe infections included 5 cases of pneumonia (3 with sepsis), 2 urinary tract infections with complicating pneumonia or sepsis, 1 diverticulitis with perforation, and 1 staphylococcal scalded skin syndrome. The rate of bacterial infection was 2.43 per patient-year for controls and 0.29 per patient-year for the TMP-SMX group (p = .001). Toxicity (skin rash in 6 patients, nausea in 1 patient) was not life-threatening but required discontinuation of TMP-SMX in 25% of patients. A randomized, double-blind placebo-controlled trial demonstrated that IVIg significantly reduced the number of infections in high-risk patients with plateau-phase multiple myeloma (1064). Eighty-two such patients received either IVIg (0.4 g/kg per month) or an equal volume of placebo for 1 year. There were no episodes of septicemia or pneumonia in patients receiving IVIg, compared with 10 in placebo patients (p = .002). There were 38 serious infections in 470 patient-months for the placebo group, compared with 19 in 449 patient-months for the IVIg group (p = .019). A poor antibody response to pneumococcal vaccination (less than twofold increase) identified patients who had maximum benefit from IVIg. However, IVIg is expensive and inconvenient and can be associated with toxicity. Therefore, use of this agent is recommended only for patients with a significant history of severe infections.

Differential Diagnosis

The diagnosis of multiple myeloma is made from a constellation of findings, including anemia, monoclonal proteins, bone lesions, renal complications, hypercalcemia, and bone marrow plasmacytosis. Often the diagnosis is straightforward, but other disease entities associated with hypergammaglobulinemia or monoclonal bone marrow plasma cells must also be considered. These include reactive plasmacytosis, MGUS, primary systemic amyloidosis, Waldenström macroglobulinemia, light-chain deposition disease, acquired Fanconi syndrome, solitary plasmacytoma, osteosclerotic myeloma or POEMS syndrome, and PCL.

Reactive Plasmacytosis and Polyclonal Hypergammaglobulinemia

Reactive plasmacytosis and polyclonal hypergammaglobulinemia must be distinguished from a clonal process. Patients with liver disease, chronic infections including human

immunodeficiency virus, connective tissue diseases, other lymphoproliferative disorders, and carcinoma can have increased bone marrow plasmacytosis (polyclonal) and hypergammaglobulinemia (polyclonal) (24,119). These conditions should not be confused with multiple myeloma or MGUS, which are clonal processes.

MGUS

Two percent of patients >50 years old have MGUS, which is a benign counterpart or precursor lesion of multiple myeloma (108). It is characterized by an M protein in the serum or urine, without evidence of multiple myeloma or other serious gammopathy-related disorder. MGUS patients do not have bone marrow suppression, lytic bone lesions, hypercalcemia, renal failure, or susceptibility to infection. Standard clinical features do not accurately predict which patients will remain stable, and multiple myeloma develops in ~1% per year (108). The clinical distinction between MGUS and asymptomatic multiple myeloma is derived from an arbitrary definition (Table 99.2), although the underlying biologic conditions may prove to be different.

The greatest challenges in differentiating MGUS from myeloma occur in patients who have MGUS and (a) senile osteoporosis, (b) renal insufficiency from another cause, or (c) hypercalcemia due to hyperparathyroidism. Approximately 50% of women >60 years have osteoporosis, and a fraction of these have vertebral compression fractures. CT scan of the spine may help distinguish between senile osteoporosis and myelomatous bone disease. Similarly, renal insufficiency due to long-standing diabetes, hypertension, or nonsteroidal drug use is not uncommon. In such cases, a patient may still have MGUS (or asymptomatic myeloma, for that matter) and “end-organ damage.” The key is whether the damage is attributable to the plasma proliferative disorder or another cause. In some instances, renal biopsy may be required to clarify this issue.

Primary Systemic Amyloidosis

Primary systemic amyloidosis is a rare disorder that is characterized by the deposition of amyloid fibrils. These fibrils are composed of immunoglobulin light-chain fragments in a β-pleated sheet conformation. It should be suspected when a patient with a monoclonal protein in the serum or urine presents with nephrotic-range proteinuria (primarily albumin) with or without renal insufficiency, cardiomyopathy, hepatomegaly, or peripheral neuropathy. Patients usually present with weight loss or fatigue. Anemia is rare at presentation. Symptoms related to the affected organ are also seen. A monoclonal light chain is found in the serum or urine in nearly 90% of patients with amyloidosis. Most of the remaining patients have monoclonal plasma cells detectable in the bone marrow; median percentage of clonal plasma cells in these patients is only 5%. A histologic diagnosis is made by demonstrating the amyloid fibrils—green birefringence under polarized light by using a Congo red stain, or 8- to 10-nm nonbranching fibrils by electron microscopy. The fat aspirate is positive 70 to 80% of the time. The bone marrow demonstrates amyloid deposits approximately half the time. Nearly 90% of patients with amyloid have a bone marrow or fat aspirate specimen that is positive for amyloid. In the remaining 10%, a biopsy specimen of the affected organ is positive.

