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Current Trends in Multiple Myeloma Management

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Treatment of multiple myeloma, a B-cell cancer, is usually palliative, however, as a result of intensive clinical research there are numerous new treatment options available today. The present review summarizes non-transplant treatment options for multiple myeloma on the basis of available publications. Treatment with new substances, such as immunomodulatory agents, farnesyl transferase inhibitors and apoptosis stimulators, and their mechanisms of action are discussed. In addition to this systematic review of the available evidence on multiple myeloma therapy we have also summarized current recommendations from national and international organizations on aspects of the treatment of multiple myeloma. This should enable readers to see different points of view at a glance and, hopefully, will provide a basis for translation of the available evidence into the best possible therapy.

KEY WORDS: Myeloma; Bisphosphonates; Bortezomib; Thalidomide; Lenalidomide; Tipifarnib; Arsenic trioxide

Multiple myeloma

Multiple myeloma is a cancer of the plasma cells that produces abnormal antibodies called paraproteins (also known as M proteins) and various blood and urine tests are available for the quantitative measurement of paraproteins.

Multiple myeloma grows on the interior or exterior of bones; healthy bone marrow contains < 5% of plasma cells. Osteolytic lesions may lead to fractures of the long bones or compression fractures in the spine and bone pain is often a symptom of multiple myeloma. Furthermore, when myeloma cell growth occurs inside marrow-producing bones, healthy cells (e.g. red blood cells, white blood cells, platelets) are 'crowded out' by the cancer cells, causing immune system impairment, with an increased susceptibility to infections, as well as tiredness and weakness. Myeloma cells also produce growth factors in their microenvironment which promote either their own growth or angiogenesis, the creation of new blood vessels.

CLINICAL SYMPTOMS

A mnemonic sometimes used to remember common myeloma-related organ or tissue impairment (end-organ damage) is CRAB (C, calcium [elevated]; R, renal failure; A, anaemia; B, bone lesions). Patients with monoclonal plasma cell proliferation in their bone marrow without end-organ

damage can be considered asymptomatic. They do not require therapy but must be regularly monitored since they have a life-long risk of progressing to multiple myeloma or developing related malignancies. Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant condition that may progress to multiple myeloma.

In clinical practice, the Durie–Salmon staging system[1] (Table 1) was replaced by the International Staging System (ISS) (Table 2).[2,3] The ISS system, however, is based on only two factors, serum β_2-microglobulin and serum albumin, and is independent of age, type of therapy and geographical region. Analysis of prognostic factors is essential to compare outcomes within and between clinical trials. For individual patients the best staging system can predict survival outcome with around 70% sensitivity and specificity.[3] Whether staging systems can beneficially influence choice of therapy is unproven.[4]

TABLE 1:
The Durie–Salmon staging system for multiple myeloma[1]

	Stage I	Stage II	Stage III
Criteria	All of the following: • Haemoglobin > 10 g/dl • Bone X-ray, normal bone structure (scale O), or solitary bone plasmacytoma only • Low M-component production rates • IgG < 5.0 g/dl • IgA < 3.0 g/dl • Urine light-chain M-component in electrophoresis < 4 g/24 h	Fitting neither Stage I nor Stage III	One or more of the following: • Haemoglobin < 8.5 g/dl • Serum calcium > 12 mg/dl • Advanced lytic bone lesions (scale 3) • High M-component production rates • IgG > 7.0 g/dl • IgA > 5.0 g/dl • Urine light chain M-component in electrophoresis > 12 g/24 h
Cancer cell mass	< 0.6 x 10^{12} cells/m^2 of body surface	> 0.6 x 10^{12} cells/ m^2 of body surface	> 1.2 x 10^{12} cells/m^2 of body surface
Renal function	Serum creatinine < 2 mg/dl: Stage A		Serum creatinine > 2 mg/dl: Stage B

IgA, immunoglobulin A; IgG, immunoglobulin G.

TABLE 2:
The International Staging System (ISS) for multiple myeloma[2,3]

	Stage I	Stage II	Stage III
Criteria	β_2-Microglobulin < 3.5 g/l Albumin > 3.5 g/dl	β_2-Microglobulin < 3.5 g/l Albumin < 3.5 g/dl or β_2-microglobulin 3.5 – 5.5 g/l	β_2-Microglobulin > 5.5 g/l
Median survival	62 months	45 months	29 months

EPIDEMIOLOGY AND RISK FACTORS

With an estimated 86 000 new multiple myeloma cases per year worldwide,[5] multiple myeloma is the second most prevalent blood cancer after non-Hodgkin's lymphoma, making up 1% of all cancers.[5] It accounts for 62 546 deaths per year,[6] which is approximately 2% of all cancer deaths. In the USA, multiple myeloma is more common amongst the Afro-American population than in the white population, and occurs more often in men than in women (with a ratio of 3:2). This distribution probably only reflects the fact that lower socioeconomic status is associated with a higher risk[7] and that men are more likely to work in low-income industrial sectors associated with more risk factors. Recently, associations between obesity and multiple myeloma have been established.[8] Finally, the risk of developing multiple myeloma increases with age.[9] Multiple myeloma cannot be cured; mean survival is 3 years with fewer than 10% of patients living longer than 10 years.[10,11]

Therapy management

Treatment strategy for multiple myeloma is determined mainly by the stage of the disease, defined according to the ISS,[2,3] and by the patient's age. Asymptomatic patients with multiple myeloma do not benefit from early initiation of treatment[12,13] and drug therapy is, therefore, not indicated in this group. Patients with disease stage II and III should always start treatment.

