Novel Therapies for Relapsed/Refractory Multiple Myeloma: How Can We Improve on "Salvage" Therapy?—Introduction

Treatment of patients with multiple myeloma (MM) continues to evolve, with the introduction of highly effective novel agents expanding treatment options in the front-line and relapsed setting. Despite the activity of front-line therapy, MM remains an incurable disease and development of relapsed/refractory MM is an inevitable reality for almost all patients. This creates a need to not only choose the most effective front-line therapy possible to achieve deep disease response and prolong the duration of remission, but also to develop feasible strategies for 'sequencing' therapy through multiple relapses. As our understanding of MM biology and pathogenesis continues to increase, it is accompanied by investigation of new therapeutic targets and novel treatment approaches. There are many unanswered questions regarding the optimal treatment of patients with relapsed/refractory MM. This supplement provides an overview of the biology and underlying mechanisms of relapsed/refractory MM, current clinical perspectives on management of recurrent disease, and emerging data focused on novel agents demonstrating therapeutic potential.

Substantial clinical research has focused on the pathogenesis of MM, seeking to identify the genetic abnormalities and molecular events that lead to development and progression of this hematologic malignancy. While understanding of the mechanisms of drug resistance in MM is still limited, the bone marrow microenvironment has emerged as a major contributing factor to disease relapse and resistance to current therapies. This provides a rationale for simultaneously targeting MM tumor cells and the bone marrow microenvironment, a strategy that has already demonstrated significant efficacy in patients with relapsed/refractory disease. Expanding insight regarding the biology of MM provides the opportunity to discover new therapeutic targets and improve response monitoring to enhance patient care. In the first article, Dr David S. Siegel from Hackensack University Medical Center in New Jersey, United States, defines relapsed and refractory MM and outlines our current understanding of the biology and pathogenesis of the disease, including the role of the bone marrow microenvironment. Mechanisms of resistance and the rationale for design of novel therapies to overcome resistance in MM will also be reviewed, as well as current guidelines for response monitoring.

The introduction of the immunomodulatory agents thalidomide and lenalidomide and the proteasome inhibitor bortezomib has greatly improved patient outcomes in relapsed/refractory MM compared to traditional chemotherapy. While there is no widely accepted standard of care for relapsed/refractory disease, treatment decisions must be carefully based on patient and disease characteristics. Consideration of treatment-associated adverse events and appropriate implementation of adjunctive treatment and supportive care can greatly improve patient quality of life, which is a primary goal in the treatment of relapsed/refractory MM. Decisions regarding optimal therapy selection, the use of single-agent versus combination regimens, and optimal dosing and durations of therapy are often unclear, making these issues the focus of ongoing investigation. The second article in this supplement reviews the safety and efficacy of currently available treatment options for patients with relapsed/refractory MM, providing clinical perspectives on strategies for patient selection and management of adverse events to improve patient care.

Development of resistance or intolerance to the established novel therapies thalidomide, lenalidomide, and/or bortezomib is surprisingly common in patients with MM, creating an intense focus on development of newer therapeutic options for relapsed/refractory disease. Clinical trials are investigating novel agents aimed at signaling pathways involved in MM pathogenesis and/or the interaction between MM cells and the bone marrow microenvironment, including new proteasome inhibitors, immunomodulatory agents, histone deacetylase inhibitors, monoclonal antibodies, and signal transduction modulators. The diversity of these investigational therapies provides an opportunity to target multiple signaling pathways and develop rational combinations with established therapies to improve disease response. Ultimately, further study is needed to establish

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the role of these agents in current treatment paradigms and guide therapy selection. In the third article, Dr Philippe Moreau from the University Hospital Hôtel-Dieu in Nantes, France, reviews novel therapeutic strategies and agents demonstrating efficacy in patients with relapsed/refractory MM, including recent clinical trial data and important ongoing trials.

Although the management of relapsed/refractory MM remains a challenge, exciting advances in the genomic and molecular understanding of MM pathogenesis and the emergence of active, novel therapies have the potential to dramatically improve clinical management of relapsed/refractory disease. By effectively incorporating patient and disease-related factors into treatment selection, individualization of therapy can be achieved. The clinical implications of individualized treatment planning and the integration of effective novel therapies are far-reaching, pointing to improved disease outcomes for patients with relapsed/refractory MM.

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Relapsed/Refractory Multiple Myeloma: Defining Refractory Disease and Identifying Strategies to Overcome Resistance

David S. Siegel

Despite the development of more effective therapies for multiple myeloma (MM) over the past decade, nearly all patients will eventually experience disease relapse and require further therapy. Designing the next generation of therapies for relapsed and refractory disease will depend on understanding the complex molecular pathogenesis of MM and mechanisms of resistance. Oncogenomic studies have identified many potential therapeutic targets and have led to emerging models of the multistep molecular pathogenesis of MM. The key to overcoming resistance may depend on interrupting the complex interactions between MM cells and the bone microenvironment. Direct interaction between MM cells and bone marrow cells activates pleiotropic signaling pathways that mediate growth, survival, and migration of MM cells as well as resistance to chemotherapy (known as cell adhesion–mediated drug resistance). The bone marrow also secretes growth factors and cytokines that maintain MM cells and inhibit apoptosis. Therefore, successful therapeutic strategies must target not only the MM plasma cell but also the bone microenvironment. The benefit of immunomodulatory drugs such as thalidomide and lenalidomide and the proteasome inhibitor bortezomib in relapsed/refractory MM is related to their ability to target both. Novel agents and combination strategies are building on the success of these agents and targeting synergistic pathways.
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Multiple myeloma (MM) accounts for approximately 13% of hematologic malignancies and 20% of related deaths.[1] In Western countries, the annual age-adjusted incidence is 5.6 cases per 100,000 persons, and the median age at diagnosis is approximately 70 years.[2] Despite the development of more effective therapies over the past decade, MM remains incurable. Nearly all patients will eventually experience disease relapse and require further therapy. Even patients with an excellent response to first-line induction therapy and those who undergo autologous stem cell transplantation will progress, and, unfortunately, most patients will ultimately become refractory to standard therapeutic agents. That reality has driven the search for new agents and combinations that are effective in patients with relapsed and/or refractory disease. The foundation for this line of investigation is a better understanding of the underlying biology of MM and the mechanisms of resistance. This involves elucidating not only the oncogenomics of MM and the molecular mechanisms that control tumor growth and survival, but also understanding the complex interactions between myeloma cells and the bone microenvironment. This research has led to the development of novel therapeutic approaches for relapsed/refractory MM.

CURRENT DEFINITION OF RELAPSED/REFRACTORY DISEASE

In 2006, the International Myeloma Working Group (IMWG) established new uniform response criteria for MM (Table 1).[3,4] These updated criteria represent an important expansion and clarification of response criteria established in 1998 by the European Group for Blood and Bone Marrow Transplant (EBMT) and the International Bone Marrow Transplant Registry.[5] Both the IMWG and EBMT have established standard definitions of disease progression or relapse that are fairly

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Table 1. International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma[3,4]

Category	Criteria
CR[a]	Negative immunofixation of serum and urine and Disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow plus Normal serum FLC ratio of 0.26–1.65 (for patients without measurable M-protein)
sCR[a]	CR as defined above plus Normal serum FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
VGPR[a]	Serum and urine M-protein detectable by immunofixation but not by electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
PR[a]	≥50% reduction of serum M-protein and ≥90% reduction in 24-hour urinary M-protein or to <200 mg/24 hours If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels If serum and urine M-protein and serum FLC are unmeasurable, ≥50% reduction in bone marrow plasma cells, provided baseline percentage was ≥30% In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas
SD	Not meeting criteria for CR, VGPR, PR, or progressive disease
PD	≥25% increase from lowest response value in any one or more of the following: Serum M-protein (absolute increase must be ≥0.5 g/100 mL)[b] and/or Urine M-protein (absolute increase must be ≥200 mg/24 hours) and/or Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >100 mg/L) Bone marrow plasma cell percentage (absolute % must be ≥10%) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/100 mL) that can be attributed solely to the plasma cell proliferative disorder

Abbreviations: CR, complete response; FLC, free light chain; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

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[a]All response categories (CR, sCR, VGPR and PR) require two consecutive assessments made at any time before the institution of any new therapy; CR, PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed.

[b]A ≥1 g/100 mL increase in serum M-protein is sufficient to define disease progression if the starting M-protein level is ≥5 g/100 mL.

well aligned. Within the context of the response criteria, the term "disease progression" is used to describe a definite increase in disease activity in patients in partial response (PR) or plateau phase, whereas the term "relapse from complete remission" applies to recurrence of evident disease in patients previously in complete response (CR).

Three distinct patient populations can be defined within the relapsed/refractory setting: (1) patients with relapsed disease; (2) patients with relapsed and refractory disease; and (3) patients with primary refractory disease.[4,6,7] Relapsed MM is the broadest category and includes any disease progression that requires salvage therapy, or alternatively one could define it as the presence of clinically active disease in a patient who received one or more prior therapies. Relapsed and refractory MM is typically defined as either lack of response or disease progression on last prior therapy, or disease progression within 60 days of the last prior therapy.[6,7] Primary refractory disease refers to patients who fail to achieve a response to initial anti-myeloma therapy. Although the relapsed and refractory population is heterogeneous with respect to the duration and quality of prior response and the extent of prior exposure, it is important to distinguish these patients from those with relapsed or primary refractory disease when evaluating new therapies. The modern definition of refractory disease is not specific to any particular therapy. Historically, the definition was based on sensitivity to standard vincristine, doxorubicin, and dexametha-

sone (VAD), but the introduction of novel agents such as thalidomide and bortezomib has made this distinction obsolete. As therapeutic options expand, the term refractory is most useful if expressed in the context of which agent(s) or combination regimens the patient has been exposed to (eg, bortezomib-refractory).

The criteria for disease progression are designed to reliably identify a clear increase in disease activity, but that activity may not be clinically apparent. Many patients in progression are asymptomatic and may not require immediate treatment. Disease progression is usually defined by a >25% increase in serum or urinary M-protein from the nadir levels documented at the time of best response (Table 1).[3,4] However, for patients with very low or undetectable M-protein, there must be a minimum threshold increase to qualify as relapse (absolute increase ≥0.5 g/100 mL serum M-protein or ≥200 mg per 24-hour urinary M-protein).[3,4]

RESPONSE MONITORING IN PATIENTS WITH MULTIPLE MYELOMA

The IMWG has developed detailed guidelines for response assessment in the context of clinical trials.[3] It is recommended that patients undergoing therapy be tracked monthly for the first year and every other month thereafter. This is particularly important for evaluating novel therapies because the speed of response may have clinical implications. Patients with measurable disease should be followed for response assessment with both serum protein and urine protein electrophoresis (SPEP and UPEP). Assessment of CR also requires bone marrow (BM) aspiration (<5% plasma cells) and immunofixation. Patients without otherwise measurable disease should be followed using the serum free light chain (FLC) assay. A skeletal survey is not required for assessment of response unless clinically indicated, but it is recommended once a year in clinical practice, and BM biopsy is required only for determination of stringent CR (sCR) and for patients with nonsecretory disease. Once a patient achieves a response, it is no longer necessary to perform consecutive confirmations 6 weeks apart based on evidence that 6-week duration of response is not clinically significant and is not a surrogate for durability of response. Therefore, a confirmatory test can be performed at any time following the first test, provided it is before any new/non-protocol therapy. Durability of response or plateau phase is important and should be captured as either time to progression or duration of response.[8] Outside of clinical trials, a full blood count, SPEP and UPEP and/or serum FLC determination, creatinine, and calcium should be assessed every 3 to 4 months, and a skeletal x-ray or magnetic resonance imaging should be performed if the patient experiences any bone pain.[9]

With regard to the serum FLC assay, the standard assay (Freelite, The Binding Site, Birmingham, UK) is highly sensitive, and the FLC ratio is an excellent indicator of clonality.[10] Normalization of the serum FLC ratio (involved:uninvolved) is an indicator of sCR and may correlate with durable response.[3,11,12] In patients with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio will normalize if the patient achieves a sCR. To ensure the test is accurate, serum FLC should not be used to assess response if the baseline serum FLC level is <10 mg/dL and laboratory variability in assay results should be strictly monitored.[3,13] Variability in results can occur if the assay kit has expired.

One of the limitations of current response criteria for MM is that they do not measure any markers of myeloma stem cells. Current disease markers only measure the activity of myeloma plasma cells (PCs). Recent data suggest that myeloma stem cells are a rare cell population with a phenotype resembling that of normal memory B cells, and in vitro data with cell lines suggest that they are relatively resistant to standard therapies.[14] Although the clinical significance of these findings are not clear, it has been suggested that myeloma stem cells may persist after treatment and repopulate the malignant clone, leading to disease progression and relapse. Unfortunately, the molecular pathways responsible for proliferation of myeloma stem cells are poorly understood.

CURRENT UNDERSTANDING OF THE BIOLOGY AND PATHOGENESIS OF MULTIPLE MYELOMA

Origin of the Malignant Plasma Cell

MM is a neoplasm of postgerminal center, terminally differentiated B cells and is characterized by a multifocal proliferation/accumulation of clonal, long-lived, $CD138^+$ PCs within the BM. The final stages of B-cell development involve proliferation, multiple rounds of somatic hypermutation of immunoglobulin H (IgH) and immunoglobulin L (IgL) V(D)J sequences, affinity maturation, and class-switch recombination of immunoglobulin genes, culminating in secretion of high-affinity antibody.[15–17] Terminally differentiated PCs typically home to the BM, where they receive survival signals from surrounding stromal cells (SCs), and can live for many months to years.[18,19] Progression of MM appears to be driven in some cases by the $CD138^+$ PCs and in other cases by myeloma stem cells.[20,21] Although the disease is phenotypically characterized by PCs, recent studies have suggested that PCs lack significant proliferative capacity.[22–25] In vitro and in vivo studies of the growth fraction of MM PCs have found that the majority of PCs are quiescent, especially at diagnosis, suggesting that tumor growth is restricted to a specialized subpopulation of cells.[26] The indolent nature of MM and

the fact that the majority of MM cells are not actively proliferating, present a difficult therapeutic challenge.

Little is known about the transcriptional regulatory mechanisms involved in the maintenance of long-lived PCs. Recent studies have shown that continued expression of the transcription factors B lymphocyte-induced maturation protein 1 (BLIMP1) and X-box-binding protein 1 (XBP1) in the context of continued absence of transcription factors paired box protein 5 (PAX-5), B cell lymphoma 6 (BCL-6), and metastasis-associated 1 family, member 3 (MTA3) is required to maintain the differentiated phenotype of PCs.[15,16,27–30] BLIMP1 is believed to serve as the master regulator of PC differentiation that prevents the reversion of PCs to a less mature B-cell stage. Understanding the mechanisms of transcriptional control in long-lived PCs may allow for the rational development of therapeutic agents designed to inhibit the activity and proliferation of PCs in MM.

Monoclonal Gammopathy of Undetermined Significance

Unlike other hematologic malignancies, MM is consistently preceded by a premalignant, asymptomatic phase known as monoclonal gammopathy of undetermined significance (MGUS). MGUS is defined by serum monoclonal immunoglobulin concentration ≤3 g/100 mL, ≤10% PCs in the BM, and no anemia, hypercalcemia, lytic bone lesions, renal insufficiency or other end-organ damage related to proliferation of monoclonal PCs.[4] Approximately 1% of adults over the age of 50 years have MGUS, which progresses to MM at a rate of 0.5% to 3% per year.[31,32] A large US cancer screening trial of more than 77,000 individuals demonstrated that, among those who eventually developed MM (n = 71), MGUS was present in 100%, 98%, 95%, 93%, and 82% of patients at 2, 4, 5, 7, and 8+ years prior to their MM diagnosis, respectively.[33] This suggests that MM results from the slow accumulation of genetic abnormalities over many years.