Waldenström Macroglobulinemia

Waldenström macroglobulinemia should not be confused with IgM myeloma, which comprises only ~1% of myeloma cases (132). Patients with Waldenström macroglobulinemia may have anemia, hyperviscosity, B symptoms, bleeding, and neurologic symptoms. Significant lymphadenopathy or splenomegaly may also be present. Lytic bone disease is markedly uncommon; if it is present, consider whether the patient has IgM myeloma. In Waldenström macroglobulinemia, bone marrow biopsy typically reveals infiltration with clonal lymphoplasmacytic cells (CD20-positive). The natural history and treatment options for Waldenström macroglobulinemia are different from those of multiple myeloma (1066).

Light-Chain Deposition Disease

The nonamyloidogenic light-chain deposition diseases (LCDDs) are due to pathologic protein deposition in various tissues and organs. Unlike the light-chain deposits observed in patients with primary systemic amyloidosis, these infiltrates are not congophilic by light microscopy, and by electron microscopy nonbranching fibrils are not observed. Instead, amorphous nodular deposits are seen.

LCDD may occur with or without coexisting multiple myeloma. Renal involvement is most common, followed by cardiac and hepatic deposits. Clinically, LCDD can be differentiated from multiple myeloma and primary systemic amyloidosis by the following findings. As in primary systemic amyloidosis, early in the disease course the light-chain deposits have a predilection for the renal glomeruli rather than the tubules. This results in nonselective proteinuria, that is, a predominance of albuminuria, which is not

usual in multiple myeloma. It is impossible without tissue biopsy to distinguish clinically the cardiomyopathy and hepatopathy from primary systemic amyloidosis. In LCDD, the underlying clone is more commonly monoclonal κ rather than λ.

The prognosis of patients who have this disorder depends on whether there is underlying multiple myeloma. In one retrospective study of 19 patients with LCDD, 5-year actuarial patient survival and survival free of end-stage renal disease were 70 and 37%, respectively (1067).

Acquired Fanconi Syndrome

Fanconi syndrome is a rare complication of plasma cell dyscrasias characterized by diffuse failure in reabsorption at the level of the proximal renal tubule and resulting in glycosuria, generalized aminoaciduria, and hypophosphatemia (179). Fanconi first described the syndrome in children. Subsequently, acquired forms were described in adults. Acquired Fanconi syndrome is usually associated with MGUS. Overt hematologic malignancies may occur, such as multiple myeloma, Waldenström macroglobulinemia, or other lymphoproliferative disorders. The prognosis is good in the absence of overt malignant disease. Clinical manifestations include slowly progressive renal failure and bone pain due to osteomalacia. The diagnosis of Fanconi syndrome can be made when a patient with a monoclonal plasma cell disorder presents with aminoaciduria, phosphaturia, and glycosuria. Electrolyte abnormalities typically include hypokalemia, hypophosphatemia, and hypouricemia. Bence Jones proteinuria is usually present and is almost always of the κ type. Rare patients have been reported with Fanconi syndrome associated with λ Bence Jones proteinuria.

Treatment consists of supplementation with phosphorus, calcium, and vitamin D. Chemotherapy may benefit patients with rapidly progressive renal failure or symptomatic malignancy.

Solitary Plasmacytomas

Solitary Plasmacytoma of Bone (Intramedullary Plasmacytoma)

Solitary plasmacytoma of bone is a rare form of plasma proliferative disease. Its true incidence has not been described, but it accounts for ~2 to 5% of malignant plasma cell dyscrasias treated at large referral centers (223,1068,1069). In most series, the definition has required the following characteristics: (a) histologic proof that the solitary lesion is a plasmacytoma; (b) no other bone lesions on metastatic bone survey; (c) <5% plasma cells from a random bone marrow biopsy site; and (d) the absence of anemia, hypercalcemia, or renal insufficiency that had no attributable cause. Some definitions allow for <10% bone marrow plasma cells (718), and others have restricted the quantity of the serum or urine M spike. Others have excluded patients who developed disseminated myeloma within a year after diagnosis of the solitary plasmacytoma (1070). The International Myeloma Working Group has adopted the above definition, but adds that if MRI is done, it should not demonstrate any other areas of marrow involvement (220).