CONVENTIONAL THERAPY OPTIONS

Until very recently, the standard therapy for multiple myeloma involved glucocorticoids in combination with alkylating agents and/or anthracyclines. Melphalan/prednisone has been used as a first-line treatment for 30 years, however melphalan, like other alkylating drugs, is associated with an increased risk of marrow toxicity, including myelodysplasia, acute leukaemia and impaired stem cell production, and long-term melphalan/prednisone treatment increases the risk of drug-induced acute myeloid leukaemia.[14] This is an important consideration in patients who are candidates for high-dose therapy with stem cell rescue (autologous transplants). Variations of the melphalan/prednisone regimen (e.g. vincristine, carmustine, melphalan, cyclophosphamide, prednisone) have not proven to be superior.[15] Conventional therapy achieves up to 5% complete remissions.[16]

For salvage therapy, relapsed or primary refractory disease, a vincristine, doxorubicin and dexamethasone (VAD) regimen is used. This, or similar, combination therapies achieve remission in 50 – 75% of patients.[17 – 19] These regimens also show greater toxicity. The most active agent in the combination is dexamethasone, however a recent prospective, randomized trial, compared the efficacy and safety of several dexamethasone-based regimens (dexamethasone plus melphalan; dexamethasone plus interferon α-2b; or dexamethasone alone) with melphalan/prednisone in 500 patients aged > 65 years.[20] After 3 years, this trial was stopped because of the poor rate and length of progression free survival among patients receiving dexamethasone without melphalan, although there was no significant disadvantage with respect to overall survival.

BONE DISEASE MANAGEMENT: BISPHOSPHONATES

Appropriate supportive treatment to prevent and treat disease-related complications, particularly of the osteolytic lesions, and the resulting hypercalcaemia and their consequences, such as bone pain and fractures, is a particularly important part of

the management of multiple myeloma. Bisphosphonates are potent osteoclast inhibitors and, therefore, suppress both natural and pathological bone resorption.[21,22] Bisphosphonates are pyrophosphate analogues in which the oxygen bridge has been replaced by a carbon with various side chains (P–C–P).[23] Clodronate and etidronate are non-aminobisphosphonates because they do not contain nitrogen in a side chain, in contrast to alendronate, risedronate, pamidronate, zoledronic acid and ibandronate which are called aminobisphosphonates.

As bisphosphonates have an inhibitory effect on bone resorption these clinical studies were able to show a reduction in pathological bone fractures in multiple myeloma and in breast cancer.[24 – 26] The latest Cochrane Collaboration Systematic Review by Djulbegovic *et al.*[27] on the role of bisphosphonates in multiple myeloma supports the standard use of bisphosphonates in multiple myeloma. In clinical practice, patients with multiple myeloma are usually treated with bisphosphonates throughout their cancer therapy.

In general, serious side-effects due to bisphosphonate treatment are rare. The most frequent side effects are gastro-intestinal.[27] Osteonecrosis of the jaw (ONJ) has been reported[28 – 31] and Woo *et al.*[32] recently showed that 94% of published ONJ cases were in patients with multiple myeloma and metastatic carcinoma who were receiving intravenous, nitrogen-containing bisphosphonates; accordingly, these patients are at the greatest risk for ONJ. Other recent studies have aimed to identify the frequency of ONJ (7.4% and 11%).[33,34] A retrospective review established the following risk factors for developing ONJ: dental extraction; treatment with pamidronate/zoledronate; long follow-up time; and older age at diagnosis of multiple myeloma.[35] Further investigations, particularly randomized studies, are undoubtedly needed in order to be able to offer patients the best possible and safest treatments.

Novel agents

The key challenge facing developers of multiple myeloma therapies is how to improve cure rates. The best active induction therapies may kill most myeloma cells, although some cells will have resistant mutations that allow them to survive and propagate, which is why patients relapse. Identifying the cells that survive induction chemotherapy and finding more effective means of killing a greater proportion of myeloma cells are important goals. Myeloma cells must interact with the microenvironment of the bone marrow to survive and proliferate. Interfering with the components of this interaction is a target of new therapies. Several 'new' tumour targeting agents appear to be effective in combination with conventional agents and clinical trials should confirm the expectation of the limited toxicity of this 'targeted' therapy.

BORTEZOMIB

Bortezomib is a low molecular weight protease inhibitor that acts via several pathways, including those that influence apoptosis and angiogenesis. Proteases are enzymatic complexes that are responsible for protein breakdown and that also play a role in cell division. One example of such an enzymatic complex is nuclear factor-κB (NF-κB), which is inhibited by bortezomib.

The latest studies have shown that bortezomib can produce a response in about 30% of patients with relapsed disease, while additional administration of dexa-methasone can produce remission in

patients who do not respond to bortezomib as a single agent.[36]

The recent approval of bortezomib in the USA for second-line treatment in patients with multiple myeloma was based on data from the randomized phase III APEX study. Patients with relapsed multiple myeloma were included in this international multicentre trial and randomized to receive bortezomib or dexamethasone. Interim results were presented at the 2004 meeting of the American Society of Hematology (ASH).[37] APEX was terminated early because of favourable results for bortezomib therapy and updated results of the APEX trial after extended follow-up were presented at the ASH meeting in 2005.[38]

Richardson *et al.*[38] reported a further analysis of this phase III trial of 669 patients. Median duration of therapy for responders (complete or partial response) was 7.2 months. Improved response with longer therapy (after cycle 6) was observed in 76 patients (56% of responders) in the bortezomib arm (20 patients improved from minor or partial response to complete response, and 56 patients from minor response to partial response). Furthermore, 28 of 135 responders (21%) achieved first response (complete or partial response) after cycle 4, including 18 patients (13%) on or after cycle 6, and 10 patients (7%) on or after cycle 8. Overall survival increased substantially with increased follow-up time. These results support the findings of the original analysis,[37] which demonstrated a superior response rate, time to progression and survival for bortezomib over dexamethasone alone.

THALIDOMIDE

Thalidomide has been shown to have pleiotropic effects including antiangiogenic, immunomodulatory, neurological and anti-inflammatory effects.[39,40] With regard to its antiangiogenic effects, it has been proposed that it downregulates tumour necrosis factor-α (TNF-α), basic fibroblast growth factor and vascular endothelial growth factor (VEGF), and corresponding activity has been found *in vivo* in the chick chorioallantoic membrane assay.[41]

Thalidomide was first shown to be effective as a single agent in patients with relapsed and refractory multiple myeloma.[42] Numerous subsequent studies have confirmed its efficacy, with a response rate of around 30% when used alone[43,44] and around 60% when used in combination with dexamethasone.[45] A review by Glasmacher *et al.*[46] identified 42 uncontrolled phase II trials of thalidomide as monotherapy in relapsed/refractory patients. Complete or partial response was 29.4% and the median overall survival from all trials was reported to be 14 months.

