The Emerging Role of Novel Therapies for the Treatment of Relapsed Myeloma

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Key Words

Bortezomib, proteasome inhibitor, thalidomide, immunomodulatory drug (IMiD), lenalidomide, multiple myeloma, relapsed

Abstract

Despite advances in the first-line treatment of multiple myeloma, almost all patients eventually relapse, become chemoresistant, and die of the disease. Improved understanding of potential myeloma targets and molecular mechanisms of drug resistance, along with the development and clinical investigation of targeted antitumor agents, have led to new strategies for the treatment of relapsed myeloma. The proteasome inhibitor bortezomib, the immunomodulatory agent thalidomide, and the thalidomide derivative lenalidomide, are all recently approved treatment options for myeloma. Single-agent bortezomib has been shown to provide significantly greater efficacy than high-dose dexamethasone, and bortezomib has also been investigated in combination with other agents commonly used to treat myeloma, including thalidomide and lenalidomide, with high overall and complete response rates. The safety profile of bortezomib has been well characterized, and side effects have been shown to be generally predictable and manageable, including in high-risk and elderly patients and those with renal impairment. Thalidomide has been extensively studied alone and in combination in patients with relapsed myeloma, demonstrating substantial efficacy, and is therefore widely used in this setting. The toxicity profile is dose- and duration-linked, with lower doses appearing to be better tol-

erated. Lenalidomide plus dexamethasone has been shown to have significantly greater activity than dexamethasone alone in the relapsed setting, with impressive duration of disease control. Other combinations are also under investigation, with promising early results. Some aspects of the toxicity profile appear significantly reduced relative to thalidomide, although myelosuppression is increased. Other novel therapies at earlier stages of development are being studied and may provide further options in the treatment of relapsed myeloma. This review focuses on results from key phase II and III trials of bortezomib, thalidomide, and lenalidomide alone or in combination, and their emerging role in improving outcomes. (*JNCCN* 2007;5:149–162)

Despite advances in the first-line treatment of multiple myeloma (MM), including the introduction and widespread adoption of stem cell transplantation in patients younger than 70 years,¹ the disease remains incurable. Almost all patients eventually experience relapse and develop drug-resistant disease. The pathophysiology of MM is intricate, involving many pathways and interactions between cytokines, adhesion molecules, mediators of angiogenesis, and signal transduction pathways. These elements taken together confer complex mechanisms of resistance while also providing multiple targets for novel therapeutic modalities. These targets are being exploited by a wide range of agents currently approved or under investigation, including bortezomib (Velcade, Millennium Pharmaceuticals, Cambridge, MA and Johnson & Johnson Pharmaceutical Research and Development, Raritan, NJ), thalidomide (Thalomid, Celgene Corporation, Summit, NJ), and the thalidomide analogue lenalidomide (Revlimid, Celgene).

Single-agent bortezomib and lenalidomide plus dexamethasone are approved treatments for patients with relapsed MM who have undergone at least one previous therapy, and thalidomide plus dexamethasone is approved for the first-line treatment of MM. These novel therapeutic agents have substantially changed the treatment

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of MM and are widely used in the relapsed setting. However, the ultimate failure of therapy and the complex pathogenesis of this disease provide a rationale for further investigation of these agents, predominantly in combination, to determine their optimal use in the management of relapsed MM.

Criteria of Response to Treatment

Readers should note that trials investigating treatment for relapsed and for relapsed, refractory MM have used different systems for classifying patients' response to therapy. The Southwest Oncology Group (SWOG) and Eastern Cooperative Oncology Group have different standard sets of response criteria for their clinical trials, and different criteria again are used by the Intergroupe Francophone du Myelome in France and Medical Research Council in the UK. The stringent European Group for Blood and Marrow Transplantation (EBMT) criteria² are currently considered a standard in clinical trials. These criteria result in reduced response rates compared with some earlier criteria.

Recognizing the need for uniform response criteria for MM, the International Myeloma Working Group recently published its International Response Criteria, updating the EBMT criteria.³ These are expected to become widely used in future clinical trials; in the meantime, comparisons of response rates and time to event data between trials should only be undertaken with due consideration for the response criteria used. The response rates reported herein are based on the EBMT criteria, unless otherwise stated.