Determining the molecular events that promote evolution of MGUS to MM is an area of active research, and several factors have been implicated in this process including radiation exposure, environmental causes, chronic antigen stimulation, and genetics. However, the data linking radiation exposure and environmental causes to an increased risk of developing MM are inconclusive.[34–37] It is possible that chronic antigen stimulation, with its associated lymphocyte activation, may play a role in MM development. Several studies have shown a higher than expected incidence of MM among patients with rheumatoid arthritis (RA); however, factors such as a shared predisposition for the development of RA and MM, a high rate of RA among first-degree relatives of patients with MM, and use of corticosteroids may also play a role.[38–43] Additionally, certain viral infections such as hepatitis C virus, hepatitis B virus, and human immunodeficiency virus have been implicated in the development of MM, albeit with variable findings and quality of supporting data.[44–47] For some patients, there may be a genetic predisposition to developing MM. Individuals who have a first-degree relative with MM have a 3.7-fold higher risk of developing MM than those with unaffected relatives.[48] Alternatively, the transition from MGUS to symptomatic MM may not be related to intrinsic changes in the MM cells themselves but rather to an acquired defect in the immune response to the premalignant MM cells.[49,50]

Bone Marrow Microenvironment in Multiple Myeloma

It is well established that the physical interaction between MM cells and the BM microenvironment plays a crucial role in MM pathogenesis and drug resistance (Figure 1).[51] Direct interaction between MM cells and BM cells activates pleiotropic signaling pathways that mediate growth, survival, drug resistance, and migration of MM cells, as well as angiogenesis, and BM osteoclastogenesis.[52–57] Bone marrow endothelial cells (BMECs) and BMSCs secrete a variety of chemokines such as stromal-derived factor 1 (SDF-1) and insulin-like growth factor 1 (IGF-1) that serve as chemoattractants for MM cells. Adhesion of MM cells to BMSCs, through interaction with $\alpha 4\beta 1$ integrin–vascular cell adhesion molecule 1 (VCAM-1), induces BMSCs to secrete cytokines including interleukin(IL)-6, IL-1b, IL-11, tumor necrosis factors (TNFs), transforming growth factor-β (TGF-β), and receptor activator of NF-κB ligand (RANKL). The production of IL-6 by BMSCs requires activation of nuclear factor-kappa B (NF-κB), which triggers the proliferation of MM cells and protects them against apoptosis. The activation of NF-κB also stimulates BMSCs and MM cells to secrete other growth factors and adhesion molecules, such as vascular endothelial growth factor (VEGF), VCAM-1 and E-selectin. Importantly, activation of NF-κB in MM cells confers cell adhesion-mediated drug resistance (CAMDR) to conventional chemotherapy.[58,59] In addition to NF-κB, additional signaling pathways are involved in the proliferative and antiapoptotic response of MM cells upon interaction with the BM microenvironment. These pathways include the phosphatidylinositol-3 kinase (PI3K)/Akt pathway, the Ras/Raf/MEK/ERK pathway, and the Janus kinase 2 (JAK2)/signal transducers and activators of transcription 3 (STAT3) pathway. Activation of these pathways has been implicated in MM progression and constitutive drug resistance.[53,60]

Induction of angiogenesis is also critical for MM pathogenesis (Figure 1).[51,57,61–63] Myeloma cells secrete a variety of factors that promote angiogenesis, which in turn promotes MM cell growth and enhances secretion of growth factors from BMECs.[64] Growth factors and cytokines such as VEGF and IL-8 allow MM cells to recruit new blood vessels.[65] The BMECs in these new

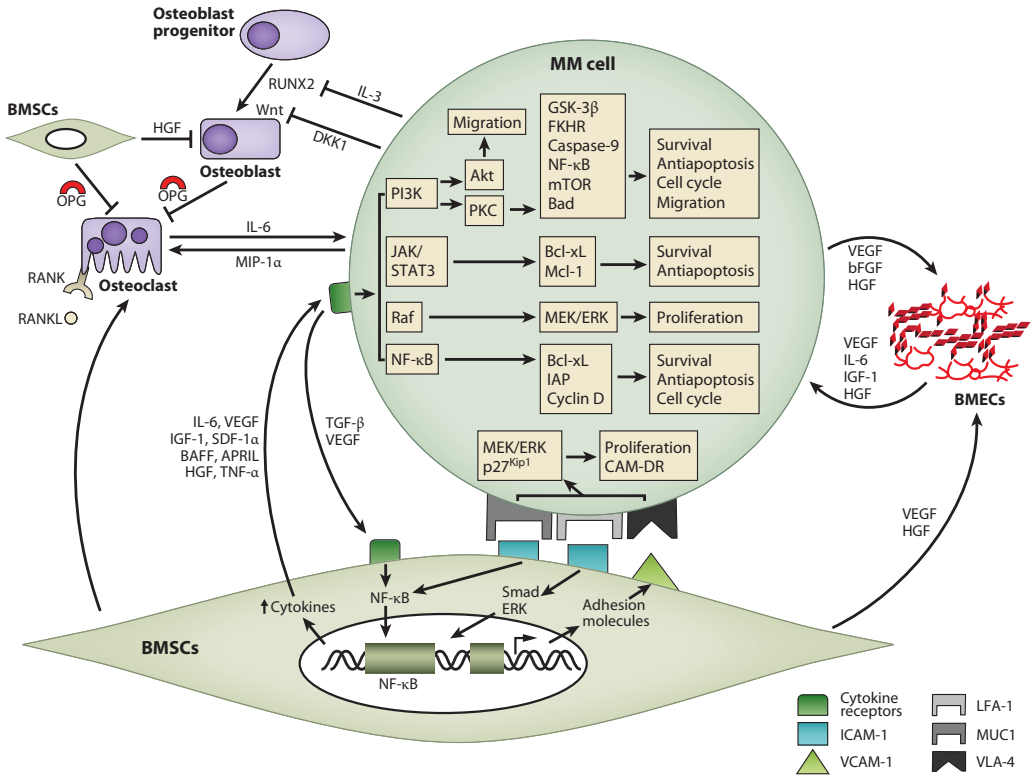

Figure 1. The role of the bone marrow microenvironment in multiple myeloma. Abbreviations: bFGF, basic fibroblast growth factor; CAM-DR, cell adhesion–mediated drug resistance; DKK1, Dickkopf-related protein 1; GSK-3β, glycogen synthase kinase 3β; HGF, hepatocyte growth factor; ICAM-1, intercellular adhesion molecule 1; IGF, insulin-like growth factor 1; IL, interleukin; JAK/STAT3, Janus kinase/signal transducer and activator of transcription 3; LFA-1, leukocyte function–associated antigen 1; MEK/ERK, Ras/Raf/mitogen-activated protein kinase kinase/extracellular signal–regulated kinase; MIP-1α, macrophage inflammatory protein 1α; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; OPG, osteoprotegerin; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; RANK, receptor activator of NF-κB; RANKL, RANK ligand; SDF-1α, SC-derived factor 1α; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α; VCAM-1, vascular cell–adhesion molecule 1; VEGF, vascular endothelial growth factor; VLA-4, very late antigen 4. Reprinted with permission from Anderson KC. Annu Rev Pathol 2011.[51] Permission conveyed through the Copyright Clearance Center Inc.

MM-associated vessels further support MM cells through secretion of cytokines and direct interactions. These autocrine and/or paracrine loops in the BM microenvironment may mediate the progression of MM.

Bone destruction is a characteristic feature in MM. It is related to increased osteoclastic activity, which is not accompanied by a compensatory increase in osteoblast activity (Figure 1).[51,56,66] This uncoupling of bone resorption and formation leads to rapid bone loss, osteoporosis, osteolytic lesions, and fractures. A number of cytokines and growth factors produced either by MM cells or BMSCs have been implicated in the increased osteoclast formation and activity associated with MM. These include IL-6, IL-1b, IL-11, TNF-α, TNF-β, basic fibroblast growth factor (bFGF), IGF, and, more recently, macrophage inflammatory protein-1α (MIP-1α) and hepatocyte growth factor (HGF). These factors contribute to activation of the RANKL pathway, which stimulates osteoclastogenesis. Myeloma cells also produce inhibitors of Wnt-mediated osteoblast differentiation, such as dickkopf-1 (DKK1) and soluble frizzled-related protein-2 (sFRP2), which leads to reduced bone formation.[67–70]

Oncogenomics of Multiple Myeloma

In large genomic studies, karyotypic abnormalities have been detected at a frequency of 30% to 50%.[71–74] The frequency and extent of these abnormalities correlates with disease stage, prognosis, and response to therapy. For example, approximately 20% of abnormal karyotypes are present in stage I disease, 60% in stage III disease, and >80% in extramedullary tumors.[72–74] It is important to note, however, that these findings are dependent on obtaining reliable metaphase preparations, and they likely under-represent the true extent of DNA alterations in these infrequently dividing MM cell populations. Using interphase fluorescence in situ hybridization (FISH), two studies reported that approximately 90% of MM tumor samples harbor at least one trisomic chromosome.[75,76] Although conventional

karyotypes are not routinely reported for MGUS, it appears that a substantial fraction of MGUS PCs also have cytogenetic abnormalities. Two studies using FISH demonstrated that the incidence of trisomy for at least one chromosome was approximately 50% in MGUS cells.[75-77]

The MM genome is characterized by a distinctive combination of whole chromosome gains and losses, nonrandom chromosomal translocations, and point mutations. Table 2 describes the most clinically important cytogenetic abnormalities observed in MM.[78] The picture that has emerged is that MM is a genetically heterogeneous disease with a multitude of genetic subtypes that share the common feature of accumulation of clonal PCs.[79] Several subtypes of MM have been identified based on characteristic genetic abnormalities, and are associated with unique clinicopathological features and outcomes. At the top hierarchical level, MM can be divided into hyperdiploid and nonhyperdiploid subtypes.[80,81] Approximately 55% to 60% of MM primary tumors are characterized by a hyperdiploid karyotype with 48 to 74 chromosomes and multiple trisomies of odd-numbered chromosomes including 3, 5, 7, 9, 11, 15, 19, and 21.[80,82] The nonhyperdiploid group includes tumors with a hypodiploid, near-diploid, pseudodiploid, or near-tetraploid chromosome number (ie, <47 or >74 chromosomes).[80,82] Nonhyperdiploid MM frequently harbors IgH translocations including t(11;14)(q13;q32), t(4;14)(p16;q32), and t(14;16)(q32;q23).[78] Importantly, ploidy status rarely changes during disease progression, and patients with hyperdiploid MM tend to have less aggressive clinical features and a better prognosis compared with nonhyperdiploid disease.[79,83,84] Deletions of chromosomes 13 and 17, and abnormalities of chromosome 1 (eg, 1p

Table 2. Cytogenetic Abnormalities and Involved Oncogenes in Multiple Myeloma[78]

Cytogenetic Abnormality	Genetic Location	Incidence Detected by Conventional Cytogenetics or (FISH)	Involved Oncogene	Function
13q deletion	Usually 13q14	15% (50%)	RB-1	Cell cycle regulator
t(4;14)	4p16.3 14q32	Undetected (15%)	FGFR3	Growth factor receptor tyrosine kinase
			MMSET	Transcriptional regulator
			TACC3	Unknown
			Cyclin D2	Cell cycle regulator
t(6;14)(p21;q32)	6p21 14q32	(3% to 4%)	Cyclin D3	Cell cycle regulator
t(6;14)(p25;q32)	6p25 14q32	(5%)	MUM/IRF4	Transcriptional regulator of IFN
t(14;16)	14q32 16q23	(2% to 10%)	c-MAF	Transcription factor
t(8;14)(q24;q32)	8q24 14q32	(4% to 5%)	c-myc	Cell cycle regulator
t(14;20)	14q32 20q12	Recently defined	b-MAF	Transcription factor
t(14;18)	14q32.33 18q21.3	(5%)	BCL-2	Apoptosis inhibitor
17p deletion	17p13	5% (10% to 15%)	p53	Cell cycle regulator; DNA repair
Chromosome 1 abnormalities	Chromosome 1	20%	K-RAS, N-RAS gene mutations	Signal transduction regulator; cell cycle regulator
t(11;14)	14q32	5% (15% to 20%)	Cyclin D1	Cell cycle regulator
			MYEOV	Unknown

Abbreviations: BCL-2, B cell CLL/lymphoma 2; b-MAF, v-myc myelocytomatosis viral oncogene homolog B (avian); c-MAF, v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian); c-myc, v-myc myelocytomatosis viral oncogene homolog (avian); FGFR3, fibroblast growth factor receptor 3; FISH, fluorescence *in situ* hybridization; IFN interferon; K-RAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; MMSET, multiple myeloma SET domain; MUM/IRF4, maternal effect uncoordinated and malformed/IFN regulatory factor 4; MYEOV, myeloma overexpressed; N-RAS, neuroblastoma RAS viral (v-ras) oncogene homolog; p53, protein 53; RB-1, retinoblastoma protein-1; TACC3, transforming, acidic coiled-coil-containing protein 3; WWOX, WW domain-containing oxidoreductase.

Dimopoulos MA, et al. Multiple myeloma. Ann Oncol. 2010;21 Suppl 7:vii143–50, by permission of Oxford University Press.[78]

deletion and 1q amplification) are associated with an aggressive clinical course and poor prognosis.[80,85] Other adverse risk factors associated with high-risk MM include translocations t(4;14) and t(14;16).[80,85,86]

To date, oncogenomic studies have identified only a few cytogenetic differences that distinguish MGUS from MM.[80] Both conditions can present with either a hyperdiploid or a nonhyperdiploid karyotype and similar chromosomal translocations that affect the IgH or IgL locus.[79,87] Some, but not all, studies have reported a higher incidence of t(4;14) in MM compared with MGUS.[88] Currently, the frequency of *RAS* mutations appears to be the major genetic difference between MGUS and MM. Two members of the Ras family (*N-RAS* and *K-RAS*) are mutated at codons 12, 13, and 61 in 40% to 55% of patients with MM versus only 5% of patients with MGUS, which suggests an important role for activation of the mitogen-activated protein kinase (MAPK) pathway in progression from MGUS to MM.[89,90]

Figure 2 describes a potential model for the multistep molecular pathogenesis of MM.[91] Two essentially nonoverlapping pathways, hyperdiploid and nonhyperdiploid chromosomal alterations, are primary events associated with dysregulated cyclin D expression. A second genetic hit leading to transformation from MGUS to MM may be mediated by activation of oncogenes such as *MYC*, *FGFR3*, *K-RAS*, *N-RAS*, and *NF-kB*.[92-94] Late rearrangements, often involving an Ig locus, may further dysregulate these pathways. Activating mutations of the NF-kB pathway and inactivating mutations of *TP53* are associated with extramedullary disease, and inactivation of *CDKN2C* (p18) and *RB1* are associated with increasingly proliferative disease.

DRUG RESISTANCE

An important challenge in the treatment of patients with MM is the development of drug resistance after

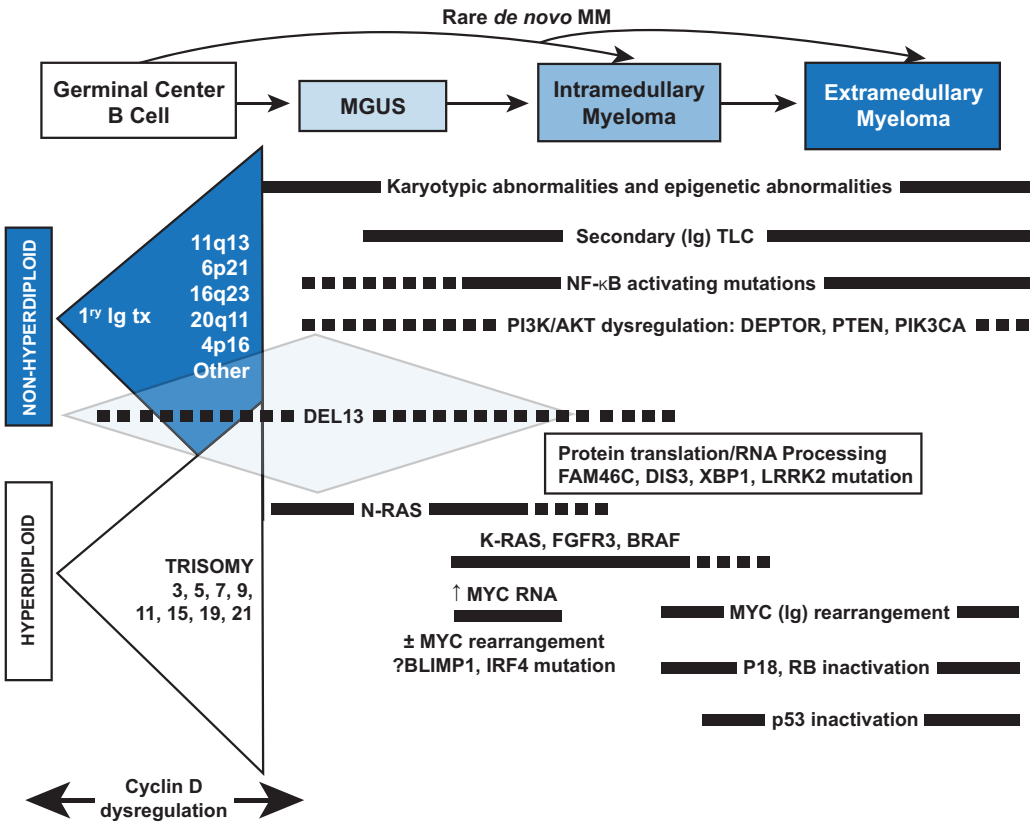

Figure 2. Model for the multistep molecular pathogenesis of multiple myeloma. Abbreviations: BLIMP1, B lymphocyte-induced maturation protein; BRAF, v-Raf murine sarcoma viral oncogene homolog B1; DEL, deletion; DEPTOR, DEP domain containing MTOR-interacting protein; DIS3, exosome complex exonuclease RRP44; FAM46C, family with sequence similarity 46, member C; FGFR3, fibroblast growth factor receptor 3; IRF4, interferon regulatory factor 4; K-RAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; LRRK2, leucine-rich repeat kinase 2; MGUS, monoclonal gammopathy of undetermined significance; myc, v-myc myelocytomatosis viral oncogene homolog; NF-$\kappa\beta$, nuclear factor kappaB; N-RAS, neuroblastoma RAS viral (v-ras) oncogene homolog; p18, protein 18; p53, protein 53; PI3K/AKT, phosphatidyl inositol 3-kinase/protein kinase B; PIK3CA, phosphatidyl inositol 3-kinase catalytic subunit; PTEN, phosphatase and tensin homolog, RB, retinoblastoma protein; RNA, ribonucleic acid; TLC, translocation; XBP1, X-box binding protein 1. From Chesi M. Hematology Am Soc Hematol Educ Program 2011.[91] Copyright 2011. Reproduced with permission of the American Society of Hematology (ASH). Permission conveyed via the Copyright Clearance Center, Inc.