Ludwig *at al.*[47] reported a phase II/III study of a thalidomide/dexamethasone combination versus the standard melphalan/prednisone for first-line treatment in 350 patients. A per protocol analysis in 125 patients evaluable for response revealed an overall response rate of 89% in the thalidomide/dexamethasone group and 66% in the melphalan/prednisone group.[48,49] Addition of thalidomide to standard melphalan/prednisone in a study conducted by French investigators showed significantly superior outcomes in terms of overall survival and time to progression in the melphalan/prednisone/thalidomide group compared with either the melphalan/prednisone or autologous stem cell transplantation (auto-SCT) groups.[50] A prospective trial of melphalan/prednisone/thalidomide treatment conducted by the Italian Multiple Myeloma Network also showed promising

results.[51] The 2-year event-free survival rate in the melphalan/prednisone/thalidomide group with 129 evaluated patients was 54% versus 27% in the melphalan/prednisone group with 126 evaluated patients.

Thalidomide-based therapies have revolutionized the treatment of multiple myeloma in recent years, but the toxicity associated with thalidomide, notably its well-known teratogenic effects and the risk of venous thromboembolism, remains problematic and the drug should, therefore, be administered with specific precautions,[52] including strict contraceptive precautions, in both sexes.

THALIDOMIDE-DERIVED IMMUNOMODULATORY DRUGS

The shortcomings of thalidomide have prompted the development of more potent thalidomide analogues with improved safety profiles and some potent thalidomide-derived immunomodulatory drugs (IMiD®s) are available. Like thalidomide, IMiD®s stimulate the proliferation of activated T cells, increase levels of interferon-γ and interleukin-2, and promote natural killer cell-mediated killing of myeloma cells.[53] IMiD®s may also directly inhibit mitogen-activated protein kinase signalling, which may account for the downregulation of interleukin-6 seen with IMiD® treatment of cells *in vitro*.[54]

Lenalidomide

The thalidomide derivative, lenalidomide, is a lead compound of the second generation of IMiD®s. This new group of thalidomide analogues are immunomodulatory drugs initially developed as more potent inhibitors of TNF-α.[55,56] and lenalidomide is 2000 times more potent than thalidomide at inhibiting TNF-α.[57] The immunomodulatory effects of lenalidomide include: growth arrest or apoptosis of drug-resistant myeloma cell lines; abrogation of myeloma cell adhesion to bone marrow stromal cells; and modulation of cytokines that promote the growth, survival and drug resistance of myeloma cells.[58 – 60] Lenalidomide is non-teratogenic in rabbits and has a different clinical toxicity profile to that of thalidomide.[61]

Lenalidomide has been evaluated in a large phase III clinical trial and in several phase II studies. In a multicentre, phase II, open-label trial of 222 patients with relapsed or refractory multiple myeloma conducted by Richardson *et al.*[62] lenalidomide monotherapy achieved complete or partial response in 25% of patients, stable disease or better in 71%, and a median time to progression of approximately 6 months. The study data also suggest a manageable toxicity of lenalidomide with a very low incidence of deep venous thromboembolism (DVT) and minimal treatment-emergent neuropathy. Another phase II study by Rajkumar *et al.*,[63] in 34 patients not previously treated, examined the results of a combination of lenalidomide and high-dose dexamethasone. The objective remission rate was 91%. No cases of deep-vein thrombosis were seen.

In two phase III studies involving a combined total of 705 patients with symptomatic refractory myeloma, the combination of lenalidomide and high-dose dexamethasone (Len–Dex) was compared with high-dose dexamethasone plus placebo (Dex–placebo).[64,65] The overall response rate in the USA trial by Weber *et al.*[64] was greater with Len–Dex than with Dex–placebo (59.4% versus 21.1%). Complete response was achieved in 12.9% of patients treated with Len–Dex and in 0.6% of patients treated with Dex–placebo. The overall response rate in the international trial by Dimopoulous *et al.*[65] was greater in patients

who received Len–Dex than in patients who were given Dex–placebo (58% versus 22%).

In a phase II study by Richardson *et al.*,[66] lenalidomide was used in 102 patients for second-line therapy. Patients were randomized to receive 15 mg twice daily or 30 mg once daily. After two cycles of monotherapy, patients with progressive or stable disease received lenalidomide plus dexamethasone. After lenalidomide monotherapy, 12% of the patients in the once-daily group and no patient in the twice-daily group had complete remission. Partial remissions rates were 6% and 14%. After combination of lenalidomide plus dexamethasone, 2% of patients in the once-daily group and no patient in the twice-daily group achieved complete response. Partial remission rates were 20% and 22%, respectively. After dexamethasone addition, one case of deep-vein thrombosis was reported in the once-daily group and two cases in the twice-daily group.

In June 2006, the USA's Food and Drug Administration (FDA) granted approval for lenalidomide in combination with dexamethasone for multiple myeloma patients with at least one prior therapy.

FARNESYL TRANSFERASE INHIBITORS

Farnesyl transferase inhibitors are a promising new group of drugs aimed at selective *ras* (proto)oncogene inhibition. Ras proteins are small guanosine-5′-triphosphate (GTP)-binding proteins that are involved in the regulation of various cellular processes, such as cell growth, differentiation and intracellular signal transduction.[67,68] Ras mutations lead to uncontrolled Ras activation, which in turn plays an important role in carcinogenesis. They occur in up to 39% of newly diagnosed multiple myeloma patients.[69] In the underlying Ras modifications the phenylation reactions by farnesyl transferase play a particularly important role.[70] Their blockade by farnesyl transferase inhibitors is a potentially important therapeutic approach that is currently being investigated in a number of ongoing studies.

Tipifarnib

Tipifarnib is the farnesyl transferase inhibitor at the most advanced stage of clinical development. It is an oral non-peptidomimetic farnesyl transferase inhibitor[71] developed to inhibit a variety of farnesylated targets potentially relevant to the therapy of various malignancies. The agent has, thus far, been tested in a wide array of both solid tumours and myeloid malignancies.[72]

Despite its modest single-agent activity in multiple myeloma,[73] tipifarnib in combination with other agents should be useful for treating multiple myeloma. In a preclinical study, Kaufman *et al.*[74] investigated the mechanism of action of tipifarnib in combination with bortezomib. The investigators presented their hypothesis that the combination of bortezomib and tipifarnib results in synergistic cell death by overcoming the antiapoptotic effects of an antiapoptotic protein, Akt; Akt overexpression has been associated with resistance to bortezomib induced apoptosis. Their results showed, however, that this combination is effective and synergistic in human myeloma cell lines and patient myeloma cells. In addition, good apoptosis rates were found, suggesting a potential future role of tipifarnib as an adjunctive therapy.