Bortezomib

Bortezomib is the first approved agent in a new class of anticancer drugs called *proteasome inhibitors*, which block the ubiquitin–proteasome pathway. This pathway is responsible for the degradation of intracellular pro-

teins; thus, blocking the proteasome results in disruption of protein homeostasis within the cell and dysregulation of cell cycle progression. Bortezomib has been shown to have multiple effects on molecular regulatory pathways within MM cells, causing changes in stress response, increased apoptotic susceptibility, and growth arrest (Figure 1, left). Furthermore, bortezomib affects the host environment by the inhibition of cytokine circuits, inhibition of angiogenesis in the bone marrow, and inhibition of MM cell adhesion (Figure 1, right).⁴⁻⁷

MM is a particularly attractive target for proteasome inhibition because of the impact of the transcription factors nuclear factor (NF)- κ B and interleukin (IL)-6, both indirectly regulated by proteasomal degradation, on the proliferation and survival of MM cells (Figure 1). Both indirect inhibition of NF- κ B activity and activation of caspases by

Figure 1 Effect of bortezomib on the MM cell and host microenvironment. Bortezomib inhibition of NF- κ B and its effects on downstream targets and alternative pathways (Bcl-2-Bax-Bad, p53/mdm2, JNK, caspases 8 and 9, sensitization to TNF/TRAIL-mediated apoptosis, and gp130 cleavage) causes changes in the susceptibility to apoptosis and survival mediated by cell adhesion pathways ICAM-1 and VCAM-1. NF- κ B inhibition increases chemo- and radiosensitization and reverses chemoresistance. Affected cell signaling pathways include cyclins and CKIs, MAPK pathways, and cytokine circuits. Bortezomib directly and indirectly affects the host microenvironment by blocking the secretion of growth, survival, and migratory factors (IL-6, IGF-1, SDF-1 α , VEGF, bFGF, TNF- α and TGF- β), angiogenic factors (VEGF and bFGF), and cell adhesion molecules (ICAM-1 and VCAM-1). Legend:—| and $\perp$ = inhibition; $\rightarrow$ and $\uparrow$ = stimulation; $\downarrow$ = downregulation. Abbreviations: bFGF, basic fibroblast growth factor; BM, bone marrow; BMSC, bone marrow stromal cells; CKI, cyclin-dependent kinase inhibitor; ICAM, intracellular adhesion molecule; IGF, insulin-like growth factor; IL, interleukin; JNK, c-Jun-N-terminal kinase; MAPK, mitogen-activated protein kinase; MM, multiple myeloma; NF- κ B, nuclear factor- κ B; SAPK, stress-activated protein kinase; SDF, stromal-derived factor; TGF, transforming growth factor; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

bortezomib trigger interruption of IL-6 and IL-6 signaling cascades, respectively, which significantly inhibit the anti-apoptotic effects of IL-6 in MM cells.⁸ Other sequelae from the blockade of NF- κ B include downregulation of antiapoptotic proteins such as Bcl-2, upregulation of proapoptotic proteins such as Bax, and inhibition of adhesion molecules such as intracellular adhesion molecule 1 and vascular cell adhesion molecule (VCAM)-1.⁶ Furthermore, bortezomib leads to activation of both caspase 8- and 9-dependent apoptotic pathways, induction of p53 and c-Jun-N-terminal kinase in myeloma cells, and sensitization to tumor necrosis factor (TNF) and TNF-related apoptosis-inducing ligand (TRAIL)-dependent apoptosis.^{4,5,9-11}

Other important pathways in the growth regulation of myeloma cells known to be influenced by proteasome inhibition are stabilization of cyclins and cyclin-dependent kinase inhibitors and inhibition of signaling through the p44/42 mitogen-activated protein kinase pathways.^{4,9,11} Additional studies suggest that modulation of proteasome function could sensitize cells to chemotherapy and reverse chemoresistance.¹²⁻¹⁴ Supporting the possibility of chemosensitization, studies have shown that bortezomib-based regimens can result in enhanced antitumor activity in models of MM with a variety of agents, including steroids, alkylating agents, anthracyclines, and immunomodulatory analogues of thalidomide.^{4,12,14,15}

Single-Agent Bortezomib

The activity of single-agent bortezomib in patients with relapsed or relapsed, refractory MM was initially shown in 2 phase II studies, in which response rates between 27% and 38% were reported.^{16,17} Single-agent bortezomib was subsequently compared with high-dose dexamethasone in the international Assessment of Proteasome Inhibition for Extending Remissions (APEX) phase III trial of 669 patients with MM who had relapsed after 1 to 3 previous therapies. Initial analysis showed that bortezomib produced significantly greater median time to progression, response rate, and overall survival compared with dexamethasone.¹⁸ As a result, the dexamethasone arm was halted based on the recommendation of the independent data-monitoring committee, and patients on the dexamethasone arm were allowed to cross over to receive single-agent bortezomib.