There is a clear male preponderance, and the median age is 55 years (718,1070,1071,1072). Plasmacytomas most commonly arise from the axial skeleton, particularly the vertebral bodies. Pain is the usual presentation. Spinal cord or nerve root compression may also be present. If the patient also has evidence of a peripheral neuropathy, and especially if the bone lesion is sclerotic, one should consider the diagnosis of POEMS. Monoclonal proteins are present in ~50% of patients (718,1070).

Careful staging should be done in all patients, including a complete blood cell count, protein electrophoresis and immunofixation of the serum and urine, serum immunoglobulin free light chains, a complete radiographic skeletal survey, and random bone marrow aspiration and biopsy. At a minimum, immunohistochemical stains should be done on the bone marrow to identify a clone apart from the solitary plasmacytoma. MRI of the entire spine and pelvis should also be done to determine whether the lesion is solitary. Using MRI, Moulopoulos et al. (157) found unexpected bone marrow involvement in 4 of 12 patients with apparently solitary plasmacytomas of bone. FDG-PET may also provide useful information.

From a historical perspective, solitary plasmacytomas of bone were treated surgically with or without adjuvant radiation (1073). Present-day, single-modality, definitive radiation therapy is the treatment of choice. Although the optimal dose has not been established by randomized controlled trials, 4,000 to 5,000 cGy encompassing all disease with a margin of normal tissue is recommended by most experts on the basis of retrospective local relapse rate data (718,719,720,1074). This principle, however, has been challenged by recent data that show no difference in local control as long as the therapeutic dose is >3,000 cGy (721). Median 10-year disease-free survival is ~25 to 40% (718,1075). Median time to failure, that is, local relapse, appearance of another plasmacytoma, or disseminated myeloma, is about 2 years (718,721,1075). Risk factors for evolution to myeloma include absence of a monoclonal protein at presentation (nonsecretory disease), depression of immunoglobulin values at presentation, persistence of the monoclonal protein after treatment (1075), abnormal immunoglobulin free light-chain ratio at presentation (1076), tumor size of >5 cm,

and a nonvertebral presentation (721).The persistence of a monoclonal protein after radiation therapy does not guarantee relapse (223,718), even after >10 years of follow-up (1075). In rare instances, the maximum reduction of myeloma protein may take several years after completion of the radiation therapy (223,718). Median survival for all patients presenting with solitary plasmacytoma of bone—based on data from patients staged before routine use of MRI and bone marrow clonality studies—was ~10 years (718,721,1069,1075,1077). For those who progressed to myeloma, the median survival was 44 months after the start of chemotherapy (223). Adjuvant chemotherapy has not been shown to produce a survival advantage and carries the risk of treatment-related myelodysplastic syndromes or acute leukemia; it cannot be recommended.
With increasingly sensitive diagnostic techniques, the incidence of solitary myeloma will decrease, but probably the relapse rate will too.

Extramedullary Plasmacytoma

Solitary extramedullary plasmacytomas represent ~3% of all plasma cell neoplasms (1078). They most commonly affect men in their early 60s and occur in the upper respiratory tract (paranasal sinuses, nose, nasopharynx, and tonsils). They also occur in lymph nodes, lung, thyroid, gastrointestinal tract, liver, spleen, pancreas, testes, breast, or skin (1079). Amyloid involvement of the plasmacytoma occurs on occasion. Although extramedullary plasmacytomas are not common in newly diagnosed multiple myeloma, classic myeloma must be excluded by thorough staging. A monoclonal protein in the serum and urine, lytic bone lesions, anemia, renal insufficiency, and hypercalcemia should be excluded. Histologically, an extramedullary plasmacytoma should be differentiated from reactive plasmacytosis, plasma cell granuloma, poorly differentiated neoplasms, and immunoblastic lymphoma. Some extra-medullary plasmacytomas may represent marginal zone B-cell lymphomas that have undergone plasmacytic differentiation (1080). Dimopoulos et al. (1078) compiled 128 extramedullary plasmacytoma patients from eight published series (1069,1079,1081,1082,1083,1084,1085,1086) and summarized their clinical course. The local failure rate was 7%, multifocal extramedullary relapse occurred in 13%, and classic myeloma developed in 15%. Local radiation therapy is the treatment of choice, and adjuvant chemotherapy is not recommended. The 10-year disease-free survival is 70 to 80%. Ozsahin et al. (1076) compiled 52 patients through a Rare Cancer Network study. There findings were similar, with a 5-year progression rate of about 25% and a 5-year survival approaching 90%.

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