initial response to treatment. MM cells exhibit a variety of intrinsic genetic mechanisms of drug resistance, such as *TP53* mutations, and they often acquire resistance to conventional chemotherapy through overexpression of P-glycoprotein. In addition, adhesion of MM cells to BMSCs induces CAMDR to conventional chemotherapy, and activation of NF-kB appears to play an important role in that process.[53] The interaction between MM cells and cells within the BM microenvironment leads to secretion of growth factors and cytokines (eg, TGF-β and IL-6), as described above, that can confer drug resistance. For example, IL-6 has been linked to resistance to apoptosis in response to dexamethasone.[95] Although the precise mechanisms responsible for CAMDR and cytokine-mediated drug resistance are not well understood, novel agents used to treat MM, including immunomodulatory drugs (eg, thalidomide and lenalidomide) and proteasome inhibitors (eg, bortezomib), as well as agents currently in development, may overcome not only intrinsic drug resistance but also CAMDR and the protective effects of cytokines.[53]

Numerous studies have demonstrated that cancer cells are more dependent on proteasome activity for survival than normal cells, and therefore should be more sensitive to treatment with proteasome inhibitors such as bortezomib.[96–100] Both single-agent bortezomib and bortezomib-based combination therapy have shown clinical benefit in sensitizing cancer cells to conventional chemotherapy and in overcoming drug resistance.[101] In addition to having activity against MM cells, bortezomib also appears to inhibit angiogenesis and suppress interactions between MM cells and BM stromal cells.[102–106] However, an important limitation to bortezomib treatment is that, even in bortezomib-naïve relapsed patients, up to 50% have intrinsic resistance to proteasome inhibition. Acquired resistance to bortezomib, which appears to be related to mutation and overexpression of proteasome subunit β5, has also been reported.[107–110] Therefore, alternative treatment strategies are needed. Numerous agents with diverse mechanisms of action are currently in development for the treatment of relapsed/refractory MM and several of these emerging agents may play a role in overcoming drug resistance. For example, data demonstrate that epigenetic inactivation of genes is one mechanism of drug resistance. Histone deacetylase inhibitors may have the potential to reverse epigenetic silencing of genes that regulate tumor growth and survival[111,112]; they can inhibit compensatory activation of the aggresome pathway in response to bortezomib, resulting in synergistic antitumor activity and possibly overcoming resistance to bortezomib.[113] Aberrant activation of PI3K/Akt/mammalian target of rapamycin (mTOR) pathway also may contribute to development of resistance to conventional agents used to treat MM. Several novel inhibitors of this pathway appear to enhance the cytotoxic effects of doxorubicin, melphalan, dexamethasone, and bortezomib, and may overcome resistance to these agents.[114,115] Monoclonal antibodies in development may also play a role in overcoming cytokine-mediated drug resistance. Siltuximab is a chimeric anti–IL-6 antibody that is being studied in combination with dexamethasone in an effort to overcome resistance to corticosteroids.[95,116] Additionally, the antitumor activity of BT062, an immunoconjugate consisting of a chimeric anti-CD138 antibody stably linked to cytotoxic maytansinoid, an inhibitor of tubulin polymerization, is not affected by expression of IL-6 and IGF-1 or CAMDR.[117,118] The mechanisms of action and clinical evidence supporting the use of these emerging agents in relapsed/refractory MM are reviewed in more detail in the article by Philippe Moreau in this supplement.

Early-stage data also suggest some promising strategies for overcoming drug resistance in MM. Preclinical studies have demonstrated that hyperactivation of Wnt/β-catenin and CD44 plays a role in lenalidomide resistance, and that selective targeting of these cellular proteins in conjunction with lenalidomide treatment may overcome lenalidomide resistance.[119] Gene-expression profiling has identified insulin growth factor-1 (IGF-1) as one pathway involved in the development of resistance to bortezomib treatment, and data have demonstrated that targeting IGF-1 in combination with bortezomib treatment may overcome bortezomib resistance in MM.[120] Finally, recent data have shown that myeloma differentiation status is associated with sensitivity to bortezomib and that induction of differentiation may be one approach to overcoming resistance to bortezomib.[121]

RATIONALE FOR THERAPEUTIC APPROACHES IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

The rationale for development of new agents for the treatment of relapsed/refractory MM is based on decades of research into the molecular pathways involved in the pathogenesis of MM and development of resistance to current therapies. The BM microenvironment, the NF-kB pathway, the ubiquitin proteasome cascade, heat shock protein 90, histone deacetylases, and the PI3K/Akt/mTOR pathway have all been identified as promising targets for the treatment of relapsed/refractory MM.[122] The clinical utility of agents that modulate these targets, either alone or in combination with other antimyeloma therapies, will be discussed in more detail throughout this supplement.

Recently, a preliminary whole genomic analysis of 38 primary MM tumors conducted by Chapman and colleagues identified several new and unexpected pathways that seem to be involved in the pathogenesis of MM.[123] The analysis revealed that mechanisms previously suspected to play a role in the biology of MM (eg, activation of NF-kB and dysfunction of histone methyltransferases) might actually have a potentially broader

role than originally expected because mutations were found in multiple members of these pathways. This analysis also implicated several new mechanisms of transformation, including mutations in the oncogenic kinase BRAF, the RNA exonuclease DIS3, and in other genes involved in protein translation and homeostasis. Based on this analysis, further study is warranted to determine if modulating these mechanisms has an impact on the pathogenesis of MM.

In light of the role of the BM milieu in drug resistance, a new treatment paradigm has emerged.[53,124] By concurrently targeting both MM cells and the BM microenvironment, thalidomide, lenalidomide, and bortezomib have been shown to counter the protective effects of the BM by modulating expression of cytokines and adhesion molecules.[104,125–127] New agents and regimens in development are building on the success of these drugs. In fact, the most promising agents are new immunomodulatory drugs and proteasome inhibitors, and agents that overcome resistance to lenalidomide and bortezomib or synergize with them.

CONCLUSIONS

As our knowledge and understanding of the molecular pathogenesis of MM has increased, our ability to stop the inexorable progression of this disease has greatly improved. The introduction of immunomodulatory drugs and proteasome inhibitors has dramatically improved clinical outcomes for patients with relapsed/refractory disease. Further progress will require continued research in well-defined patient populations to develop novel therapeutic strategies that overcome multiple resistance mechanisms. A better understanding of myeloma stem cells and how to destroy them will also be required. Research in MM exemplifies rapid bench-to-bedside translation of new discoveries, and the future looks promising based on the wide range of targeted approaches being explored in the clinic for the treatment of relapsed/refractory disease.

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Management Strategies for Relapsed/Refractory Multiple Myeloma: Current Clinical Perspectives

Andrzej Jakubowiak

In the last decade, the introduction of novel agents including the immunomodulatory drugs thalidomide and lenalidomide, and the first-in-class proteasome inhibitor bortezomib, has dramatically improved clinical outcome in patients with relapsed/refractory multiple myeloma (MM) compared to conventional chemotherapy alone. Although combination treatment approaches with traditional cytotoxic agents and novel agents have led to response rates as high as 85% in patients with relapsed/refractory disease, not all patients will respond to established novel agents, and even those who do respond will ultimately relapse or become refractory to currently available regimens. There is no generally accepted standard treatment for patients with relapsed/refractory disease; however, both disease-related (eg, quality and duration of response to previous therapies and the aggressiveness of the relapse) and patient-related (eg, preexisting toxicities, comorbid conditions, quality of life, age, and performance status) factors should be considered when selecting the best treatment option. This article will review up-to-date approaches for managing patients with relapsed/refractory MM, including the efficacy and safety of established novel agents, the use of adjunctive/supportive care, and strategies for tailored treatment.
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Prior to the introduction of novel agents, treatment for relapsed/refractory multiple myeloma (MM) consisted of standard combinations of alkylating agents, anthracyclines, and corticosteroids with or without hematopoietic stem cell rescue.[1-5] With these traditional chemotherapy-based regimens, median survival was <2 years from first relapse.[6] The development of novel agents including immunomodulatory drugs (IMiDs; eg, thalidomide and lenalidomide) and proteasome inhibitors (eg, bortezomib), has led to a significant improvement in overall survival (OS) for patients with relapsed/refractory MM.[7] In this patient population, combination treatment approaches with traditional and established novel agents have led to response rates as high as 88% and median OS in the range of 3 years.[8] However, MM remains an incurable disease and almost all patients eventually relapse or become refractory to current treatment regimens.

Currently, there is no broadly accepted standard treatment for patients with relapsed/refractory MM; however, both disease-related and patient-related factors should be considered when selecting a treatment option. Disease-related factors include the quality and duration of response to previous therapies, and the aggressiveness of the relapse. Patient-related factors include preexisting toxicities, comorbid conditions, quality of life, age, and performance status.[7,9,10] Both the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) clinical practice guidelines take into account these disease-related and patient-related factors.[11,12] Current clinical practice strategies for managing patients with relapsed/refractory MM, including the efficacy and safety of established novel agents, the use of adjunctive/supportive care, and approaches for individualized treatment, are discussed in this article.

CURRENT TREATMENT OPTIONS

Chemotherapy and Transplant

In the relapsed/refractory setting, conventional or high-dose chemotherapy has been a longstanding approach to salvage treatment. Regimens have included high-dose melphalan; high-dose methylprednisolone; high-dose dexamethasone; vincristine, doxorubicin,

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and pulsed high-dose dexamethasone (VAD); vincristine, melphalan, cyclophosphamide, and prednisone (VMPC) alternating with vincristine, carmustine, doxorubicin, and prednisone (VBAP); doxorubicin, vincristine, dexamethasone, etoposide, and cyclophosphamide (CEVAD); cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE); and dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP).[13–26] Overall response rates for salvage combination chemotherapy are between 25% and 65%, with morbidity and mortality related to the intensity of therapy.[13–25]

Allogeneic transplant shows limited clinical benefit for the treatment of relapsed/refractory MM. Few patients, even those with poor-risk disease, are ultimately cured with this approach.[27] The majority of studies evaluating allogeneic transplant in the relapsed/refractory setting have demonstrated long-term, disease-free survival of 10% to 20%, with a significant proportion of patients developing chronic graft-versus-host disease, other treatment-related toxicities, or relapse.[28,29] Given these substantial limitations, the use of allogeneic transplant for patients with relapsed/refractory MM should be discouraged until more effective and tolerable approaches are established.

Available data suggest that second autologous transplants may be beneficial and safe for some patients with relapsed/refractory disease. The overall response rates in recent studies range from 55% to 69%, with a 100-day mortality rate <10%.[30–34] However, the small sample size of these studies makes it difficult to identify the ideal candidate for this treatment approach. One report suggests that relapse-free survival (RFS) ≥18 months following the first transplant is a reliable predictor of clinical outcome after a second transplant, regardless of the type of salvage therapy received.[35] Median OS was nearly 3 years in patients with RFS ≥18 months versus <6 months in those with RFS <18 months.

Established Novel Agents

Thalidomide

Thalidomide is an IMiD that, in addition to having direct effects on myeloma tumor cells, also targets the bone marrow microenvironment and stimulates host anti-myeloma immunity. Thalidomide was the first novel agent to be evaluated in patients with relapsed/refractory MM, and since then several studies have demonstrated the effectiveness of thalidomide as a single agent.[36–45] A systematic review of phase II trials showed that thalidomide monotherapy produced partial response or better (≥PR) in 30% of patients with relapsed/refractory disease, with a 1-year OS rate of 60% and median OS of 14 months.[46] To date, thalidomide doses of up to 1,200 mg/d have been evaluated in reported trials; however, the optimum daily dose has yet to be determined. In a recent prospective, randomized trial comparing 100-mg and 400-mg doses of thalidomide in patients with relapsed/refractory MM, low-dose thalidomide demonstrated significant activity and was noninferior to the higher dose based on the intent-to-treat analysis.[47] In the phase III OPTIMUM study, different doses of thalidomide (100 mg/d, 200 mg/d, or 400 mg/d) demonstrated significantly prolonged time to progression (TTP) and duration of response compared with standard dexamethasone in patients (N = 465) who had received two to three prior therapies; however, there was no difference in response rate and OS between the groups.[48] The NCCN guidelines recommend thalidomide monotherapy for patients who are corticosteroid-intolerant.[11]

Thalidomide has been successfully combined with multiple conventional cytotoxic agents for the treatment of relapsed/refractory MM (Table 1).[25,49–54] When compared with thalidomide alone, the addition of dexamethasone resulted in higher response rates of about 50%.[53,55–58] The addition of cyclophosphamide to thalidomide and dexamethasone led to even higher responses (≥PR: 57%–84%).[49,50,59–61] The combination of thalidomide with continuous low-dose cyclophosphamide alone was also effective, with 64% of patients experiencing ≥PR.[62] Evidence also suggests that the efficacy of thalidomide in relapsed/refractory MM may be improved when combined with melphalan (≥PR: 59%), melphalan–prednisone (≥PR: 42%), melphalan–dexamethasone (PR: 70%), pegylated liposomal doxorubicin (PLD)–dexamethasone (≥PR in 76%), PLD–vincristine–dexamethasone (≥PR: 75%), DT-PACE (≥PR: 32%), or cyclophosphamide–etoposide–dexamethasone (TCED; ≥PR: 68%)[25,54,63–67] (Table 1).[25,49–54] The NCCN guidelines have included the combinations of thalidomide–dexamethasone and DT-PACE as category 2A options (uniform NCCN consensus that the intervention is appropriate based on lower-level evidence) for relapsed/refractory MM.[11] Similarly, the ESMO guidelines recommend thalidomide (initial dose 100–200 mg/d) in combination with dexamethasone and/or chemotherapy.[12]

Lenalidomide

Lenalidomide is an amino-substituted derivative of thalidomide that was developed to minimize the toxicity associated with thalidomide while maintaining or improving its biologic activity. In vitro, lenalidomide is up to 50,000 times more potent than thalidomide at inhibiting production of tumor necrosis factor-alpha (TNF-α).[68] The activity of lenalidomide as a single agent has been demonstrated in both phase I and II studies with response rates ranging from 29% to 39% in patients who had received a median of three prior therapies.[69–71] Based on these initial studies, the maximum tolerated dose (MTD) was 25 mg once daily in patients with relapsed/refractory MM.[69] The NCCN guidelines recommend considering lenalidomide monotherapy for patients with corticosteroid intolerance.[11]

Table 1. Selected Thalidomide-Based Combinations in Treatment of Relapsed/Refractory Multiple Myeloma[25,49–54]

Study	Phase	Regimen	Schedule	N	≥PR, %	CR, %	TTE
Lee et al (2003)[25]	II	DT-PACE	D: 40 mg/d PO on days 1–4; T: 400 mg/d PO on days 1–28; Cis: 10 mg/m^2 IV on days 1–4; Dox: 10 mg/m^2 IV on days 1–4; C: 400 mg/m^2 IV on days 1–4; E: 40 mg/m^2 IV on days 1–4	229	32	7	NR
Garcia-Sanz et al (2004)[49]	II	CTD	C: 50 mg/d PO on days 1–28; T: 200–800 mg/d PO on days 1–28; D: 40 mg/d PO on days 1–4, 15–18	71	57	2	2-year PFS: 57% 2-year OS: 66%
Kyriakou et al (2005)[50]	II	CTD	C: 300 mg/m^2 PO on days 1, 8, 15, 22; T: 50–300 mg/d PO on days 1–28; D: 40 mg/d PO on days 1–4	52	78	17	2-year EFS: 34% 2-year OS: 73%
Roussou et al (2007)[51]	II	CTD	C: 150 mg/m^2/BID PO on days 1–5; T: 400 mg/d PO on days 1–5, 14–18; D: 20 mg/m^2 PO on days 1–5, 14–18	43	67	0	3-year PFS: 14%
Morris et al (2008)[52]	II	CTD	C: 250 mg BID PO on days 1–28; T: 50 mg/d PO on days 1–28; D: 10 mg/d PO on days 1–4, 15–18 (1st cycle only)	28	89	18	Median PFS: 10 mo Median OS: 16 mo
Anagnostopoulos et al (2003)[53]	I/II	TD	T: 200–600 mg/d PO on days 1–28; D: 20 mg/m^2 PO on days 1–4, 15–18	47	47	13	Median OS: 38 mo
Palumbo et al (2006)[54]	I/II	MPT	M: 20 mg/m^2 IV on day 1 every 4th month; P: 12.5 mg/d – 50 mg/d PO every other day; T: 50–100 mg/d PO on days 1–28	24	42	0	Median PFS: 9 mo

Abbreviations: BID, taken twice daily; C, cyclophosphamide; Cis, cisplatin; CR, complete response; D, dexamethasone; Dox, doxorubicin; E, etoposide; EFS, event-free survival; IV, intravenous; M, melphalan; NR, not reported; OS, overall survival; PFS, progression-free survival; PO, taken orally; PR, partial response; P, prednisone; T, thalidomide; TTE, time to event.