In an updated analysis with extended follow-up (median 22 months), bortezomib again showed a significant survival advantage compared with dexa-

methasone (29.8 vs. 23.7 months). This 6-month benefit was observed despite more than 62% of dexamethasone-treated patients having crossed over to subsequently receive bortezomib.¹⁹ Indeed, bortezomib is the only single agent to date to show a survival benefit in this setting.

Updated efficacy data for the bortezomib arm also showed that response and complete or near complete response rates were 43% and 15%, respectively (Table 1).¹⁹ The response rate and quality of responses continually improved over the course of protocol-specified treatment, after rapid initial response. In addition, greater depth of response (100% M-protein reduction) was associated with longer duration of response. These data support extending treatment with bortezomib beyond initial response to achieve optimal benefit.¹⁹

Results from a number of subgroup analyses of the APEX study have been reported. An analysis in patients who had received 1 or more previous lines of therapy showed that bortezomib retained greater efficacy than dexamethasone in both groups of patients. The data also indicated that bortezomib has greater activity when used earlier in the relapsed setting.³⁹ Furthermore, in a subgroup analysis to evaluate the impact of exposure to prior therapies on treatment outcome, bortezomib was consistently superior to dexamethasone regardless of types of prior therapies, including prior stem cell transplantation.⁴⁰ A subgroup analysis has also assessed efficacy among elderly patients (aged ≥ 65 years) and patients with other high-risk factors (including elevated β_2 -microglobulin and insensitivity to prior therapy). Bortezomib retained its statistically superior efficacy compared with dexamethasone, in terms of longer median time to progression and higher response rate, in all patient subgroups studied.⁴¹

Finally, an analysis is being undertaken measuring the efficacy of bortezomib in patients with renal dysfunction in the APEX study. Renal dysfunction or failure is seen in up to 30% of MM patients at diagnosis.^{42,43} Studies in renally impaired patients, including those on dialysis, have shown that bortezomib-based therapy is feasible and shows encouraging activity, with similar toxicity to that seen in non-renally impaired patients, and rapid normalization of renal function in some.⁴⁴⁻⁴⁸

The most common toxicities seen with bortezomib treatment in the APEX trial included gastrointestinal events, fatigue, and peripheral neuropathy, with the

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Table 1 Selected Clinical Trials of Bortezomib, Thalidomide, and Lenalidomide, Alone and In Combination, In the Treatment of Relapsed Multiple Myeloma

Citation	Study	Regimen	Patients Enrolled (N)	CR + PR	Response Rate (%)* CR/nCR	Comparative Major Toxicities
Phase 3 studies of bortezomib, and lenalidomide + dexamethasone (no phase III studies of thalidomide in the relapsed setting)						
Richardson et al. ^{18,19}	Single-agent bortezomib vs. high-dose dexamethasone	Bortezomib 1.3 mg/m ² days 1, 4, 8, and 11 for up to 8 3-week cycles followed by treatment on days 1, 8, 15, and 22 for up to 3 5-week cycles	333	43	15	Grade 3/4: thrombocytopenia 26/4%, neutropenia 12/2%; anemia 9/1%, peripheral neuropathy 7/1%
		Dexamethasone 40 mg on days 1–4, 9–12, and 17–20 for 4 5-week cycles, followed by treatment on days 1–4 for 5 4-week cycles	336	18	2	Grade 3/4: anemia 10/1%, thrombocytopenia 5/1%
Weber et al. ^{20†}	Lenalidomide + dexamethasone vs. dexamethasone	Lenalidomide 25 mg on days 1–21 Dexamethasone 40 mg on days 1–4, 9–12, 17–20 (days 1–4 only from cycle 5) 4-week cycles	171	59	13	Grade 3/4: neutropenia 36%, thrombocytopenia 12%, peripheral neuropathy 12%, anemia 12%, pneumonia >10% DVT/PE 18%
		Dexamethasone as above	170	21	1	Grade 3/4: thrombocytopenia 6%, neutropenia 5%, anemia 5%, fatigue 5%
Dimopoulos et al. ^{21‡}	Lenalidomide + dexamethasone vs dexamethasone	Lenalidomide 25 mg on days 1–21 Dexamethasone 40 mg on days 1–4, 9–12, 17–20 (days 1–4 only from cycle 5) 4-week cycles	176	59	15	Grade 3/4: neutropenia 27%, thrombocytopenia 10%, anemia 8%, DVT 5%, PE 4%
		Dexamethasone as above	175	24	3	Grade 3/4: thrombocytopenia 6%, DVT 5%
Selected phase I and II studies of bortezomib, thalidomide, and lenalidomide						
Hollmig et al. ²²	Bortezomib + doxorubicin + thalidomide + dexamethasone (phase 1)	Bortezomib 0.8–1.3 mg/m ² on days 1, 4, 8, 11 Doxorubicin 2.5–5 mg/m ² on days 1–4 and 9–12 Thalidomide 50–100 mg/day on days 1–12 Dexamethasone [√] 20–40 mg on days 1–4 and 9–12	20	63 [§]	25 [§]	Grade 3 thrombocytopenia in 40%