APOPTOSIS-STIMULATING AND CYTOTOXIC DRUGS

Apoptosis, or programmed cell death, is a common property of all multicellular

organisms and occurs in a variety of physiological situations.[75,76] An apoptotic stimulus induces an initiation and commitment phase followed by a degradation phase. The final pathway that leads to execution of the death signal involves the activation of a series of proteases, termed caspases.[77 – 79] Activation of the effector caspase cascade differs between the type I 'extrinsic' (death receptor-mediated) and the type II 'intrinsic' (mitochondria-mediated) pathways.[80] The 'extrinsic' pathway generates an apoptotic signal following the aggregation of death ligands that involves caspase-8 and caspase-10, and the 'intrinsic' pathway generates signals through mitochondria that involve caspase-9.[81] In some cases, type I activation may also proceed down the mitochondrial pathway.[82] Selective activation of caspases in cancer cells, leading to induction of their apoptosis, would be an attractive approach in the treatment of multiple myeloma.

Cytotoxic drugs may prevent DNA replication essential for cell division, or disrupt cell metabolism at any site. They act predominantly on rapidly dividing cells. Cytotoxic anticancer drugs are collectively the largest and most established chemotherapy group, however, in an effort to improve patients' tolerance of the conventional chemotherapy regimens for treating multiple myeloma, modified formulations may be of benefit. The most notable example is liposomal doxorubicin.

Arsenic trioxide

The mechanism of action of arsenic trioxide has not been fully elucidated, but it has been shown to inhibit growth and induce apoptosis in myeloma cell lines. Arsenic trioxide activates important caspases in both the 'extrinsic' and 'intrinsic' apoptotic pathways.[83] Myeloma cells thrive on interleukin-6 and VEGF secreted in the bone marrow microenvironment. Arsenic trioxide appears to reduce the production of interleukin-6 and VEGF in the bone marrow microenvironment, an action that partially explains the agent's growth-inhibitory effects.[69]

The efficacy of arsenic trioxide has been tested in a phase II study in 14 patients.[84] In two patients there was a > 50% M-protein reduction and in one patient the reduction was > 25% with an objective remission of 21%. Eight patients did not respond and three patients had progressive disease. Another multicentre phase II study evaluated a higher dose of single-agent arsenic trioxide.[85] Eight (33%) of the 24 heavily pretreated patients who were assessable experienced an objective response, six patients had stable disease and five patients had progressive disease.

Trials are underway to investigate the use of arsenic trioxide with or without ascorbic acid and in various combinations with other agents, such as dexamethasone and melphalan, which are known to be effective in myeloma.[86] A phase I and II clinical trial sponsored by the American National Cancer Institute determined the safety and efficacy of arsenic trioxide in combination with ascorbic acid in patients with relapsed or refractory multiple myeloma.[87] This combination did not show significantly different results compared with the reported efficacy and safety of arsenic trioxide alone. Cardiac arrhythmia and sudden death, which were reported in two previous small studies of arsenic trioxide alone in patients with acute promyelocytic leukaemia[88,89] were not observed.

Berenson *et al.*[90] investigated the efficacy and safety of a combination of melphalan, arsenic trioxide and vitamin C (MAC) in patients with relapsed/refractory multiple

myeloma. In their multicentre phase II study this combination was given to 65 patients and 31 (48%) patients had an objective response (two complete response, 15 partial response, 14 minor response). Median progression-free survival and overall survival were 7 and 19 months, respectively. Specific grade 3/4 haematological (3%) or cardiac adverse events were infrequently reported, as well as frequent grade 3/4 non-haematological adverse events such as fever/chills (15%), pain (8%) and fatigue (6%). The authors concluded that the MAC regimen is effective in multiple myeloma patients who have either relapsed or are refractory to standard and/or investigational multiple myeloma treatments.

Liposomal doxorubicin

Doxorubicin is an anthracycline and they interact with several different cellular targets, most importantly topoisomerase II. It is by inhibiting this DNA religation enzyme that anthracyclines exert their cytotoxic effect. Another mechanism leading to cell death, known as DNA intercalation, involves insertion of the anthracycline molecule between base pairs. This phenomenon causes single- and double-stranded breaks in DNA that inhibit cell proliferation. The free radicals generated by the reductive metabolism of anthracyclines may also damage cellular structures.

Conventional doxorubicin is a key component of the VAD regimen and liposomal doxorubicin is a component of the reduced-dose dexamethasone, vincristine and liposomal doxorubicin (dVD) regimen. Liposomal doxorubicin consists of doxorubicin incorporated into polyethylene glycol-coated liposomes. The liposomes significantly increase the length of time that doxorubicin can circulate in the body compared with the conventional doxorubicin formulation. Liposomal doxorubicin is associated with less myelotoxicity, cardiotoxicity and nephrotoxicity compared with conventional doxorubicin in the treatment of acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma and metastatic breast cancer. Preferential accumulation of liposomes at tumour sites enables administration of lower doses of the active agent.[91]

Data from randomized trials comparing dVD and VAD in newly diagnosed multiple myeloma patients showed that the two regimens produced comparable response rates (44% versus 41%[92] and 61.4% versus 61.3%[93]). Patients treated with dVD experienced significantly less grade 4 neutropenia, injection-site reactions and alopecia, but significantly more erythrodysesthesia (also known as hand-foot syndrome) which is known to be associated with liposomal doxorubicin.