Multiple combination trials of lenalidomide have been conducted in the relapsed/refractory setting (Table 2).[70–77] Two randomized, phase III studies (MM-009 and MM-010) of dexamethasone combined with lenalidomide or placebo demonstrated improved PR, complete response (CR), TTP, and OS for patients treated with lenalidomide–dexamethasone.[72,73] These results were further confirmed by a pooled analysis of both studies, which demonstrated superior overall response (60.6% *v* 21.9%; $P<.001$), median TTP (13.4 months *v* 4.6 months; $P<.001$), and median OS (38.0 months *v* 31.6 months; $P = .045$) for patients treated with lenalidomide–dexamethasone compared with patients treated with placebo–dexamethasone.[78] This was despite a 41.9% crossover to lenalidomide-based treatment for patients who previously received dexamethasone alone.[78] Moreover, the lenalidomide–dexamethasone combination also appears to be effective in very elderly (>75 years) patients with relapsed MM, demonstrating overall response rates of 62% and median progression-free survival (PFS) of 14 months.[79] Based on the phase III studies, the NCCN considers the combination of lenalidomide–dexamethasone as a category 1 treatment option (uniform NCCN consensus that the intervention is appropriate based on high-level evidence) for patients with relapsed/refractory MM,[11] and this combination is included in the ESMO guidelines.[12] Currently, all new dexamethasone combination trials use low-dose dexamethasone instead of high-dose dexamethasone. This shift in dose is supported by results from a study in newly diagnosed patients (N = 445) that demonstrated a significant improvement in 1-year OS rates with lenalidomide + low-dose dexamethasone versus lenalidomide + high-dose dexamethasone regimens (96% *v* 87%, respectively; $P = .0002$).[80] Lenalidomide has also demonstrated efficacy in combination with doxorubicin–dexamethasone (RAD; ≥PR: 73%), low-dose cyclophosphamide–prednisone (REP; minimal response or better [≥MR]: 64.3%), cyclophosphamide–dexamethasone (≥MR: 75%), and PLD–vincristine–dexamethasone (≥PR: 75%) in patients with relapsed/refractory MM[74,75,81,82] (Table 2).[70–77]

Bortezomib

Bortezomib is a first-in-class proteasome inhibitor that blocks the 26S proteasome. Initial phase I and II studies of bortezomib monotherapy demonstrated response rates of 25% to 35% in patients with relapsed/refractory MM.[83–85] A survival benefit with bortezomib was demonstrated in the randomized, phase III APEX study, which compared bortezomib to high-dose dexamethasone in patients (N = 669) who had received a median of two prior therapies.[86,87] Bortezomib treatment demonstrated superior response rates (43% *v* 18%; $P < .001$), TTP (6.2 months *v* 3.5 months; $P< .001$), and 1-year OS (80% *v* 66%; $P = .003$) compared with dexamethasone.[72] An updated analysis showed a persistent OS benefit of 6 months for patients who received bortezomib (30 months) compared to dexamethasone (24 months), despite substantial crossover (>62%) from dexamethasone to bortezomib.[87] Based on the above phase III data, bortezomib monotherapy is included as a salvage treatment option for patients with relapsed/refractory MM in both the NCCN and ESMO guidelines.[11,12]

Multiple chemotherapeutic agents have been successfully combined with bortezomib in relapsed/refractory MM (Table 3).[88–94] The addition of dexamethasone to bortezomib resulted in improvement of response in 18% to 34% of patients.[85,85,95–97] Other regimens tested in relapsed/refractory MM include bortezomib in combination with PLD (≥PR: 44%), low-dose dexamethasone–PLD (≥PR: 67% to 85%), oral or intravenous melphalan (≥PR: 47% to 68%), and low-dose cyclophosphamide–prednisone–dexamethasone (≥PR: 68% to 82%)[88,90–92,94] (Table 3).[88–94,98] The NCCN considers both bortezomib–PLD and bortezomib–dexamethasone as category 1 combination treatment options for relapsed/refractory MM,[11] and ESMO recommends bortezomib in combination with dexamethasone or chemotherapy.[12]

Combinations of Established Novel Agents

Numerous studies have evaluated the combination of two established novel agents with conventional and/or cytotoxic drugs in the relapsed/refractory setting (Table 4).[8,99–104] The combination of bortezomib–thalidomide has been studied with dexamethasone (VTD; ≥PR: 63%), dexamethasone–PLD (≥PR: 74%), dexamethasone–cyclophosphamide (VCTD; ≥PR: 88%), melphalan–prednisone (VMPT; ≥PR: 67%), and melphalan–dexamethasone (VMDT; ≥PR: 66%).[8,99–102] Several studies have evaluated the combination of lenalidomide–bortezomib–dexamethasone (≥MR: 61% to 86%),[103,105,106] which appears to achieve a response even in patients resistant to thalidomide, lenalidomide, or bortezomib.[107] This combination has now been included in the NCCN guidelines as a category 2A option for the treatment of relapsed/refractory MM.[11] The combination of lenalidomide–thalidomide has also been tested with melphalan–prednisone (≥PR: 75%).[104] Phase III studies would be needed to confirm the benefit of these combination regimens in the relapsed/refractory setting.

INCIDENCE AND MANAGEMENT OF TREATMENT-RELATED ADVERSE EVENTS

The established novel agents have different and specific toxicity profiles, which, along with patients' characteristics and comorbidities, should be considered when choosing a treatment regimen. In most cases, the adverse events (AEs) associated with these agents can be managed with patient monitoring, supportive care,

Table 2. Selected Lenalidomide-Based Combinations in the Treatment of Relapsed/Refractory Multiple Myeloma[70–77]

Study	Phase	Regimen	Schedule	N	≥PR, %	CR, %	TTE
MM-009; Weber et al. (2007)[72]	III	LD	L: 25 mg on days 1–21 of 28-day cycle; D: 40 mg on days 1–4, 9–12, 17–20 for the first 4 cycles, thereafter 40 mg on days 1–4	177	61.0	14.1	Median TTP: 11.1 mo Median OS: 29.6 mo
		D	D: 40 mg on days 1–4, 9–12, 17–20 for the first four 4-wk cycles, thereafter 40 mg on days 1–4	176	19.9	0.6	Median TTP: 4.7 mo Median OS: 20.2 mo
MM-010; Dimopoulos et al (2007)[73]	III	LD	L: 25 mg on days 1–21 of 28-day cycle; D: 40 mg on days 1–4, 9–12, 17–20 for the first four cycles, thereafter 40 mg on days 1–4	176	60.2	15.9	Median TTP: 11.3 mo Median OS: not reached
		D	D: 40 mg on days 1–4, 9–12, 17–20 for the first four 4-wk cycles, thereafter 40 mg on days 1–4	175	24.0	3.4	Median TTP: 4.7 mo Median OS: 20.6 mo
Baz et al (2006)[74]	I/II	LPLDVD	MTD: L: 10 mg on days 1–21 of 28-day cycle; PLD: 40 mg/m^2 on day 1; V: 2 mg on day 1; D: 40 mg on days 1–4	62	75	29	Median PFS: 12 mo Median OS: not reached
Knop et al (2009)[75]	I/II	RAD	MTD not reached, highest dose-level: L: 25 mg on days 1–21 of 28-day cycle; Dox: 9 mg/m^2 on days 1–4; D: 40 mg on days 1–4 and 17–20	69	73	15	Median TTP: 45 wk Median PFS: 40 wk 1-year OS: 88%
Reece et al (2009)[76]	I/II	LCP	MTD not reached, highest dose-level: L: 25 mg on days 1–21; C: 300 mg/m^2 PO on days 1, 8, 15 of 28-day cycle; P: 100 mg every other day	31	94	19	Too early to evaluate
Schey et al (2008)[77]	I	LCD	MTD: L: 25 mg on days 1–21; C: 600 mg PO on days 1, 8 of 28-day cycle; D: 20 mg on days 1–4, 8–11	31	81	29	Too early to evaluate

Abbreviations: C, cyclophosphamide; CR, complete response; D, dexamethasone; Dox (A), doxorubicin; L (R), lenalidomide; MTD, maximum tolerated dose; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PO, taken orally; PR, partial response; P, prednisone; TTE, time to event; TTP, time to progression; V, vincristine.

Table 3. Selected Bortezomib-Based Combinations in the Treatment of Relapsed/Refractory Multiple Myeloma[88–94]

Study	Phase	Regimen	Schedule	N	≥PR, %	CR, %	TTE
Orlowski et al (2007)[88]	III	B-PLD	B: 1.3 mg/m^2 on days 1, 4, 8, 11 of 21-day cycle; PLD: 30 mg/m^2 on day 4	324	44	4	Median TTP: 9.3 mo 15-month OS: 76%
		B	B: 1.3 mg/m^2 on days 1, 4, 8, 11 of 21-day cycle	322	41	2	Median TTP: 6.5 mo 15-month OS: 65%
Kropff et al (2007)[89]	II	VCD	B: 1.3 mg/m^2 on days 1, 4, 8, 11 of 21-day cycle for the first 8 cycles, followed by B 1.3 mg/m^2 on days 1, 8, 15, 22 for three 5-wk cycles; C: 50 mg PO daily D: 20 mg on day of B injection and day thereafter;	54	82	16	Median EFS: 12 mo Median OS: 22 mo
Palumbo et al (2008)[90]	II	VDD	B: 1.3 mg/m^2 on days 1, 4, 8, 11 of 28-day cycle; PLD: 20 mg/m^2 on days 1, 4 or PLD 30 mg/m^2 on day 1 D: 40 mg on days 1–4;	64	67	9	1-year EFS: 34% 1-year OS: 66%
Jakubowiak et al (2009)[91]	II	VDD	B: 1.3 mg/m^2 on days 1, 4, 8, and 11; PLD: 30 mg/m^2 IV on day 4; D: 20 mg to 40 mg daily	40	85.0	37.5	1-year PFS: 92.5% 1-year OS: 97.5%
Berenson et al (2006)[92]	I/II	BM	MTD: B: 1.0 mg/m^2 on days 1, 4, 8, 11 of 28-day cycle; M: 0.10 mg/kg PO on days 1–4	35	47	6	Median PFS: 10 mo
Reece et al (2008)[93]	I/II	BCP	MTD not reached, highest dose-level: B: 1.5 mg/m^2 on days 1, 8, 15 of 28-day cycle; C: 300 mg/m^2 PO on days 1, 8, 15, 22; P: 100 mg every 2 days	37	68	32	Median PFS: 15 mo Median OS: 24 mo
Popat et al (2009)[94]	I/II	BMD	MTD: B: 1.3 mg/m^2 on days 1, 4, 8, 11 of 28-day cycle; M: 7.5 mg/m^2 IV on day 2; D: 20 mg on days 1, 2, 4, 5, 8, 9, 11, 12 in case of progressive or stable disease after 2 or 4 cycles, respectively	53	68	19	Median PFS: 10 mo Median OS: 28 mo

Abbreviations: B (V), bortezomib; C, cyclophosphamide; CR, complete response; D, dexamethasone; Dox, doxorubicin; EFS, event-free survival; IV, intravenous; M, melphalan; MTD, maximum tolerated dose; OS, overall survival; P, prednisone; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PO, taken orally; PR, partial response; TTE, time to event; TTP, time to progression.

Table 4. Selected Combinations of Established Novel Agents in the Treatment of Relapsed/Refractory Multiple Myeloma[8,99–104]

Study	Phase	Regimen	Schedule	N	≥PR, %	CR, %	TTE
Bortezomib-thalidomide-based combinations							
Ciolli et al (2008)[99]	II	PLD-VTD	PLD: 50 mg/m^2 (30 mg/m^2 for patients >75 years) on day 4 of a 28-day cycle; V: 1.0 mg/m^2 on days 1, 4, 8, 11; T: 100 mg on days 1–28; D: 24 mg on days 1, 2, 4, 5, 8, 9, 11, 12	42	74	24	Median PFS: 15 mo 2-year OS: 66%
Terpos et al (2008)[100]	II	VMTD	V: 1.0 mg/m^2 on day 1, 4, 8, 11 of a 28-day cycle; M: 0.15 mg/kg PO on days 1–4; T: 100 mg on days 1–4, 17–20; D: 12 mg/m^2 on days 1–4, 17–20	62	66	13	Median TTP: 9.3 mo 2-year OS: 63%
Kim et al (2010)[8]	II	VCTD	V: 1.3 mg/m^2 on days 1, 4, 8, 11 of 21-day cycle; C: 150 mg/m^2 PO on days 1–4; T: 50 mg day 1–21 of 21-day cycle; D: 20 mg/m^2 on days 1, 4, 8, 11	70	88	46	Median TTP: 15 mo Median OS: 32 mo
Palumbo et al (2007)[101]	I/II	VMPT	MTD: V: 1.3 mg/m^2 on day 1, 4, 15, 22; M: 6 mg/m^2 PO on days 1–5; P: 60 mg/m^2 on days 1–5; T: 50 mg on days 1–35	30	67	17	1-year PFS: 61% 1-year OS: 84%
Pineda-Roman et al (2008)[102]	I/II	VTD	MTD: V: 1.3 mg/m^2 on days 1, 4, 8, 11 of 21-day cycle; T: 150 mg day 1–21 of 21-day cycle; D: 20 mg on day 1, 2, 4, 5, 8, 9, 11, 12 of 21-day cycle in case of no PR after 4 cycles	85	63	6	Median EFS: 6 mo Median OS: 22 mo
Lenalidomide-bortezomib-based combinations							
Richardson et al (2009)[103]	I	LB (D)	MTD: L: 15 mg on days 1–14 of 21-day cycle; B: 1.0 mg/m^2 on days 1, 4, 8, 11 of 21-day cycle; D: 20 mg or 40 mg on days 1, 2, 4, 5, 8, 9, 11, 12 in case of progression after 2 cycles	38	61	8	Median TTP: 7.7 mo Median OS: 37 mo
Lenalidomide-thalidomide-based combinations							
Cavallo et al (2009)[104]	I/II	RMPT	R: 10 mg on days 1–21 of a 28-day cycle; M: 0.18 mg/kg PO on days 1–4; P: 2 mg/kg on days 1–4; T: 50 mg or 100 mg on days 1–28	44	75	14	1-year PFS: 52% 1-year OS: 72%

Abbreviations: B (V), bortezomib; C, cyclophosphamide; CR, complete response; D, dexamethasone; EFS, event-free survival; L (R), lenalidomide; M, melphalan; MTD, maximum tolerated dose; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PO, taken orally; PR, partial response; P, prednisone; T, thalidomide; TTE, time to event; TTP, time to progression.

and dose reduction and interruption where appropriate. Additional management strategies may also be appropriate for patients aged ≥75 years.