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Table 1 Continued

Leoni et al. ^{23**}	Bortezomib + liposomal doxorubicin (Myocet) + thalidomide + dexamethasone (phase 2)	Bortezomib 1.0 mg/m ² on days 1, 4, 8, and 11 Myocet 50 mg/m ² on day 4 Thalidomide 100 mg/day Dexamethasone 24 mg on day of/day after bortezomib Up to 4 4-week cycles	27	74	33	Grade 4 hematologic toxicity in 18%
Zangari et al. ^{24†}	Bortezomib + thalidomide ± dexamethasone (phase 2)	Bortezomib 1.0–1.3 mg/m ² on days 1, 4, 8, 11 Thalidomide 50–20 mg/day from cycle 2 Dexamethasone 20 mg on day of/day after bortezomib for suboptimal response after 3 cycles Up to 8 3-week cycles	85	55 [§]	16 [§]	Most common grade 3/4: thrombocytopenia and neutropenia
Orlowski et al. ²⁵	Bortezomib + pegylated liposomal doxorubicin (phase 1)	Bortezomib 0.9–1.5 mg/m ² on days 1, 4, 8, and 11 Liposomal doxorubicin 30 mg/m ² on day 4 Up to 11 3-week cycles	24	73	36	Grade 3/4 in all 42 patients with hematologic malignancies: thrombocytopenia 43%, lymphopenia 40%, neutropenia 17%, fatigue 14%, pneumonia 14%, peripheral neuropathy 12%, febrile neutropenia 10%, diarrhea 10%
Richardson et al. ^{26†}	Bortezomib + lenalidomide ± dexamethasone (phase 1)	Bortezomib 1.0–1.3 mg/m ² on days 1, 4, 8, 11 Lenalidomide 5–20 mg on days 1–14 Dexamethasone 20 mg on day of/day after bortezomib for PD Up to 8 3-week cycles	24	52	10	Grade 3/4: thrombocytopenia, neutropenia, and hyponatremia. No significant fatigue or peripheral neuropathy
Padmanabhan et al. ^{27†}	Bortezomib + liposomal doxorubicin + thalidomide (phase 2)	Bortezomib 1.3 mg/m ² on days 1, 4, 15, and 18 Liposomal doxorubicin 20 mg/m ² on days 1 and 15 Thalidomide 200 mg/day Up to 6 4-week cycles	23	65**	23**	No grade 3/4 non-hematologic toxicities
Palumbo et al. ^{28†}	Bortezomib + melphalan + prednisone + thalidomide (phase 2)	Bortezomib 1–1.6 mg/m ² on days 1, 4, 15, 22 Melphalan 6 mg/m ² and prednisone 60 mg/m ² on days 1–5 Thalidomide 50 mg continuously 65-week cycles	30	67	17	Grade 3/4: thrombocytopenia, neutropenia, fatigue, anemia, vasculitis, infections, and sensory neuropathy