Cisplatin

The platinum complex, cisplatin, triggers antitumour effects based on its ability to bind covalently to the nucleobases of DNA leading to the formation of DNA intrastrand crosslinks. Cisplatin is not used as a single agent for the treatment of multiple myeloma,[94 – 96] however, as is obvious from the following examples, it plays an important role in multiple-drug combination regimens against this disease. The combination of dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP) has proved to be an effective salvage therapy for refractory/relapsed multiple myeloma patients and is also well tolerated and effective for peripheral blood stem cell mobilization.[97 – 99] It can be used in consolidation therapy after auto-SCT.[100,101] Other effective cisplatin-containing

TABLE 3:
Guidelines currently available for the management of multiple myeloma[106 – 111]

Guideline source	Candidates for watch and wait	Chemotherapy for nonauto-SCT candidates	Chemotherapy for auto-SCT candidates	Bisphosphonates	Second line
ESMO 2005[106]	Asymptomatic patients	Oral combination of melphalan	VAD-type regimens	For patients with stage III or relapsed disease	VAD; thalidomide alone or in combination with high-dose dexamethasone; bortezomib
UK-MF 2005[107]	Asymptomatic patients with myeloma-related organ damage	Melphalan or cyclophosphamide with or without prednisolone	VAD regimen or a VAD-type regimen	Oral clodronate or intravenous pamidronate or intravenous zoledronic acid in all myeloma patients requiring chemotherapy	MP in patients who relapse after MP; thalidomide; bortezomib for third-line therapy
SIE; SIES; GITMO 2004[108]	Selected asymptomatic patients without chromosome 13 deletion	MP	VAD x 4	Long-term clodronate, pamidronate or zoledronic acid in patients with bone lesions or severe osteopenia	For patients who are not auto-SCT candidates or are refractory to auto-SCT, thalidomide with or without conventional chemotherapy
IMF2003[109]	Asymptomatic patients	MP; cytoxan alone or in combination; VAD regimen; dexamethasone or other steroids alone; thalidomide plus dexamethasone	VAD; VAD-based; thalidomide and dexamethasone, cytoxan	Clodronate, or zoledronic acid in all patients with myeloma-related bone disease	Treatment on an individual basis depending on prior therapy

TABLE 3 (continued):
Guidelines currently available for the management of multiple myeloma[106 – 111]

NCCN 2001[110]	Asymptomatic patients	MP; vincristine/ carmustine/melphalan/ cyclophosphamide/ prednisone; VAD; dexamethasone	Stem cell toxins, such as nitrosoureas or alkylating agents and pelvic irradiation should be avoided	All patients with documented bone disease	Repetition of primary conventional dose therapy (if relapse > 6 months); cyclophosphamide with VAD; etoposide/ dexamethasone/ cytarabine(ara-C)/cisplatin; high-dose cyclophosphamide
CCO-PGI 2002[111]	Asymptomatic patients	Multi-agent chemotherapy; MP	VAD-like	N/A	N/A

auto-SCT, autologous stem cell transplantation; ESMO, European Society for Medical Oncology; UK-MF, United Kingdom Myeloma Forum; SIE, Italian Society of Hematology; SIES, Italian Society of Experimental Hematology; GITMO, Italian Group for Bone Marrow Transplantation; IMF, International Myeloma Foundation; NCCN, National Cancer Care Network; CCO-PGI, Cancer Care Ontario Practice Guideline Initiative; VAD, vincristine, doxorubicin and dexamethasone; MP, melphalan and prednisone; N/A, not available.

multiple-drug combination regimens for previously treated multiple myeloma patients are ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin) and DTPACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide).[102,103]

Furthermore, the combination of cisplatin with the nucleoside analogue, gemcitabine, was active in patients not responding to gemcitabine alone[104] and *in vitro* experiments showed that U266 multiple myeloma cells could be sensitized to cisplatin-induced apoptosis by the STAT3 pathway inhibitors, piceatannol and tyrphostin.[105]

Summary of treatment recommendations

National and international organizations have published guidelines for the treatment of multiple myeloma and a number of issues relating to current recommendations are summarized in Table 3.[106 – 111]

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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References

1 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.
2 International Myeloma Working Group: 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.
3 Greipp PR, San Miguel J, Durie BG, *et al*: International staging system for multiple myeloma. *J Clin Oncol* 2005; **23**: 3412 – 3420.
4 Smith A, Wisloff F, Samson D: Guidelines on the diagnosis and management of multiple myeloma. *Br J Haematol* 2006; **132:** 410 – 451.
5 Parkin DM, Bray F, Ferlay J, *et al*: Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55:** 74 – 108.
6 Kamangar F, Dores GM, Anderson WF: Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006; **24:** 2137 – 2150.
7 Baris D, Brown LM, Silverman DT, *et al*: Socioeconomic status and multiple myeloma among US blacks and whites. *Am J Public Health* 2000; **90:** 1277 – 1281.
8 Calle EE, Rodriguez C, Walker-Thurmond K, *et al*: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003; **348:** 1625 – 1638.
9 Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*, 2nd edn. Oxford: Oxford University Press, 1996; pp 946 – 970.
10 Myeloma Trialists' Collaborative Group: Combination chemotherapy versus melphalan plus prednisone as treatment of multiple myeloma: an overview of 6633 patients from 27 randomized trials. *J Clin Oncol* 1998; **16:** 3832 – 3842.
11 Kyle RA: Long-term survival in multiple myeloma. *N Engl J Med* 1983; **308:** 314 – 316.
12 Hjorth M, Hellquist L, Holmberg E, *et al* on behalf of the Myeloma Group of Western Sweden: Initial versus deferred melphalan–prednisone therapy for asymptomatic multiple myeloma stage I – a randomized study. *Eur J Haematol* 1993; **50:** 95 – 102.
13 Riccardi A, Mora O, Tinelli C, *et al* on behalf of the Cooperative Group of Study and Treatment of Multiple Myeloma: Long-term survival of stage I multiple myeloma given chemotherapy just after diagnosis or at progression of the disease: a multicentre randomized study. *Br J Cancer* 2000; **82:** 1254 – 1260.
14 Cuzick J: Radiation-induced myelomatosis. *N Engl J Med* 1981; **304**: 204 – 210.
15 Gregory WM, Richards MA, Malpas JS: Combination chemotherapy versus melphalan and prednisolone in the treatment of multiple myeloma: an overview of published trials. *J Clin Oncol* 1992; **10:** 334 – 342.
16 Katzel JA: Multiple myeloma; charging toward a bright future. *CA Cancer J Clin* 2007; **57:** 301 – 318.