Thalidomide

In clinical trials, the frequency of AEs varies depending on the administration of thalidomide as a single agent or in combination with other agents. A systematic review of studies in patients with relapsed/refractory MM (N = 1,674) treated with thalidomide monotherapy demonstrated that the most frequent grade 3/4 AEs were constipation (16%), somnolence (11%), neuropathy (6%), rash (3%), venous thromboembolism (VTE; 3%), and cardiac AEs (2%).[46] Generally, the addition of other agents to thalidomide increases the incidence of AEs. A systematic review of studies evaluating the combination of thalidomide and dexamethasone showed that the major AEs (all grades) in patients with relapsed/refractory MM (N = 451) were constipation (37%), neuropathy (27%), somnolence (26%), depression (10%), and VTE (5%).[108]

Peripheral neuropathy is the most serious thalidomide-related AE, and is cumulative and dose-dependent. Even low doses (25–50 mg) of thalidomide cause distal sensory peripheral neuropathy in about 50% of patients.[109] Because of the incidence and severity of peripheral neuropathy, some physicians recommend that thalidomide therapy be restricted to <6 months.[110] Prompt dose reduction and discontinuation are the main strategies for management of thalidomide-associated peripheral neuropathy, but clear dose-modification guidelines have not been established.[111]

VTE occurs frequently in patients with MM and is of particular concern for those receiving thalidomide in combination with anthracyclines and/or dexamethasone.[112] Individual risk factors for thrombosis include age, history of VTE, central venous catheter, comorbidities (eg, diabetes, infections, cardiac disease), immobilization, surgery, and inherited thrombophilia.[113] Several options, such as low-molecular-weight heparins (LMWHs), warfarin, and low-dose aspirin, have been investigated for the management of VTE.[113–116] Both LMWH and warfarin appear to be effective at reducing VTE rates to <10% for patients receiving thalidomide-based treatment.[117] The International Myeloma Working Group (IMWG) has recommended LMWH equivalent to enoxaparin 40 mg/d for patients with two or more myeloma-related risk factors, and for patients receiving concurrent high-dose dexamethasone or doxorubicin. An alternative recommendation to LMWHs is full-dose warfarin targeting a therapeutic international normalization ratio of 2:3, although data are limited to support this strategy. Low-dose aspirin is recommended for patients with one or no risk factors for VTE.[113]

Thalidomide treatment is also associated with constipation, somnolence, rash, and neutropenia, which are important to recognize and manage in order to maintain patient quality of life.

Lenalidomide

Lenalidomide is a second-generation IMiD with an improved tolerability profile compared to thalidomide, including lower rates of neuropathy, somnolence, and constipation. In a large phase II study of lenalidomide monotherapy in patients with relapsed/refractory MM (N = 222), the most common grade 3/4 AEs were neutropenia (60%), thrombocytopenia (39%), and anemia (20%).[70] Based on pooled data from the two pivotal phase III studies (MM-009 and MM-010) evaluating the combination of lenalidomide and dexamethasone in patients with relapsed/refractory MM (N = 704), the most frequent grade 3/4 AEs were neutropenia (35%), infection (16%), thrombocytopenia (13%), VTE (13%), anemia (11%), and atrial fibrillation (3%).[72,73,78] The safety profiles of other lenalidomide-based combinations evaluated in the relapsed/refractory setting are consistent with those described above.[74,75,85]

Myelosuppression is a significant lenalidomide-related AE that requires early recognition and management to avoid development of severe infections and treatment interruptions.[111] Lenalidomide treatment should be interrupted when platelet counts fall to <30,000 μL, and if neutrophil counts fall below 1,000/μL, lenalidomide treatment should be interrupted and granulocyte colony-stimulating factor added. Anemia can be managed with erythropoiesis-stimulating agents, which are only recommended when hemoglobin levels are <9 g/dL, especially in patients with cardiac disease. For patients without cardiac disease, the benefits of erythropoiesis-stimulating agents should be carefully weighed against the risks, as they could potentially increase the risk of VTE.[118]

In addition to myelosuppression, lenalidomide treatment is also associated with VTE and other AEs that may require dose-adjustment. Based on recommendations from the IMWG, lenalidomide-related VTE can be managed with LMWH, warfarin, and aspirin in the same way as thalidomide-related VTE.[113] Lenalidomide alone, however, is not believed to be associated with a high risk of VTE, therefore management strategies are only recommended for lenalidomide-based combination regimens.[113] Lenalidomide is predominately excreted via the kidney, therefore, dose adjustment is recommended in patients with moderate or severe renal impairment, and in patients on dialysis. Other AEs requiring dose reduction are grade 3/4 infection (25% to 50% reduction in dose), grade 3/4 asthenia (25% to 50%), grade 2 cutaneous toxicity (50%), and grade 2 intestinal toxicity (50%).[118] In addition, while it has been reported that patients treated with lenalidomide maintenance therapy post-transplant have an increased risk of second primary malignancies, this was not observed in patients with relapsed and refractory disease.[119,120]

Bortezomib

Bortezomib has been evaluated both as monotherapy and in combination with other agents in patients with relapsed/refractory MM. In the phase III APEX trial that evaluated bortezomib monotherapy versus high-dose dexamethasone in patients with relapsed/refractory MM (N = 669), the most relevant grade 3/4 AEs reported in 75% of bortezomib-treated patients were thrombocytopenia (30%), neutropenia (14%), and peripheral neuropathy (8%).[86] In the bortezomib group, several additional AEs were associated with early treatment discontinuation including gastrointestinal disorders, fatigue, hypercalcemia, and spinal-cord compression (2% each).[86] In two studies where dexamethasone was added to bortezomib in patients with progressive or stable disease, the addition of dexamethasone did not appear to alter the safety profile of bortezomib.[85,96] The addition of other agents to bortezomib resulted in a safety profile consistent with the known toxicities of each agent. For example, addition of PLD to bortezomib was associated with a 5% incidence of hand-foot syndrome.[88]

The main hematologic toxicity associated with bortezomib treatment is thrombocytopenia. Monitoring for signs of thrombocytopenia prior to bortezomib dosing is recommended.[121] For patients with grade 4 thrombocytopenia (platelet count $<25{,}000/\mu L$), management recommendations include a 25% to 50% reduction in bortezomib dose and platelet transfusion.[122]

Peripheral neuropathy is also a significant bortezomib-related AE, and is not necessarily dose-dependent. The predominant risk factor for bortezomib-induced peripheral neuropathy is age, with a 6% increase in risk for every year of age.[123] Management of peripheral neuropathy requires early recognition and appropriate dose reductions. Treatment discontinuation is required for grade 4 peripheral neuropathy.[122] With appropriate dose modifications, bortezomib-induced peripheral neuropathy is reversible in most patients.[124] Recent reports have indicated a substantially reduced risk of bortezomib-associated peripheral neuropathy with once-weekly versus twice-weekly dosing,[125] and with the subcutaneous route of administration, which has been approved by the US Food and Drug Administration.[126]

Additional bortezomib-related AEs that may require management include infections and gastrointestinal toxicities. Patients receiving bortezomib should be monitored for possible varicella-zoster virus reactivation, and the routine use of antiviral prophylaxis should be considered.[127] For patients with any grade 3/4 infection, a 25% to 50% bortezomib dose reduction is recommended, and consideration should be given to appropriate prophylaxis.[122] Gastrointestinal toxicities including nausea, vomiting, diarrhea, and constipation are usually mild and easily managed.[121] A 50% dose reduction is recommended for grade 2 occurrences of gastrointestinal toxicity, and grade 3/4 toxicity requires dose interruption.[122]

Patients Aged ≥75 Years

AEs are an especially important consideration when treating elderly patients, especially as increasingly effective, yet potentially more toxic, combination regimens become standard of care. Thirty-seven percent of patients with MM are ≥75 years of age at diagnosis.[128] While these vulnerable patients generally experience AEs similar to those experienced by younger patients, their ability to tolerate toxicity is lower, thus increasing the risk of serious complications and/or treatment discontinuation. Therefore, it is important to consider age, and physical and comorbid conditions, when making treatment decisions for this patient population.[129] Modified treatment regimens and dose reductions should be used appropriately to improve tolerability. For example, dexamethasone should be reduced from 40 mg to 20 mg weekly, melphalan from 0.25 mg/kg to 0.18 mg/kg or 0.13 mg/kg on days 1 to 4, thalidomide from 200 mg/d to 100 mg/d or 50 mg/d, lenalidomide from 25 mg to 15 mg on days 1 to 21, and bortezomib (at a dose of 1.0 mg/m^2 to 1.3 mg/m^2) from twice-weekly to once-weekly infusion.[107]

ADJUNCTIVE/SUPPORTIVE CARE

Important advances have occurred in adjunctive treatment and supportive care available for patients with MM. Approximately 85% of patients develop bone disease in the form of diffuse osteopenia and/or osteolytic lesions, and the related complications (eg, bone pain and pathologic fractures) are a major cause of deteriorating quality of life and performance status.[11] Treatment of bone pain should start with non-opioid analgesics such as acetaminophen; however, nonsteroidal anti-inflammatory drugs should be avoided because of the potential risk of renal damage. Opioid analgesics should be introduced when non-opioid agents are ineffective.[130] Local radiotherapy can also be used for palliation of bone pain, with fractionated radiotherapy relieving pain in 92% to 97% of patients.[131] Numerous clinical trials have demonstrated that bisphosphonates (eg, pamidronate, clodronate, and zoledronic acid) can reduce the incidence of new bone lesions and pathologic fractures in patients with MM.[132–135] In addition to its bone health benefits, zoledronic acid has also been shown to extend median OS and PFS by 5.5 months and 2.0 months, respectively, in patients with MM.[134] The NCCN guidelines recommend bisphosphonates for all patients receiving therapy for symptomatic bone disease.[11] Guidelines from the European Myeloma Network recommend that bisphosphonate therapy be continued for only 2 years to limit the possibility of

osteonecrosis of the jaw, and that concomitant calcium and vitamin D_3 treatment should be considered to prevent electrolytic imbalance.[136] The Myeloma Foundation of Australia also recommends a comprehensive dental examination before bisphosphonate therapy, maintenance of good oral hygiene, and avoidance of invasive oral procedures to reduce the risk of osteonecrosis of the jaw.[137]

In addition to bone pain, patients with MM may also experience other conditions requiring adjunctive treatment or supportive care. In patients with renal insufficiency, deterioration of renal function and the development of tumor lysis syndrome can be prevented with the use of appropriate hydration, urine alkalinization, and treatment of hypercalcemia, hyperuricemia, and infections.[138] Hypercalcemia requires immediate treatment with hydration, diuretics, glucocorticoids, and bisphosphonates.[139] To prevent infection, intravenous immunoglobulin therapy should be considered for recurrent, life-threatening infections, pneumococcal and influenza vaccines should also be considered, and *Pneumocystis carinii* pneumonia, herpes, and antifungal prophylaxis are recommended if a high-dose regimen is used.[11] Herpes prophylaxis is recommended for all patients receiving bortezomib.[127] For patients with anemia, especially those with renal failure, erythropoiesis-stimulating agents are recommended.[140]

INDIVIDUALIZED TREATMENT

Implications of Genetic Heterogeneity

MM is a disease with marked genetic heterogeneity, which has important implications for treatment because molecular subgroups respond differently to currently available regimens. Chromosomal abnormalities are detected with conventional cytogenetics or fluorescence in situ hybridization (FISH) in >90% of patients, and include deletions, trisomies, and translocations.[141] Patients with hyperdiploid and t(11;14) mutations have standard-risk disease and typically respond well to conventional chemotherapy, whereas patients with nonhyperdiploid, t(4:14), del(17p), and del(13q14) mutations have high-risk disease and respond poorly to these treatments.[142] Retrospective analyses of phase III bortezomib trials have demonstrated that this drug may overcome the poor prognosis of patients with del(13q14) and t(4:14) mutations.[143–145] There are also initial data suggesting that bortezomib-based treatment may be effective in patients with del(17p) mutation.[146] Given the preliminary encouraging data with these established novel agents, the combination of bortezomib–lenalidomide–dexamethasone may be ideal for patients with high-risk chromosomal abnormalities.

Sequencing of Treatments

Currently, no conclusive data outlining the most appropriate sequence of treatments for patients with relapsed/refractory MM exist; however, factors to consider when choosing the optimal regimen include timing of relapse and comorbid conditions. The NCCN guidelines recommend that if the previous duration of response off therapy was >6 months to 1 year, then the same agent can be used again.[11] However, after shorter durations of remission, a different treatment regimen should be considered. Even if resistance to one-drug and two-drug regimens has occurred, the guidelines suggest that there may be synergy with other drugs so that combination therapy with previously unused drugs or three-drug to four-drug regimens may be useful.[11]

Comorbidities should be taken into account when determining treatment options for patients with relapsed/refractory MM. Nearly 50% of patients with MM will develop some degree of renal impairment over the course of their disease, and since many chemotherapeutic and targeted therapies are renally excreted, impaired renal function may affect pharmacokinetics and limit choice of therapy.[147] Bortezomib and thalidomide are not renally excreted, making them a better choice for patients with renal impairment compared to lenalidomide, which undergoes renal excretion and requires dose adjustments for patients with renal impairment.[118,148–150] In contrast, both lenalidomide and thalidomide are not metabolized by the liver, making these drugs more suited for patients with hepatic impairment than bortezomib, which undergoes hepatic metabolism and should be avoided in patients with impaired liver function.[118,151,152] Diabetes is a common comorbidity, particularly in an aging population, and the nearly universal use of corticosteroids in the treatment of MM may exacerbate this condition. The corticosteroid-sparing combination of bortezomib–PLD may be well suited for patients with diabetes.[88] Another important consideration when choosing a treatment regimen is the presence of neuropathy, which can occur in up to 80% of previously treated patients.[153] Lenalidomide-based treatment regimens have lower frequencies of neuropathy compared to thalidomide-based and bortezomib-based regimens, making it a reasonable first-line salvage choice in patients with comorbid neuropathy.[72,73,153] No increase in VTE has been noted with bortezomib alone, making it a good choice for patients with a history of thromboembolic events.[152] However, bortezomib combinations such as bortezomib–PLD–dexamethasone (VDD) are associated with an increased risk of VTE.[91] Thalidomide and lenalidomide are also options for patients with thromboembolic complications as long as appropriate concomitant therapeutic anticoagulation is used.[113] Figure 1 shows a possible treatment algorithm for relapsed/

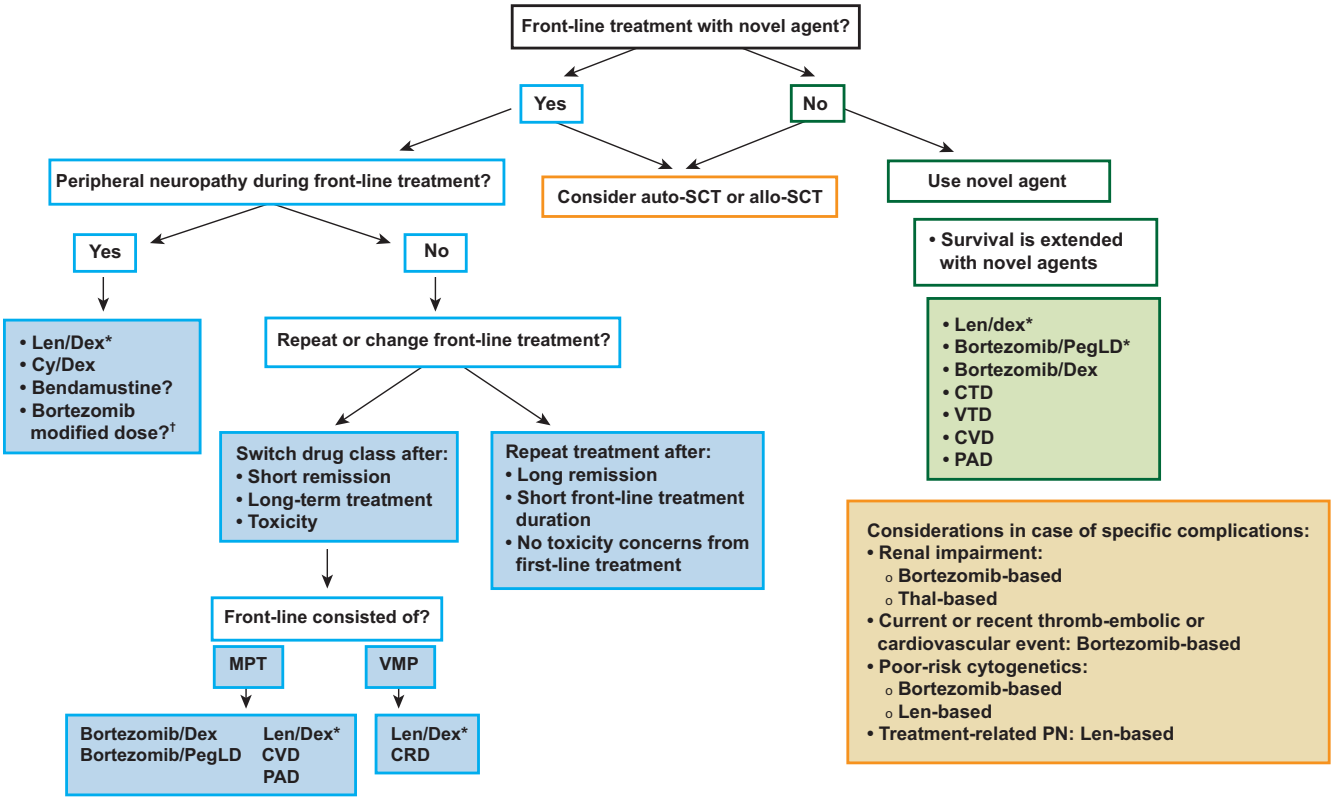

Figure 1. Treatment of relapsed/refractory multiple myeloma. Abbreviations: allo-SCT, allogeneic stem cell transplantation; auto-SCT, autologous stem cell transplantation; CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone; CVD, cyclophosphamide, bortezomib, and dexamethasone; Cy, cyclophosphamide; Dex, dexamethasone; Len, lenalidomide; MPT, melphalan, prednisone, and thalidomide; PAD, bortezomib, doxorubicin, and dexamethasone; PegLD, pegylated liposomal doxorubicin; PN, peripheral neuropathy; Thal, thalidomide; VMP, bortezomib, melphalan, and prednisone; VTD, bortezomib, thalidomide, and dexamethasone. *Indicates that data are available from a phase 3 randomized trial. †Only if PN has recovered and there is no other therapeutic alternative. From Ludwig H, et al. Oncologist 2010;15:6–25.[154] Copyright 2010 by Alphamed Press. Reproduced with permission of Alphamed Press. Permission conveyed through Copyright Clearance Center, Inc.

refractory MM.[154] It is important to note that novel agents are increasingly being incorporated into front-line therapies, which will impact treatment sequencing in the relapsed/refractory setting.