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Table 1 Continued

Terpos et al. ^{29†}	Bortezomib + melphalan + dexamethasone + thalidomide (phase 2)	Bortezomib 1.0 mg/m ² on days 1, 4, 8, and 11 Melphalan 0.15 mg/kg days 1–4 Dexamethasone 12 mg/m ² days 1–4 and 17–20 Thalidomide 100 mg/day Up to 8 4-week cycles	44	66	37	Grade 3/4: thrombocytopenia 20%, neutropenia 8%, anemia 7%, and peripheral neuropathy 6%
Barlogie et al. ³⁰	Thalidomide (phase 2)	Thalidomide 200–800 mg/day	169	30 [§]	14 [§]	Grade 3/4: CNS 25%, gastrointestinal 16%, peripheral neuropathy 9%
Palumbo et al. ³¹	Thalidomide + dexamethasone (at first relapse) (phase II)	Thalidomide 100 mg/day continuously Dexamethasone 40 mg on days 1–4 of each month	62	56 [§]	46 [§]	Grade 3/4: tingling and numbness 19%, constipation 18%, sedation 13%
	Thalidomide + dexamethasone (at second relapse and beyond)		58			
Dimopoulos et al. ³²	Thalidomide + dexamethasone + pulsed cyclophosphamide (phase II)	Thalidomide 400 mg/day on days 1–5 and 14–18 Dexamethasone 20 mg/day on days 1–5 and 14–18 Cyclophosphamide 150 mg/m ² every 12 hours on days 1–5 3 4-week cycles	53	60 [§]	5 [§]	Grade 3/4: neutropenia 18/8%, thrombocytopenia 0/2%
Offidani et al. ³³	Thalidomide + liposomal doxorubicin + dexamethasone (phase 2)	Thalidomide 100 mg/day Liposomal doxorubicin 40 mg/m ² on day 1 Dexamethasone 40 mg on days 1–4 and 9–12 4-week cycles	50	76	32	Grade 3/4: neutropenia 16%, severe infection 16%, plus venous thromboembolic disease 12%
Hussein et al. ³⁴	Thalidomide + liposomal doxorubicin + vincristine + dexamethasone (phase 2)	Thalidomide 50–400 mg/day Liposomal doxorubicin 40 mg/m ² on day 1 Vincristine 2 mg on day 1 Dexamethasone 40 mg on days 1–4 > 6 4-week cycles	49	76	20	Grade 3/4: neuropathy 22%, neutropenia 14%, pneumonia 12%, palmar plantar erythrodysesthesia 8%, fatigue 6%, thrombocytopenia 5% (includes 53 patients with newly diagnosed disease)
Palumbo et al. ³⁵	Thalidomide + melphalan + prednisone (phase 2)	Thalidomide 50–100 mg/day continuously Prednisone 50 mg/day every other day Intravenous melphalan 20 mg/m ² every fourth month	24	42	13	Grade 3/4: constipation, tingling, and sedation
Richardson et al. ^{36¶}	Lenalidomide (phase 2)	Lenalidomide 30 mg on days 1–21 4-week cycles	222	25		Grade 3/4: upper respiratory tract infection, neutropenia, thrombocytopenia

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Table 1 Continued

Gerecke et al. ^{37†}	Lenalidomide + doxorubicin + dexamethasone (phase 1)	Lenalidomide 10/15 mg on days 1–21 Doxorubicin 4/6/9 mg/m ² on days 1–4 Dexamethasone 40 mg on days 1–4 and 17–20 3–6 4-week cycles	6	All patients responded	Well tolerated at first 2 dose levels
Baz et al. ³⁸	Lenalidomide + liposomal doxorubicin + vincristine + dexamethasone (phase 2)	Lenalidomide ≤ 10 mg on days 1–21 Liposomal doxorubicin 40 mg/m ² on day 1 Vincristine 2 mg on day 1 Dexamethasone 40 mg on days 1–4 4-week cycles	62	75** 29**	Grade 3/4: neutropenia 32%, thrombocytopenia 13%, infectious 13%, DVT/PE 9%

*EBMT criteria unless otherwise stated.

†Data presented at the 2006 Annual Meeting of the American Society of Clinical Oncology.

‡Data presented at the 2006 meeting of the European Hematology Association.

§Data presented at the 2004 Annual Meeting of the American Society of Hematology.

¶M-protein reduction.

‡Data presented at the 2005 Annual Meeting of the American Society of Hematology.