17 Alexanian R, Barlogie B, Dixon D: High-dose glucocorticoid treatment of resistant myeloma. *Ann Intern Med* 1986; **105:** 8 – 11.
18 Barlogie B, Smith L, Alexanian R: Effective treatment of advanced multiple myeloma refractory to alkylating agents. *N Engl J Med* 1984; **310:** 1353 – 1356.
19 Manconduit M, Le Loet X, Bernard JF, *et al*: Combination chemotherapy with vincristine, doxorubicin, dexamethasone for refractory of relapsing multiple myeloma. *Br J Haematol* 1986; **63:** 599 – 601.
20 Facon T, Mary JY, Pégourie B, *et al*: Dexamethasone-based regimens versus melphalan–prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. *Blood* 2006; **107:** 1292 – 1298.
21 Berenson JR: The efficacy of pamidronate disodium in the treatment of osteolytic lesions and bone pain in multiple myeloma. *Rev Contemp Pharmacother* 1998; **9:** 195 – 203.
22 Fleisch H: *Bisphosphonates in Bone Disease: from the Laboratory to the Patient*, 3rd edn. New York: Parthenon Publishing Group, 1997; pp 1 – 184.
23 Rodan GA, Fleisch HA: Bisphosphonates: mechanisms of action. *J Clin Invest* 1996; **97:** 2692 – 2696.
24 Elomma I, Blomqvist C, Porkka L, *et al*: Treatment of skeletal disease in breast cancer: a controlled clodronate trial. *Bone* 1987; **8(suppl 1):** S53 – S56.
25 Martoni A, Guaraldi M, Camera P, *et al*: Controlled clinical study on the use of dichloromethylene diphosphonate in patients with breast carcinoma metastasizing to the skeleton. *Oncology* 1991; **48:** 97 – 101.
26 Hortobagyi GN, Theriault RL, Porter L, *et al* on behalf of the Protocol 19 Aredia Breast Cancer Study Group: Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. *N Engl J Med* 1996; **335:** 1785 – 1791.
27 Djulbegovic B, Wheatley K, Ross J, *et al*: Bisphosphonates in multiple myeloma. *Cochrane Database Syst Rev* 2002; CD003188.
28 Marx RE: Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003; **61:** 1115 – 1117.
29 Ruggiero SL, Mehrotra B, Rosenberg TJ, *et al*: Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004; **62:** 527 – 534.
30 Durie BGM, Katz M, Crowley J: Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med* 2005; **353:** 99 – 102.
31 Bagan JV, Murillo J, Jimenez Y, *et al*: Avascular jaw osteonecrosis in association with cancer chemotherapy: series of 10 cases. *J Oral Pathol Med* 2005; **34:** 120 – 123.
32 Woo SB, Hellstein JW, Kalmar JR, *et al*: Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006; **144:** 753 – 761.
33 Zervas K, Verrou E, Teleioudis Z, *et al*: Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients. *Br J Haematol* 2006; **134:** 620 – 623.
34 Dimopoulos MA, Kastritis E, Anagnostopoulos A, *et al*: Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. *Haematologica* 2006; **91**: 968 – 971.
35 Badros A, Weikel D, Salama A, *et al*: Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. *J Clin Oncol* 2006; **24:** 945 – 952.
36 Bross PF, Kane R, Farrell AT, *et al*: Approval summary for bortezomib for injection in the treatment of multiple myeloma. *Clin Cancer Res* 2004; **10:** 3954 – 3964.
37 Richardson P, Sonneveld P, Schuster M, *et al*: Bortezomib demonstrates superior efficacy to high-dose dexamethasone in relapsed multiple myeloma: final report of the APEX study. *Blood* 2004; **104:** 1479 [ASH Annual Meeting Abstract].
38 Richardson P, Sonneveld P, Schuster M, *et al*: Bortezomib continues demonstrates superior efficacy compared with high-dose dexamethasone in relapsed multiple myeloma: updated results of the APEX trial. *Blood* 2005; **106:** 2547 [ASH Annual Meeting Abstract].
39 D'Amato RJ, Loughnan MS, Flynn E, *et al*: Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci USA* 1994; **91:** 4082 – 4085.
40 Thomas DA, Kantarjian HM: Current role of thalidomide in cancer treatment. *Curr Opin Oncol* 2000; **12:** 564 – 573.
41 Little RF, Wyvill KM, Pluda JM, *et al*: Activity of thalidomide in AIDS-related Kaposi's sarcoma. *J Clin Oncol* 2000; **18:** 2593 – 2602.
42 Singhal S, Mehta J, Desikan R, *et al*: Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 1999; **341:** 1565 – 1571.
43 Juliusson G, Celsing F, Turesson I, *et al*: Frequent good partial remission from thalidomide including best response ever in patients with advanced refractory and relapsed myeloma. *Br J Haematol* 2000; **109:** 89 – 96.
44 Barlogie B, Desikan R, Eddlemon P, *et al*: Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a phase 2 study of 169 patients. *Blood* 2001; **98:** 492 – 494.
45 Dimopoulos MA, Zervas K, Kouvatseas G, *et al*: Thalidomide and dexamethasone combination for refractory multiple myeloma. *Ann Oncol* 2001; **12:** 991 – 995.
46 Glasmacher A, Hahn C, Hoffmann F, *et al*: A systematic review of phase-II trials of

thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. *Br J Haematol* 2006; **132:** 584 – 593.
47 Ludwig H, Drach J, Tóthová E, *et al*: Thalidomide–dexamethasone versus melphalan–prednisone as first line treatment in elderly patients with multiple myeloma: an interim analysis. *Blood* 2005; **106**: 782 [ASH Annual Meeting Abstract].
48 Singhal S, Mehta J, Desikan R, *et al*: Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 1999; **341:** 1565 – 1571.
49 Dimopoulos MA, Zervas K, Kouvatseas G, *et al*: Thalidomide and dexamethasone combination for refractory multiple myeloma. *Ann Oncol* 2001; **12:** 991 – 995.
50 Facon T, Mary J, Harousseau J, *et al*: Superiority of melphalan–prednisone (MP) + thalidomide (THAL) over MP and autologous stem cell transplantation in the treatment of newly diagnosed elderly patients with multiple myeloma. *J Clin Oncol* 2006; **24(suppl):** 1 [ASCO Annual Meeting Abstract].
51 Palumbo A, Bringhen S, Caravita T, *et al*: Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet* 2006; **367:** 825 – 831.
52 Cavenagh JD, Oakervee H, UK Myeloma Forum and the BCSH Haematology/Oncology Task Forces: Thalidomide in multiple myeloma: current status and future prospects. *Br J Haematol* 2003; **120:** 18 – 26.
53 Davies FE, Raje N, Hideshima T, *et al*: Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood* 2001; **98:** 210 – 216.
54 Hideshima T, Chauhan D, Shima Y, *et al*: Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood* 2000; **96:** 2943 – 2950.
55 Bartlett JB, Dredge K, Dalgleish AG: The evolution of thalidomide and its IMiD derivatives as anticancer agents. *Nat Rev Cancer* 2004; **4:** 314 – 322.
56 Anderson KC: The role of immunomodulatory drugs in multiple myeloma. *Semin Hematol* 2003; **40:** 23 – 32.
57 Muller GW, Chen R, Huang SY, *et al*: Amino-substituted thalidomide analogs: Potent inhibitors of TNF-α production. *Bioorg Med Chem Lett* 1999; **9:** 1625 – 1630.
58 Lentzsch S, LeBlanc R, Podar K, *et al*: Immunomodulatory analogs of thalidomide inhibit growth of Hs Sultan cells and angiogenesis *in vivo*. *Leukemia* 2003; **17:** 41 – 44.
59 Mitsiades N, Mitsiades CS, Poulaki V, *et al*: Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications. *Blood* 2002; **99:** 4525 – 4530.
60 Teo SK: Properties of thalidomide and its analogues: implications for anticancer therapy. *AAPS J* 2005; **7:** E14 – E19.
61 Bartlett JB, Tozer A, Stirling D, *et al*: Recent clinical studies of the immunomodulatory drug (IMiD®) lenalidomide. *Br J Cancer* 2005; **93:** 613 – 619.
62 Richardson P, Jagannath S, Hussein M, *et al*: A multicenter, single-arm, open-label study to evaluate the efficacy and safety of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma; preliminary results. *Blood* 2005; **106:** 1565 [abstract].
63 Rajkumar SV, Hayman S, Lacy MQ, *et al*: Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood* 2005; **106:** 781 [abstract].
64 Weber DM, Chen C, Niesvizky R, *et al*: Lenalidomide plus high-dose dexamethasone provides improved overall survival compared to high-dose dexamethasone alone for relapsed or refractory multiple myeloma (MM): Results of a North American phase III study (MM-009). *J Clin Oncol* 2006; **24(suppl):** 7521 [ASCO Annual Meeting Abstract].
65 Dimopoulos MA, Spencer A, Attal M, *et al*: Study of lenalidomide plus dexamethasone versus dexamethasone alone in relapsed or refractory multiple myeloma (MM): results of a phase 3 study (MM-010). *Blood* 2005; **106:** 6 [ASH Annual Meeting Abstract].
66 Richardson PG, Blood E, Mitsiades CS, *et al*: Randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. *Blood* 2006; **108:** 3458 – 3464.
67 Boguski MS, McCormick F: Proteins regulating Ras and its relatives. *Nature* 1993; **366:** 643 – 654.
68 Lowy DR, Willumsen BM: Function and regulation of RAS. *Annu Rev Biochem* 1993; **62:** 851 – 891.
69 Hayashi T, Hideshima T, Akiyama M, *et al*: Arsenic trioxide inhibits growth of human multiple myeloma cells in the bone marrow microenvironment. *Mol Cancer Ther* 2002; **1:** 851 – 860.
70 Kohl NE, Mosser SD, deSolms SJ, *et al*: Selective inhibition of ras-dependent transformation by a farnesyltransferase inhibitor. *Science* 1993; **260:** 1934 – 1937.
71 End DW, Smets G, Todd AV, *et al*: Characterization of the antitumor effects of the selective farnesyl protein transferase inhibitor R115777 *in vivo* and *in vitro*. *Cancer Res* 2001; **61:** 131 – 137.
72 Mesa RA: Tipifarnib: farnesyl transferase inhibition at a crossroads. *Expert Rev Anticancer Ther* 2006; **6:** 313 – 319.
73 Alsina M, Fonseca R, Wilson EF, *et al*:

Farnesyltransferase inhibitor tipifarnib is well tolerated, induces stabilization of disease, and inhibits farnesylation and oncogenic/tumor survival pathways in patients with advanced multiple myeloma. *Blood* 2004; **103:** 3271 – 3277.
74 Kaufman JL, David E, Torre C, *et al*: Enhanced levels of apoptosis by combination of farnesyl transferase inhibition (tipifarnib) and proteasome inhibition (bortezomib) in myeloma cell lines and primary myeloma cells and its mechanistic effects on Akt and caspase pathways. *Blood* 2005; **106:** 1573 [ASH Annual Meeting Abstract].
75 Krammer PH: CD95's deadly mission in the immune system. *Nature* 2000; **407:** 789 – 795.
76 Danial NN, Korsmeyer SJ: Cell death: critical control points. *Cell* 2004; **116:** 205 – 219.
77 Thornberry NA, Lazebnik Y: Caspases: enemies within. *Science* 1998; **281:** 1312 – 1316.
78 Cohen GM: Caspases: the executioners of apoptosis. *Biochem J* 1997; **326:** 1 – 16.
79 Nicholson DW: Caspase structure, proteolytic substrates, and function during apoptotic cell death. *Cell Death Differ* 1999; **6:** 1028 – 1042.
80 Lavrik IN, Golks A, Krammer PH: Caspases: pharmacological manipulation of cell death. *J Clin Invest* 2005; **115:** 2665 – 2672.
81 Jiang X, Wang X: Cytochrome *c* promotes caspase-9 activation by inducing nucleotide binding to Apaf-1. *J Biol Chem* 2000; **275:** 31199 – 31203.
82 Korsmeyer SJ, Wei MC, Saito M, *et al*: Pro-apoptotic cascade activates BID, which oligomerizes BAK or BAX into pores that result in the release of cytochrome *c*. *Cell Death Differ* 2000; **7:** 1166 – 1173.
83 Liu Q, Hilsenbeck S, Gazitt Y: Arsenic trioxide-induced apoptosis in myeloma cells: p53-dependent G1 or G2/M cell cycle arrest, activation of caspase-8 or caspase-9, and synergy with APO2/TRAIL. *Blood* 2003; **101:** 4078 – 4087.
84 Munshi NC, Tricot G, Desikan R, *et al*: Clinical activity of arsenic trioxide for the treatment of multiple myeloma. *Leukemia* 2002; **16:** 1835 – 1837.
85 Hussein MA, Saleh M, Ravandi F, *et al*: Phase 2 study of arsenic trioxide in patients with relapsed or refractor multiple myeloma. *Br J Haematol* 2004; **125:** 470 – 476.
86 Douer D, Tallman MS: Arsenic trioxide: new clinical experience with an old medication in hematologic malignancies. *J Clin Oncol* 2005; **23:** 2396 – 2410.
87 Bahlis NJ, McCafferty-Grad J, Jordan-McMurry I, *et al*: Feasibility and correlates of arsenic trioxide combined with ascorbic acid-mediated depletion of intracellular glutathione for the treatment of relapsed/refractory multiple myeloma. *Clin Cancer Res* 2002; **8:** 3658 – 3668.
88 Westervelt P, Brown RA, Adkins DR, *et al*: Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide. *Blood* 2001; **98:** 266 – 271.
89 Unnikrishnan D, Dutcher JP, Varshneya N, *et al*: Torsades de pointes in 3 patients with leukemia treated with arsenic trioxide. *Blood* 2001; **97:** 1514 – 1516.
90 Berenson JR, Boccia R, Siegel D, *et al*: Efficacy and safety of melphalan, arsenic trioxide and ascorbic acid combination therapy in patients with relapsed or refractory multiple myeloma: a prospective, multicentre, phase II, single-arm study. *Br J Haematol* 2006; **135:** 174 – 183.
91 Gabizon AA: Pegylated liposomal doxorubicin: metamorphosis of an old drug into a new form of chemotherapy. *Cancer Invest* 2001; **19:** 424 – 436.
92 Rifkin RM, Gregory SA, Mohrbacher A, *et al*: Pegylated liposomal doxorubicin, vincristine, and dexamethasone provide significant reduction in toxicity compared with doxorubicin, vincristine, and dexamethasone in patients with newly diagnosed multiple myeloma: a phase III multicenter randomized trial. *Cancer* 2006; **106:** 848 – 858.
93 Dimopoulos MA, Pouli A, Zervas K, *et al*: Prospective randomized comparison of vincristine, doxorubicin and dexamethasone (VAD) administered as intravenous bolus injection and VAD with liposomal doxorubicin as first-line treatment in multiple myeloma. *Ann Oncol* 2003; **14:** 1039 – 1044.
94 Galanski M, Jakupec MA, Keppler BK: Update of the preclinical situation of anticancer platinum complexes: novel design strategies and innovative analytical approaches. *Curr Med Chem* 2005; **12:** 2075 – 2094.
95 Boulikas T, Vougiouka M: Cisplatin and platinum drugs at the molecular level. *Oncol Rep* 2003; **10:** 1663 – 1682 [review].
96 Ott I, Gust R: Special qualities of inorganic cytostatics. Medicinal chemistry of platinum complexes. *Pharm Unserer Zeit* 2006; **35:** 124 – 133 [in German].
97 Corso A, Mangiacavalli S, Nosari A, *et al*: Efficacy, toxicity and feasibility of a shorter schedule of DCEP regimen for stem cell mobilization in multiple myeloma. *Bone Marrow Transplant* 2005; **36:** 951 – 954.
98 Corso A, Arcaini L, Caberlon S, *et al*: A combination of dexamethasone, cyclophosphamide, etoposide, and cisplatin is less toxic and more effective than high-dose cyclophosphamide for peripheral stem cell mobilization in multiple myeloma. *Haematologica* 2002; **87:** 1041 – 1045.
99 Lazzarino M, Corso A, Barbarano L, *et al*: DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin) is an effective regimen for peripheral blood stem cell collection in multiple myeloma. *Bone Marrow Transplant* 2001; **28:** 835 – 839.

100 Gojo I, Meisenberg B, Guo C, *et al*: Autologous stem cell transplantation followed by consolidation chemotherapy for patients with multiple myeloma. *Bone Marrow Transplant* 2006; **37:** 65 – 72.
101 Barlogie B: High-dose therapy and innovative approaches to treatment of multiple myeloma. *Semin Haematol* 2001; **38:** 21 – 27.
102 D'Sa S, Yong K, Kyriakou C, *et al*: Etoposide, methylprednisolone, cytarabine and cisplatin successfully cytoreduces resistant myeloma patients and mobilizes them for transplant without adverse effects. *Br J Haematol* 2004; **125:** 756 – 765.
103 Lee CK, Barlogie B, Munshi N, *et al*: DTPACE: an effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. *J Clin Oncol* 2003; **21:** 2732 – 2739.
104 Offidani M, Mele A, Corvatta L, *et al*: Gemcitabine alone or combined with cisplatin in relapsed or refractory multiple myeloma. *Leuk Lymphoma* 2002; **43:** 1273 – 1279.
105 Alas S, Bonavida B: Inhibition of constitutive STAT3 activity sensitizes resistant non-Hodgkin's lymphoma and multiple myeloma to chemotherapeutic drug-mediated apoptosis. *Clin Cancer Res* 2003; **9:** 316 – 326.
106 Harrouseau JL, Greil R, Kloke O, *et al*: ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of multiple myeloma. *Ann Oncol* 2005; **16(suppl 1):** 45 – 47.
107 Smith A, Wisloff F, Samson D, *et al*: Guidelines on the diagnosis and management of multiple myeloma 2005. *Br J Haematol* 2006; **132:** 410 – 451.
108 Barosi G, Boccadoro M, Cavo M, *et al*: Management of multiple myeloma and related-disorders: guidelines from the Italian Society of Hematology (SIE), Italian Society of Experimental Hematology (SIES) and Italian Group for Bone Marrow Transplantation (GITMO). *Haematologica* 2004; **89:** 717 – 741.
109 Durie BG, Kyle RA, Belch A, *et al*: Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation. *Hematology J* 2003; **4:** 379 – 398.
110 Traynor AE, Noga SJ, NCCN Multiple Myeloma Practice Guidelines Panel: NCCN: Multiple myeloma. *Cancer Control* 2001; **8(6 suppl 2):** 78 – 87.
111 Imrie K, Esmail R, Meyer RM, *et al*: The role of high-dose chemotherapy and stem-cell transplantation in patients with multiple myeloma: a practice guideline of the Cancer Care Ontario Practice Guidelines Initiative. *Ann Int Med* 2002; **136:** 619 – 629.

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