CONCLUSIONS

In recent years, the introduction of thalidomide, lenalidomide, and bortezomib has changed the treatment paradigm for patients with relapsed/refractory MM and dramatically improved clinical outcome compared with conventional chemotherapy alone. However, not all patients will respond to established novel agents, and even those who do respond will eventually relapse or become refractory to treatment, owing in part to the changing biology of the tumor and development of drug-resistant phenotypes within the tumor. Thus, there is an urgent need to develop targeted agents that provide durable disease control, symptomatic relief, and a more tolerable safety profile for patients who no longer derive benefit from or cannot tolerate currently approved therapies. Several new agents that target specific pathways involved in the pathogenesis of MM are at various stages of development in the relapsed/refractory setting. Those agents in late-stage clinical development, including new IMiDs, second-generation proteasome inhibitors, signal transduction modulators, monoclonal antibodies, and histone deacetylase inhibitors, are reviewed by Philippe Moreau in this supplement.

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The Future of Therapy for Relapsed/Refractory Multiple Myeloma: Emerging Agents and Novel Treatment Strategies

Philippe Moreau

Treatment of relapsed or refractory multiple myeloma (MM) continues to present a therapeutic challenge. The immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, and the proteasome inhibitor (PI) bortezomib, have dramatically improved clinical outcomes for patients with newly diagnosed and relapsed/refractory MM. However, nearly all patients will eventually relapse or become refractory to these drugs. Numerous agents are currently in development for the treatment of relapsed/refractory MM. Those farthest along in clinical development include new IMiDs (pomalidomide), new PIs (eg, carfilzomib, MLN9708, and marizomib), histone deacetylase inhibitors (eg, panobinostat and vorinostat), monoclonal antibodies (eg, elotuzumab, siltuximab, and BT062), and signal transduction modulators (eg, perifosine). These emerging agents with diverse mechanisms of action have demonstrated promising anti-tumor activity in patients with relapsed/refractory MM, and rationally designed combinations with established agents are being investigated in the clinic. These new agents are creating opportunities to target multiple pathways, overcome resistance, and improve clinical outcomes, particularly for those patients who are refractory to approved novel agents. This article describes emerging antimyeloma agents in mid-stage to late-stage clinical development, and highlights the novel treatment approaches and combination strategies being evaluated in the relapsed/refractory setting.
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The introduction of novel agents, including the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide and the proteasome inhibitor (PI) bortezomib, has revolutionized the treatment paradigm for relapsed/refractory multiple myeloma (MM). In this setting, IMiD-containing and bortezomib-containing combinations have demonstrated improved response rates and overall survival (OS) compared with the response rate and OS for high-dose dexamethasone.[1,2] More recently, IMiDs and bortezomib have become increasingly incorporated into standard first-line regimens for treatment of elderly patients or those eligible for high-dose therapy, and have demonstrated improved disease outcomes compared with the disease outcomes of standard upfront regimens. However, as their disease progresses, most patients will eventually relapse or become refractory to these agents whether received as part of first-line or second-line therapy. Studies have shown that re-treatment with IMiDs or bortezomid can induce clinically meaningful responses in some patients, particularly those who relapsed after a prolonged treatment-free interval,[3–9] but increasingly patients are becoming refractory to all available agents. This is a particularly challenging group of patients, with poor clinical outcomes.[10] That reality highlights the significant unmet need for newer agents with activity in patients who develop resistance to IMiDs and bortezomib. This article will focus on the specific mechanism of action (MOA) of emerging anti-myeloma agents in phase II or III clinical development, and will describe the clinical evidence of activity and toxicity, as well as novel treatment strategies and combination schedules being investigated for the treatment of relapsed/refractory MM.

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ANTI-MYELOMA THERAPIES IN CLINICAL DEVELOPMENT

A variety of agents are currently in development for the treatment of relapsed/refractory MM. Those that

are farthest along in clinical development include new IMiDs, new PIs with novel MOA, monoclonal antibodies, and small molecule inhibitors of histone deacetylase (HDAC), Akt, mammalian target of rapamycin (mTOR), and heat shock protein 90 (Hsp90). The rationale for investigating these different classes of agents in relapsed/refractory MM is reviewed in the article by David Siegel in this supplement.

Immunomodulatory Drugs

Thalidomide and lenalidomide are highly effective agents in MM.[2] These agents modulate expression of a wide range of cytokines such as interleukin (IL)-2 and interferon gamma (IFN-γ) that stimulate T cells and natural killer (NK) cells to destroy MM cells, and they downregulate expression of cytokines such as IL-6 and tumor necrosis factor alfa (TNF-α) that contribute to angiogenesis.[11] Lenalidomide is a second-generation IMiD, which, compared with thalidomide, demonstrates improved activity and a better safety profile.[12] Lenalidomide is effective in patients who relapse or are refractory to thalidomide, and, compared with thalidomide, is associated with less peripheral neuropathy but a similar risk of thromboembolic events.[13] The newest IMiD is pomalidomide, which has demonstrated greater activity than thalidomide in vitro,[12,14] and may have a better safety profile than either thalidomide or lenalidomide.[13] The primary toxicity associated with pomalidomide is myelosuppression[15]; neuropathy and thromboembolic events are rare, but patients require deep vein thrombosis (DVT) prophylaxis,[16,17] as described for other IMiDs. In vitro studies demonstrate that pomalidomide is more effective than thalidomide at inhibiting proliferation of malignant B cells.[12] Preclinical studies have further shown that pomalidomide significantly increases serum levels of IL-2 receptor and IL-12, and may promote the switch to an effector T-cell phenotype.[16] In addition, some evidence suggests that pomalidomide may inhibit the destructive effects of MM in the bone microenvironment by inhibiting osteoclast differentiation.[14]

Several phase I and II studies have shown that the combination of pomalidomide plus dexamethasone is effective in patients with MM who relapse or are refractory to thalidomide or lenalidomide-containing regimens (Table 1). Initial reports in 2009 demonstrated promising activity with pomalidomide alone (2–5 mg/d for 21 days every 28-day cycle), or pomalidomide (2 mg/d) plus low-dose dexamethasone (40 mg weekly) in the relapsed/refractory setting.[36,17] In a phase II study of 60 patients, of whom 62% had received prior treatment with thalidomide or lenalidomide, pomalidomide plus low-dose dexamethasone resulted in a 63% objective response rate (ORR), which included 5% complete response (CR), 28% very good partial response (VGPR), and 30% partial response (PR).[36] Objective responses were also achieved in 74% of patients with high-risk cytogenetics. More recent data with this combination have also demonstrated activity in patients who are refractory to lenalidomide.[18] Among 34 patients treated, best response was VGPR in 9%, PR in 23%, and minor response (MR) in 15%. Moreover, these responses were durable (median 9.1 months), and median OS was 13.9 months. As expected, the primary toxicity was myelosuppression, and no thromboembolic events occurred in this study, which employed standard venous thromboembolism prophylaxis. Two additional phase II studies with this combination have been reported. The final results of the Intergroupe Francophone du Myélome (IFM) 2009–02 study showed that pomalidomide (4 mg/d for 21 or 28 days every 28-day cycle) plus dexamethasone (40 mg weekly) is effective in heavily pretreated patients (N = 84) who had at best stable disease (SD) with their last course of bortezomib and lenalidomide, or were refractory to bortezomib and lenalidomide per International Myeloma Working Group (IMWG) criteria.[19] The ORR was 35% (5% VGPR) with the 21-day schedule and 34% (7% VGPR) with the 28-day schedule. In a similar phase II study (N = 221) that enrolled a majority of patients who were refractory to both bortezomib and lenalidomide, pomalidomide (4 mg/day, days 1–21 every 28-day cycle) plus dexamethasone (40 mg weekly) yielded at least a PR in 34% of patients, including 1 CR, and median progression-free survival (PFS) was 4.6 months.[20] These data indicate a lack of cross-resistance between pomalidomide and lenalidomide, and suggest that in combination with dexamethasone, pomalidomide may improve clinical outcomes in relapsed/refractory MM. Accordingly, a phase III trial known as NIMBUS is currently comparing pomalidomide plus low-dose dexamethasone with high-dose dexamethasone in patients with relapsed or relapsed/refractory MM (Table 2).

Proteasome Inhibitors

The ubiquitin-proteasome system is responsible for maintaining cellular protein homeostasis through timely degradation of intracellular proteins. Consequently, proteasome inhibition affects a wide range of fundamental cellular functions, including cell cycle regulation, apoptosis, and the stress response.[37,38] Cancer cells appear to be highly dependent on proteasome-regulated homeostatic pathways,[39–41] and MM cells, especially, upregulate the ubiquitin-proteasome cascade making them particularly sensitive to the effects of PIs. Most cells express the constitutive 26S proteasome, and lymphocytes express the immunoproteasome.

Bortezomib is the prototypical PI with a boronate active moiety. It primarily inhibits the β5-proteasome subunit in the constitutive proteasome and the LMP7 subunit in the immunoproteasome in a slowly reversible manner. These subunits have chymotrypsin-like activity and are critically important for proteasome function. Based on the activity of bortezomib in MM, a number of novel PIs are

Table 1. Reported Phase Ib, Phase II, and Phase III Studies of Emerging Novel Agents in Relapsed/Refractory Multiple Myeloma

Agent/Study	Phase	N	Dose and Combination Partner	Prior Therapy or Patient Population	ORR, %
Pomalidomide					
Lacy et al (2009, 2010)[15,18]	II	60	2 mg/day + low-dose DEX	Prior THAL or LEN (62%)	63
				LEN-refractory (n = 34)	32
IFM-2009–02; Leleu et al (2011)[19]	II	84	4 mg/day + low-dose DEX	Relapsed or refractory to LEN and BTZ	35
Richardson et al (2011)[20]	II	221	4 mg/day + low-dose DEX	Majority refractory to LEN and BTZ	34
Carfilzomib					
PX-171–004; Vij et al (2011)[21]	II	129	Monotherapy (20 mg/m^2 or 20/27 mg/m^2)	Prior IMiD (>90%); BTZ-naive	48
Vij et al (2010)[22]		35	Monotherapy (20 mg/m^2)	Prior BTZ; refractory (40%)	17
PX-171–003-A1; Jakubowiak et al (2011)[23]	II	266	Monotherapy (20 mg/m^2)	Relapsed or refractory; unfavorable cytogenetics (31%)	25 (229 eval)
Niesvizky et al (2009)[24]	Ib	32	15 mg/– 27 mg/m^2 + LEN + DEX	Relapsed or refractory	55
Panobinostat					
Siegel et al (2008)[25] San Miguel et al (2009)[26]	Ib	29	10 mg − 30 mg + BTZ	Prior BTZ	50
PANORAMA-2; Richardson et al (2011)[27]	II	55	20 mg + BTZ + DEX	BTZ-refractory	29
Vorinostat					
VANTAGE-095; Siegel et al (2011)[28]	IIb	143	400 mg + BTZ ± low-dose DEX	BTZ-refractory; IMiD-refractory (87%)	17
VANTAGE-088; Dimopoulos et al (2011)[29]	III	635	400 mg + BTZ *v* BTZ	Relapsed or refractory; prior BTZ (BTZ-refractory not eligible)	56 41
Perifosine					
Richardson et al (2011)[30]	I/II	84	P II: 50 mg + BTZ ± low-dose DEX	BTZ refractory (73%) BTZ/DEX refractory (51%)	22 (73 eval)
Elotuzumab					
Lonial et al (2010)[31]	I/II	29	5–20 mg/kg + LEN	Prior BTZ (69%); prior THAL (59%); prior LEN (21%)	82
Lonial et al (2011)[32]	II	73	10 or 20 mg/kg + LEN + low-dose DEX	Prior THAL and BTZ; LEN naïve	82
Siltuximab					
Voorhees et al (2011)[33]	II	49	6 mg/kg + high-dose DEX	Prior BTZ and DEX (100%); prior IMiD (90%)	19 (47 eval)
Temsirolimus					
Ghobrial et al (2011)[34]	II	43	25 mg + BTZ	Relapsed or refractory	33
				BTZ refractory (n = 19)	11
Tanespimycin					
Richardson et al (2010)[35]	II	22	50, 175, 340 mg/m^2 + BTZ	Relapsed or refractory	9

Abbreviations: BTZ, bortezomib; DEX, dexamethasone; eval, evaluable; IMiD, immunomodulatory drug; LEN, lenalidomide; ORR, overall response rate; P II, phase II; THAL, thalidomide.

Table 2. Ongoing Phase III Trials of Emerging Novel Agents in Relapsed/Refractory Multiple Myeloma

Agent	Clinicaltrials.gov Identifier/ Trial Name	Study Design; Primary Endpoint	Patient Population	Treatment Arms	Estimated Enrollment
Pomalidomide	NCT01324947	Open label, multicenter, single arm; Response (IMWG criteria)	Relapsed or relapsed/ refractory MM	Pomalidomide	85
	NCT01311687 NIMBUS	Open label, multicenter, randomized; Time to disease progression	Relapsed or relapsed/ refractory MM	Pomalidomide + low-dose DEX *v* high-dose DEX	426
Carfilzomib	NCT01080391 ASPIRE	Multicenter, randomized; Progression-free survival	Relapsed MM	Carfilzomib + LEN + DEX *v* LEN + DEX	780
	NCT01302392 FOCUS	Open label, multicenter, randomized; Overall survival	Relapsed and refractory MM	Carfilzomib *v* best supportive care	302
Panobinostat	NCT01023308 PANORAMA-1	Multicenter, randomized, double blind, placebo controlled; Progression-free survival	Relapsed MM	Panobinostat + BTZ + DEX *v* placebo + BTZ + DEX	762
Perifosine	NCT01002248	Randomized, placebo controlled Progression-free survival	Relapsed MM	Perifosine + BTZ +DEX *v* placebo + BTZ + DEX	450
Elotuzumab	NCT01239797 ELOQUENT-2	Open label, randomized; Progression-free survival	Relapsed or refractory MM	Elotuzumab + LEN/low-dose DEX *v* LEN/low-dose DEX	640

Abbreviations: BTZ, bortezomib; DEX, dexamethasone; IMWG, International Myeloma Working Group; LEN, lenalidomide; MM, multiple myeloma; POM, pomalidomide.

Table 3. Key Features of Proteasome Inhibitors[37,42]

Characteristic	Bortezomib	Carfilzomib	MLN9708	Marizomib
Active moiety	Boronate	Epoxyketone	Boronate	β-lactone
Subunits inhibited				
Constitutive proteasome	β5	β5	β5	β5 and β2
Immunoproteasome	LMP7, β1	LMP7	NR	NR
IC_{50}, nM				
Chymotrypsin	2.4–7.9	6	3.4	3.5
Trypsin	590–4200	3600	3500	28
Caspase	24–74	2400	31	430
IC_{50} against RPMI-8226, nM	5.7	5	NR	9.1
Binding kinetics	Slowly reversible	Irreversible	Reversible	Irreversible
Half life, minutes	110	< 30	18	< 10–15
Route of administration	IV	IV	Oral	IV

Abbreviations: IC_{50}, half-maximal inhibitory concentration; IV, intravenous; LMP, low molecular mass polypeptide; NR, not reported.

currently in development, each with unique pharmacologic properties (Table 3). These agents fall into three distinct classes based on their active moiety: boronates, epoxyketones, and salinosporamides.

Carfilzomib

Carfilzomib (PR-171) is a member of the epoxyketone class and is structurally and mechanistically distinct from bortezomib,[43] but with similar activity. Both bortezomib and carfilzomib inhibit the constitutive proteasome and immunoproteasome, and carfilzomib has equivalent potency against the β5 and LMP7 subunits. However, carfilzomib is an irreversible inhibitor and appears to be more selective for the chymotrypsin-like protease, with lower affinity for the trypsin-like and caspase-like proteases of the constitutive proteasome.[37] Thus, compared with bortezomib, carfilzomib provides more sustained and selective inhibition of proteasome activity, and unlike the boronate PIs, it has minimal activity against off-target enzymes, including serine proteases. In addition to their anti-myeloma effects, the epoxyketone PIs have also been shown to inhibit bone resorption in preclinical models.[44] Carfilzomib has been shown to trigger cell cycle arrest, induce apoptosis, and activate stress response pathways in a variety of human tumor cell lines, including MM, Burkitt lymphoma, acute lymphoblastic leukemia, and B-cell non-Hodgkin lymphoma, as well as colorectal, pancreatic, and lung cancer.[43] Most importantly, carfilzomib has minimal cross-reactivity with other protease classes and has demonstrated activity against bortezomib-resistant cell lines and primary MM cells.

Clinical studies have shown that carfilzomib has durable anti-cancer activity in patients with relapsed/refractory MM, including those previously treated with bortezomib (Table 1). In a large multicenter phase II study (PX-171-004), two dosing regimens were investigated in a cohort of bortezomib-naïve patients (n = 129) and a smaller cohort (n = 36) of patients previously treated with bortezomib.[21,22] In this study, carfilzomib was administered on days 1, 2, 8, 9, 15, and 16 every 28-day cycle, and patients received either 20 mg/m^2 for cycles 1–12 or 20 mg/m^2 in cycle 1 with dose escalation to 27 mg/m^2 for cycles 2–12. Patients enrolled in this study had received between one and four prior regimens, and more than 90% had received prior therapy with an IMiD. In the cohort of 129 bortezomib-naïve patients, the overall ORR by IMWG criteria was 48%, and patients who received the 20/27-mg/m^2 regimen had a better response rate (52%) compared with the response rate for patients receiving the 20-mg/m^2 regimen (42%).[21] In the 20/27-mg/m^2 group, best response was CR in 2%, VGPR in 27%, and PR in 24%. In the 20-mg/m^2 group, which had sufficient follow-up for analysis, responses to carfilzomib were durable (median 13.1 months), and median PFS was 8 months. The most common adverse events (AEs) were fatigue and hematologic toxicity. The risk of peripheral neuropathy was low with both regimens despite the fact that approximately 50% of patients had neuropathy at study entry. Results for the group of patients previously treated with bortezomib were reported in 2010.[22] In this cohort (n = 35), which included 14 patients who were refractory to most recent treatment, carfilzomib (20 mg/m^2) yielded one CR, one VGPR, and four PRs. Although the response rate was fairly low (17%), median duration of response was 9 months and median time to progression (TTP) was 5.3 months.

An integrated safety analysis of 526 patients with relapsed/refractory MM who were treated in three phase II studies of carfilzomib (20/27 mg/m^2) was also recently reported. This analysis showed that the most common grade ≥3 AEs were thrombocytopenia (23%), anemia (22%), lymphopenia (18%), pneumonia (11%),

and neutropenia (10%).[45] Peripheral neuropathy was reported infrequently (14% overall) across all studies and was generally mild to moderate in severity. Although 72% of patients had grade ≥2 peripheral neuropathy at study entry, only 13% reported treatment-emergent symptoms during the study. Thus, the safety profile of carfilzomib is quite different from that of bortezomib, which is associated with a high risk of peripheral neuropathy. However, the risk of peripheral neuropathy associated with the recently approved subcutaneous administration of bortezomib is significantly lower than that associated with intravenous bortezomib administration.[46]

Preliminary results of another large multicenter phase II study of carfilzomib (20 mg/m^2) in relapsed/refractory MM (PX-171–003-A1) have recently been reported.[23] This study enrolled 266 patients, of whom 229 are currently evaluable for response by IMWG criteria, and 71 of these patients (31%) had unfavorable cytogenetics. The available data from this study demonstrate an objective response in 25% of evaluable patients (mostly VGPR and PR), and patients with unfavorable cytogenetics had a 28% ORR compared with 24% in patients with normal or favorable cytogenetics.

Carfilzomib has also been investigated in combination with lenalidomide and low-dose dexamethasone in patients with relapsed/refractory MM. A phase Ib study combined carfilzomib (15–27 mg/m^2, days 1, 2, 8, 9, 15, and 16) with daily lenalidomide (10–27 mg, days 1–21) plus weekly dexamethasone (40 mg) every 28-day cycle.[24] This regimen yielded an ORR of 78% (18% CR/sCR, 22% VGPR, 38% PR), and the most common grade ≥3 toxicities were hematologic (neutropenia, anemia, and thrombocytopenia).[47]

Two large, randomized, phase III trials are currently ongoing in patients with relapsed or relapsed/refractory MM (Table 2). The ASPIRE trial (N = 700) is comparing carfilzomib plus lenalidomide and dexamethasone with lenalidomide–dexamethasone alone in the relapsed setting, and the primary endpoint is PFS.[48] The FOCUS trial (N = 302) is comparing carfilzomib monotherapy with best supportive care in the relapsed/refractory setting, and the primary endpoint is OS.[49]

MLN9708

MLN9708 is a boronate PI similar to bortezomib that reversibly inhibits the constitutive proteasome, and it is the first oral PI. To date, phase I studies have investigated the safety, tolerability, and preliminary antimyeloma activity of both oral and intravenous (IV) dosing in patients with relapsed/refractory MM. Preliminary data indicate that MLN9708 has promising activity and produces durable responses in heavily pretreated patients. A phase I dose-escalation study investigated biweekly oral doses ranging from 0.24 mg/m^2 to 2.23 mg/m^2 on days 1, 4, 8, and 11 of each 21-day cycle for up to 12 cycles using a modified Fibonacci dose sequence, and concomitant corticosteroids were permitted.[50] The maximum tolerated dose (MTD) was determined to be 2.0 mg/m^2. To date, data have been reported on 56 patients: 26 participated in the dose-escalation phase and 36 were treated at the MTD in the expansion phase. The median number of prior therapies was four (range, 1–28). All patients had received an IMiD, nearly all had been previously treated with bortezomib, and approximately 7% had been treated with either carfilzomib or marizomib. Approximately 50% of patients were refractory to their most recent previous therapy, and approximately one third were refractory to bortezomib as their most recent previous therapy. Oral MLN9708 was well tolerated. The most common grade ≥3 AEs were thrombocytopenia (34%), neutropenia (14%), fatigue (9%), and rash (9%). Only 11% of patients developed peripheral neuropathy, which was grade 1 or 2 in severity. Among 46 response-evaluable patients, the ORR was 13% (one CR and five PRs), and responses were durable for up to 16 months.

A phase I dose-escalation study of once-weekly oral dosing has also been reported.[51] Twenty-eight patients were treated with oral MLN9708 at doses ranging from 0.24 mg/m^2 to 3.95 mg/m^2 on days 1, 8, and 15 of each 28-day cycle. These patients had received a median of five prior regimens (range, 2–15), and 59% were refractory to their last therapy, including bortezomib (26%) and lenalidomide or thalidomide (41%). No dose-limiting toxicity occurred at doses up to 3.95 mg/m^2, and thus the MTD has not been reached. Similar to biweekly dosing, the most common AEs were fatigue and thrombocytopenia. Among 16 response-evaluable patients, one patient treated with 2.97 mg/m^2 had a PR and remains in response after eight cycles, and five patients had SD for up to 10 months. These data suggest that once-weekly administration of this novel oral PI is well tolerated and has anti-myeloma activity in heavily pretreated relapsed/refractory MM.

Marizomib

Marizomib (NPI-0052) is a natural lactone compound derived from the marine bacterium *Salinospora tropica*. This unique class of PIs is known as the salinosporamides. Marizomib is also an irreversible PI, but unlike bortezomib and carfilzomib, it inhibits all three catalytic activities of the proteasome, namely chymotrypsin-like, trypsin-like, and caspase-like proteases. As a result, marizomib has a unique efficacy and safety profile and does not exhibit cross-resistance with other PIs. Results from two parallel phase I dose-escalation studies conducted in Australia and the United States in patients with relapsed/refractory MM were recently reported together.[52] Marizomib was given IV on days 1, 4, 8, and 11 of each 21-day cycle with or without

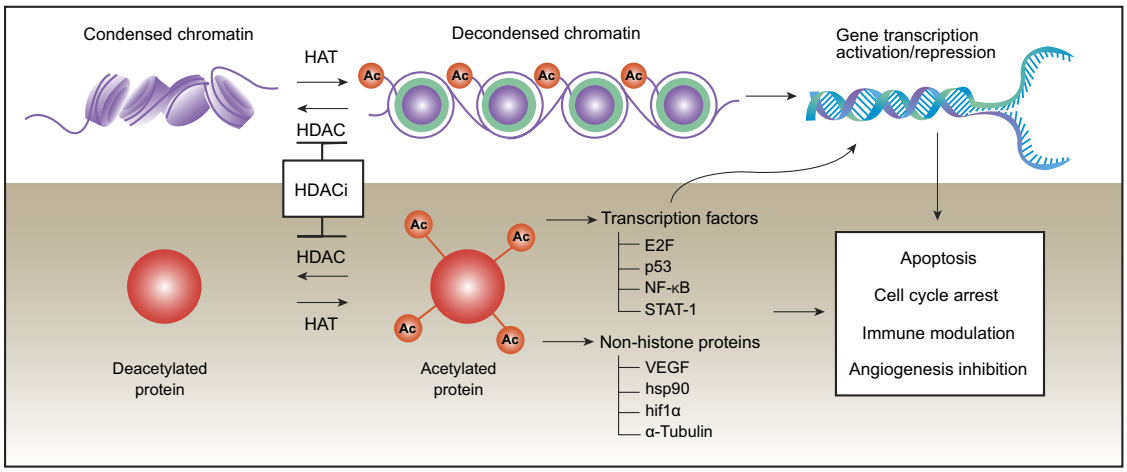

Figure 1. Effects of histone deacetylase (HDAC) inhibitors on histone protein acetylation and chromatin structure, acetylation of transcription factors resulting in changes in gene expression, and acetylation of other nonhistone proteins leading to diverse biologic effects underlying the pathogenesis and treatment of multiple myeloma.

Abbreviations: HAT, histone acetylase; HDACi, histone deacetylase inhibitor; hif1α, hypoxia-inducible factor 1 alpha; hsp90, heat shock protein 90; NF-κB, nuclear factor kappaB; VEGF, vascular endothelial growth factor. Reprinted with permission from Paik PK, Krug LM. Histone deacetylase inhibitors in malignant pleural mesothelioma: preclinical rationale and clinical trials. J Thorac Oncol. 2010;5:275–279.[54] Copyright © 2010, International Association for the Study of Lung Cancer.

dexamethasone, and response was assessed by modified European Group for Blood and Marrow Transplantation (EBMT) and Uniform Criteria. These studies have enrolled 34 patients, of whom 88% had been previously treated with bortezomib, and 71% were bortezomib-refractory. The MTD was 0.4 mg/m^2 over a 60-minute infusion or 0.5 mg/m^2 over a 120-minute infusion. Dose-limiting toxicities included transient hallucinations, cognitive changes, and loss of balance, which were reversible. The most common drug-related AEs were fatigue, nausea, vomiting, dizziness, headache, diarrhea, constipation, insomnia, anorexia, and dyspnea. There was no evidence of peripheral neuropathy or thrombocytopenia. Preliminary efficacy analysis of 15 patients treated in the active dose range (0.4 – 0.6 mg/m^2) demonstrated a PR in three patients (20%), all of whom were bortezomib-refractory. These early data suggest that marizomib has a safety profile that is not overlapping with that of other PIs and is active in bortezomib-refractory patients. A twice-weekly regimen of marizomib (0.5 mg/m^2) in combination with low-dose dexamethasone is being investigated further.

Histone Deacetylase Inhibitors

Beyond the IMiDs and PIs that have an established role in the treatment of MM, a number of other drug classes are actively being explored for their potential benefits in this setting. The HDAC inhibitors panobinostat (LBH589) and vorinostat have shown promise as an adjunct to current treatment options in MM, and panobinostat is currently being tested in a large, randomized, phase III trial.[53] Inhibition of HDAC promotes acetylation of both histone and nonhistone proteins (Figure 1). Histone acetylation affects higher-order DNA/chromatin structure, resulting in decondensation of chromatin and increasing transcription of genes that are epigenetically silenced by chromatin condensation.[55] Therefore, inhibition of HDAC can reverse epigenetic silencing of genes that regulate tumor growth and survival, such as genes that promote apoptosis and regulate the cell cycle or angiogenesis. Acetylation of nonhistone proteins also affects tumor growth and survival. For example, acetylation of transcription factors such as nuclear factor kappaB (NF-κB) and acetylation of p53 can induce cell cycle arrest and promote expression of proapoptotic proteins (eg, BAX and Bid) while downregulating Bcl-2.[56,57] These are just a few of the potential mechanisms whereby HDAC inhibitors can affect the regulation of critical pathways involved in cancer progression. Among the oral HDAC inhibitors, panobinostat and vorinostat are farthest along in clinical development for MM.

Panobinostat

Panobinostat has been investigated both as monotherapy and in combination with other established agents for the treatment of relapsed or relapsed/refractory MM (Table 1).[2] Panobinostat potently inhibits class I, II, and IV deacetylases and is often referred to as a pandeacetylase inhibitor.[58] The initial phase II study of single-agent panobinostat demonstrated modest antimyeloma activity (one PR, one minimal response) in heavily pretreated patients (N = 38) who were refractory to at least two prior lines of therapy, including bortezomib and lenalidomide or thalidomide.[59] More recently, panobinostat has been investigated in combi-

nation with lenalidomide and dexamethasone, melphalan, or bortezomib. In a small phase I study, for 12 evaluable patients with relapsed/refractory MM who were previously treated with melphalan, the combination of panobinostat plus melphalan yielded a 33% ORR.[60] The most common grade ≥3 AEs were neutropenia and thrombocytopenia.

To date, the most promising combination appears to be panobinostat plus bortezomib. The rationale for this combination is based on evidence that proteasome inhibition causes a shift in the unfolded/misfolded protein response pathway leading to increased HDAC-mediated aggresome formation and degradation of lysosomes.[61] Panobinostat inhibits activation of the aggresome pathway, resulting in accumulation of misfolded/unfolded proteins that can trigger apoptosis. Data from a phase IB study in 29 heavily pretreated patients, of whom 55% had received prior bortezomib, demonstrated a 50% ORR, including PRs in patients who were refractory to previous bortezomib therapy.[25,26] The most common grade ≥3 AEs were thrombocytopenia (n = 25), neutropenia (n = 18), and anemia (n = 6).[26] This study set the stage for a multicenter phase II study (PANORAMA-2) of panobinostat (20 mg on days 1, 3, 5, 8, 10, 12) plus bortezomib (1.3 mg/m^2 on days 1, 4, 8, 11) and low-dose dexamethasone (20 mg on days 1, 2, 4, 5, 8, 9, 11, 12) every 21-day cycle in patients with relapsed and bortezomib-refractory MM.[27] Patients received the regimen described above for the first eight cycles, and those achieving clinical benefit could continue to receive treatment on 6-week cycles until disease progression. This phase II study enrolled 55 patients who had received a median of four prior regimens (range, 2–14); the median number of prior bortezomib-containing regimens was two (range, 1–6). At the time of the analysis, 16 patients (29%) had an objective response by modified EBMT criteria (two near CRs, three VGPRs, and 11 PRs). As in the previous study, the primary grade ≥3 toxicities were hematologic (thrombocytopenia, anemia, and neutropenia) and were manageable with dose reduction or interruption. The most frequent nonhematologic toxicity was fatigue. Based on these results, the combination of panobinostat plus bortezomib and dexamethasone is currently being evaluated in a large, international, randomized, placebo-controlled trial known as PANORAMA-1 (Table 2). Patients who received previous bortezomib-based therapy are eligible; however, patients with bortezomib-refractory MM (defined as not achieving at least a minimal response or having progressed on or within 60 days of the last bortezomib-containing regimen) are excluded. Preliminary blinded safety data from the first 273 patients enrolled have been reported and suggest that the safety profile is similar to that demonstrated in the phase II study.[62] Peripheral neuropathy (all grades) was observed in 19% of patients, and 3% experienced grade 3 or 4 symptoms.

Vorinostat

Vorinostat inhibits class I and II HDACs, and has a safety profile similar to that of panobinostat. It has been investigated as monotherapy and in combination with bortezomib, lenalidomide, and dexamethasone, or pegylated liposomal doxorubicin (PLD) and bortezomib for the treatment of relapsed/refractory MM (Table 1).[2] Initial phase I data in heavily pretreated patients demonstrated an MTD of 400 mg/d on days 4–11 of each 21-day cycle in combination with bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11). Similar to panobinostat, the primary toxicities were myelosuppression and fatigue.[63] This led to a global phase IIb study (VANTAGE 095) of this combination in heavily pretreated bortezomib-refractory patients (defined as <25% response on therapy, or progression during or within 60 days of completing therapy) and patients considered to be refractory, intolerant, or ineligible for IMiD-based regimens.[28] Patients were treated with vorinostat (400 mg/d on days 1 to 14) plus IV bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11) every 21-day cycle. After 4 cycles, oral low-dose dexamethasone (20 mg on the day of and day after each dose of bortezomib) could be added to the treatment regimen if patients had suboptimal response. Patients enrolled (N = 143) had received a median of four prior regimens (range, 2–17), all were refractory to bortezomib, and 87% were refractory to at least one previous IMiD-containing regimen. Final results of this study demonstrated a median OS of 11 months and 2-year OS rate of 32%. Assessment of response by IMWG criteria showed a 17% ORR (1% CR, 4% VGPR, and 12% PR), and median duration of response was 6 months. The most common grade ≥3 AEs were thrombocytopenia (68%), anemia (38%), neutropenia (32%), diarrhea (17%), and fatigue (13%). Grade ≥3 peripheral neuropathy occurred in only 2% of patients. These results are similar to those of the PANORAMA-2 trial described above and further support the conclusion that the combination of an HDAC inhibitor with bortezomib can overcome resistance to bortezomib. These results also led to a global phase III trial of this combination.

The VANTAGE 088 trial was a randomized, placebo-controlled, phase III trial of vorinostat plus bortezomib in patients with relapsed/refractory MM. Eligible patients had received one to three prior regimens. Previous exposure to bortezomib and the presence of extracellular plasmacytoma were allowed, but patients with resistance to bortezomib were excluded. Patients were randomized to IV bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11) combined with vorinostat (400 mg/d) or placebo on days 1 to 14 of each 21-day cycle. A total of 637 patients have received study medication, with a median exposure of seven cycles, which compares favorably to reported bortezomib monotherapy studies. Interim results of the primary and secondary end-

points were recently reported.[29] Compared with patients who received bortezomib plus placebo, patients treated with vorinostat plus bortezomib had a significantly prolonged median PFS (6.8 *v* 7.6 months, respectively; hazard ratio 0.77, $P = .01$) and significantly higher ORR (56% *v* 41%, $P < .0001$). Although the survival analysis is not yet mature, the OS rate was approximately 60% in both groups. Overall, the combination of bortezomib plus vorinostat was generally well tolerated, and side effects were as expected and clinically manageable. The final results of this trial are eagerly awaited.

Signal Transduction Modulators

Another novel agent that appears promising in the treatment of relapsed/refractory MM is perifosine. Perifosine (KRX-0401) is an oral bioactive alkylphospholipid that is thought to target cell membranes and modulate multiple signaling pathways, including inhibition of Akt, activation of c-Jun NH2-terminal kinase, and upregulation of death receptor DR4/DR5 expression, which can promote apoptosis in MM cells.[64,65] Inhibition of Akt phosphorylation downregulates signal transduction via the phosphatidylinositol 3-kinase/Akt/mTOR pathway, a key regulator of cellular growth and survival. Aberrant activation of this signaling pathway may contribute to development of resistance to conventional agents used to treat MM. Preclinical studies have shown that perifosine has cytotoxic activity against MM cell lines,[64] and it enhances the cytotoxic effects of dexamethasone, doxorubicin, melphalan, and bortezomib by promoting apoptosis.[66]

Clinical studies have tested the combination of perifosine with bortezomib and dexamethasone in patients with relapsed/refractory MM (Table 1). A phase I/II study enrolled 84 heavily pretreated patients; 73% were refractory to bortezomib, and 51% were refractory to bortezomib and dexamethasone.[30] Patients received 50 mg/d or 100 mg/d perifosine plus bortezomib (1.3 mg/m^2) with addition of low-dose dexamethasone (20 mg) if progression occurred on perifosine plus bortezomib alone. This regimen was well tolerated with mainly grade 1 or 2 gastrointestinal toxicity, fatigue, and musculoskeletal pain; 50 mg was chosen as the phase II dose. The most frequent grade ≥3 toxicities were thrombocytopenia (23%), neutropenia (15%), and anemia (14%). Among 73 evaluable patients, the ORR was 22% (4% CR and 18% PR), and among 53 bortezomib-refractory patients, the ORR was 13% (2% CR and 11% PR). Median PFS was 6 months, with a median OS of 25 months (22.5 months in bortezomib-refractory patients). Based on the promising activity observed in the phase I/II study, a randomized phase III trial is underway comparing perifosine plus bortezomib and dexamethasone with placebo plus bortezomib and dexamethasone in patients with relapsed/refractory MM previously treated with bortezomib (Table 2).[67]

Monoclonal Antibodies

Several diverse monoclonal antibodies are currently in clinical development in the relapsed/refractory setting. These include elotuzumab (anti-CS1), siltuximab (anti–IL-6), and BT062 (anti-CD138). Currently, elotuzumab is farthest along in clinical development and is being investigated in a randomized phase III trial in combination with lenalidomide and dexamethasone.[68]

Elotuzumab

Elotuzumab (HuLuc63), a humanized immunoglobulin G1 monoclonal antibody, targets the cell surface adhesion molecule CS1 that is selectively expressed on the majority of MM cells along with CD138 (syndecan-1).[69,70] Preclinical studies have shown that elotuzumab can induce high rates of tumor cell lysis when CD138$^+$ MM cells are incubated with elotuzumab in the presence of autologous peripheral blood mononuclear cells containing NK cells.[56] Moreover, tumor cell lysis was enhanced in MM cells that had been pretreated with subtherapeutic doses of bortezomib, lenalidomide, or perifosine.[70,71]

These preclinical findings provided the rationale for phase I and II studies of elotuzumab in combination with lenalidomide or bortezomib (Table 1). In a phase I/II study in 29 patients (69% had received prior bortezomib, 59% thalidomide, and 21% lenalidomide), treatment with elotuzumab (5–20 mg/kg) weekly for two cycles then every other week combined with lenalidomide (25 mg, days 1–21 every 28-day cycle) yielded an ORR of 82% (18% VGPR; 64% PR).[31] Preliminary results from a phase II study of elotuzumab (10 mg/kg or 20 mg/kg) in combination with lenalidomide (25 mg) and weekly low-dose dexamethasone (40 mg) in 73 patients with relapsed/refractory MM have also been reported.[32] Patients enrolled in this study had been previously treated primarily with thalidomide and bortezomib. All patients were lenalidomide naïve. The ORR in the combined treatment groups (36 patients treated at 10 mg/kg and 37 treated at 20 mg/kg) was 82% (12% CR/sCR, 32% VGPR, and 38% PR), and patients treated with 10 mg/kg elotuzumab (recommended phase III dose) had an ORR of 92%. Most impressive is the fact that only 22% of patients progressed after a median of 11 months follow-up. The most common grade ≥3 treatment-emergent AEs were lymphopenia (16%), thrombocytopenia (16%), neutropenia (15%), and anemia (11%). Based on these encouraging results, a randomized phase III trial (ELOQUENT 2) is ongoing and will compare the efficacy and safety of lenalidomide plus low-dose dexamethasone with or without 10 mg/kg elotuzumab in patients with relapsed or refractory MM (Table 2).[68] The primary endpoint is PFS. In addition, a phase I, dose-escalation study of elotuzumab

(2.5, 5, 10, or 20 mg/kg on days 1 and 11) plus bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11) every 21-day cycle was recently reported.[72] Among 27 evaluable patients (19 treated at the highest dose of elotuzumab) there was no dose-limiting toxicity, and the ORR was 48%, including two of three patients who were refractory to bortezomib. Median TTP was 9.5 months. This combination is being explored further in an ongoing randomized phase II trial of bortezomib plus dexamethasone with or without elotuzumab (10 mg/kg) in relapsed and refractory MM.[73]

Siltuximab

Siltuximab (CNT0328) is a chimeric anti–IL-6 antibody. Preclinical studies have shown that IL-6 promotes proliferation and survival of MM cells in the context of the bone marrow microenvironment and can inhibit apoptosis in the presence of corticosteroids.[74] Therefore, siltuximab has been studied as an adjunct to dexamethasone in relapsed/refractory MM in an effort to overcome resistance to corticosteroids. The results of a phase II study of siltuximab in combination with high-dose dexamethasone were recently reported.[33] Patients in this study (N = 49) had received a median of four prior regimens (range, 2–9), including bortezomib and corticosteroids in 100% and IMiDs in 90%. Patients were treated with IV siltuximab (6 mg/kg on days 1 and 15 of each 28-day cycle) plus oral dexamethasone (40 mg on days 1–4, 9–12, and 17–20 for a maximum of four cycles, and days 1–4 for subsequent cycles). Among 47 evaluable patients, nine had a PR (19%) by IMWG criteria, and median response duration was 6 months.

BT062

BT062 is an immunoconjugate consisting of a chimeric anti-CD138 antibody (nBT062) stably linked to cytotoxic maytansinoid (DM4), an inhibitor of tubulin polymerization.[75,76] BT062 has demonstrated selective cytotoxic activity against CD138$^+$ MM cells in vitro and in vivo,[75] and these studies have shown that its antitumor activity is not affected by IL-6 and insulin-like growth factor 1 expression or cell adhesion–mediated drug resistance. Based on promising preclinical results, a phase I dose-escalation study was conducted in heavily pretreated patients with relapsed or relapsed/refractory MM.[77] Administration of BT062 every 3 weeks at doses up to 200 mg/m^2 demonstrated an acceptable toxicity profile and early signs of clinical activity. The most recent data from a multicenter phase I dose-escalation study in 32 patients with relapsed or relapsed/refractory MM who had received previous treatment with an IMiD and a PI determined the MTD to be 160 mg/m^2 every 3 weeks.[78] Mucositis was the primary dose-limiting toxicity. However, only one of 27 evaluable patients had a PR. Further study of a dose-intensified schedule (ie, more frequent dosing) is planned.

Other Agents in Development

Two additional classes of agents that appear promising for the treatment of relapsed/refractory MM are mTOR inhibitors (eg, temsirolimus and everolimus) and Hsp90 inhibitors (eg, tanespimycin). These agents are still in early clinical trials (Table 1).

In patients with relapsed/refractory disease, temsirolimus and everolimus have demonstrated modest anti-tumor activity as single agents.[79,80] However, preliminary data suggest that the combination of temsirolimus plus bortezomib may be more active. A phase I/II study determined the MTD to be 25 mg temsirolimus combined with 1.6 mg/m^2 bortezomib (both IV on a weekly schedule) in a heavily pretreated population.[34] This combination was well tolerated with predominantly hematologic toxicity. In the phase II portion of the study (n = 43), the ORR was 33% overall and 11% among 19 patients who were refractory to bortezomib.

Preclinical data suggest that the combination of tanespimycin and bortezomib may have synergistic antitumor activity due to enhanced suppression of the chymotrypsin-like activity of the 20S proteasome,[81] and this is consistent with the observation that bortezomib causes upregulation of heat shock proteins.[82,83] In relapsed/refractory MM, the combination of tanespimycin plus bortezomib was well tolerated and associated with durable responses.[35,82] In a phase I/II study in 72 patients (69% had received prior bortezomib), IV tanespimycin (340 mg/m^2) plus bortezomib (0.7–1.3 mg/m^2) on days 1, 4, 8, and 11 of each 21-day cycle produced ≥MR in 48% of patients, including 13% of bortezomib-refractory patients, and median response duration was 12 months.[84] A subsequent phase II study assessed the activity of bortezomib (1.3 mg/m^2) in combination with three doses of tanespimycin (50 mg/m^2, 175 mg/m^2, and 340 mg/m^2) in 22 heavily pretreated patients. Two patients treated with 175 mg/m^2 had a PR (9%), and one patient treated with 340 mg/m^2 had an MR.[35]

CONCLUSIONS AND FUTURE DIRECTIONS

A better understanding of the complex interplay between signaling pathways, regulation of apoptosis, and regulation of the cell cycle in MM cells, as well as the interactions between MM cells and the bone marrow microenvironment, is informing the design of novel combination regimens that strive to achieve enhanced, possibly even synergistic, anti-tumor activity (Figure 2).[82] Many of the new agents in development are proving complementary to the available agents, and rationally designed combinations are being tested in the clinic. For example, HDAC inhibitors can inhibit

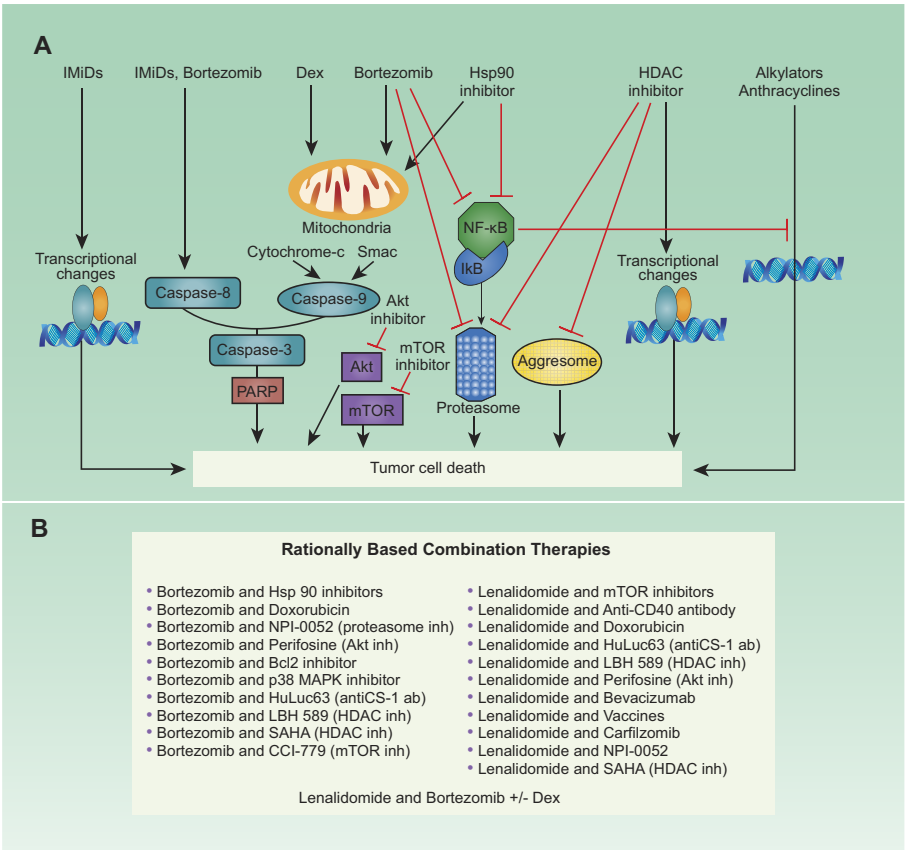

Figure 2. Rationally based combination regimens in multiple myeloma.

Abbreviations: Dex, dexamethasone; HDAC, histone deacetylase; Hsp90, heat shock protein 90; IMiDs, immunomodulatory drugs; mTOR, mammalian target of rapamycin; PARP, poly-ADP ribose polymerase. From Anderson KC. New insights into therapeutic targets in myeloma. *Hematology Am Soc Hematol Educ Program*. 2011;2011:184–190.[82] Copyright 2011 Reproduced with permission of American Society of Hematology (ASH). Permission conveyed through Copyright Clearance Center, Inc.

aggresome activity, and this complements the effects of PIs on the proteasome. It is also possible that Hsp90 inhibitors can synergize with PIs by targeting the compensatory upregulation of heat shock proteins. Likewise, IMiDs and antibodies such as siltuximab may help to overcome resistance to corticosteroids by modulating cytokine activity, and this can also play an important role in regulating the interactions between MM cells and the bone microenvironment to minimize bone complications. These are just a few examples of how these new tools are creating opportunities to target multiple pathways, overcome resistance, and improve clinical outcomes, which may be of particular importance in those patients refractory to established novel agents. Bringing these new tools together into the best treatment strategy for each individual patient is the ultimate goal.

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