**SWOG criteria.

Abbreviations: CNS, central nervous system; CR, complete response; DVT, deep vein thrombosis; nCR, near complete response; PD, progressive disease; PE, pulmonary embolism; PR, partial response.

most common grade 3 or 4 bortezomib-associated toxicities being thrombocytopenia, neutropenia, anemia, and peripheral neuropathy.¹⁸ Grade 3 or 4 adverse events were more common with bortezomib than with high-dose dexamethasone; however, a substantial proportion of these events in the bortezomib arm were thrombocytopenia or neutropenia, which have been shown to be transient and cyclical.^{49,50} For example, in patients with thrombocytopenia, platelet counts decrease during each cycle of bortezomib dosing and then recover predictably during the rest period, with no evidence of cumulative toxicity.⁴⁹ Notably, despite a higher incidence of grade 3 or 4 thrombocytopenia in the bortezomib arm compared with the dexamethasone arm, the incidence of significant bleeding events was similar between arms.⁴⁹ Bortezomib-associated peripheral neuropathy has been shown to be reversible in most patients.^{51,52} In the APEX study, 27% of patients developed grade 2 or higher peripheral neuropathy. Of these patients, the neuropathy resolved or improved in approximately two-thirds: 55% experienced complete return to baseline and 9% improved by at least 1 grade.⁵²

Bortezomib-Based Combinations

Bortezomib has been extensively investigated in combination with other agents commonly used to treat MM, including thalidomide and lenalidomide (Table

1). Ongoing phase III studies, from which results have yet to be reported, are investigating the combination of bortezomib plus thalidomide and dexamethasone (VTD regimen) versus thalidomide and dexamethasone or VTD plus doxorubicin (VATD regimen). Both the VTD and VATD regimens have been shown to be active in phase II studies in patients with relapsed or relapsed, refractory MM.^{22–24} A response rate (M-protein reduction) of 55%, including 16% complete or near complete responses, was reported in 1 study of VTD, along with median event-free and overall survival times of 9 and 22 months, respectively.²⁴ VATD has been shown to produce a 63% response rate, with 25% complete or near complete responses (M-protein reduction),²² and recently reported data show that the addition of liposomal doxorubicin to the VTD regimen can increase the response rate to 74%, with 33% complete or near complete responses.²³

Other combinations that have produced high response rates (up to 73%)²⁵ and complete or near complete response rates (up to 36%)²⁵ in the relapsed setting include bortezomib plus liposomal doxorubicin alone³⁷ or with thalidomide,²⁷ lenalidomide,²⁶ and melphalan plus thalidomide, with or without steroids.^{28,29} The safety profile in these combination studies has been as expected, with no additive toxicities reported, and, in fact, better tolerability described. Bortezomib can thus be combined safely and effectively with a

broad range of both commonly used and novel MM agents.

Thalidomide

Multiple studies have shown that thalidomide has various effects on myeloma cell growth and the host microenvironment.⁵³ Given its broad spectrum of therapeutic activity, thalidomide may have several possible mechanisms of action in MM cells (Figure 2).⁵⁴ First, it may inhibit myeloma or bone marrow stromal cell growth and survival while concurrently activating pro-apoptotic pathways.⁵⁵ Second, thalidomide may inhibit vascular endothelial growth factor and basic fibroblast growth factor activity and angiogenesis⁵⁶ and modulate adhesion, thereby affecting tumor cell growth, survival, and drug resistance.⁵⁷ Third, thalidomide may alter the secretion and bioactivity of cytokines released into the bone marrow environment.⁵⁵ Finally, its activity may in part be exerted via the immunomodulatory properties of the compound.⁵⁸

Thalidomide as a Single-Agent and in Combination

No phase III studies have been reported on thalidomide in the relapsed setting, although a number are in progress. However, it has been extensively used either alone or in combination regimens in this setting (Table 1). Single-agent thalidomide has been shown to be effective in approximately one third of patients with relapsed or refractory MM in a number of phase II studies,^{30,59-62} and a recent systematic review of published clinical trials found the mean complete and partial response rate (>50% reduction in M-protein) to be 29%, with a median overall survival of 14 months.⁶³ Most studies of thalidomide monotherapy have used a single daily dose administered in the evening to minimize the effect of sedation, as opposed to multiple divided dosing. One trial directly compared single- to multiple-dose thalidomide; patients receiving divided daily doses showed an improved response rate (M-protein reduction) (50%) compared with those who received a single daily

dose (29%).⁶⁴ Further studies to confirm this observation therefore seem to be warranted.

The toxicity profile of thalidomide appears both dose- and duration-linked. Drug-related adverse events associated with thalidomide treatment in heavily pretreated patients with refractory disease include neurologic (drowsiness, numbness, dizziness, confusion, tremor, lack of coordination, and tingling) gastrointestinal (constipation, stomatitis, nausea, and vomiting), and constitutional (weight loss, weakness, and fever) effects.^{65,66} Thromboembolic events reported during thalidomide therapy include deep vein thrombosis, pulmonary embolus, and clotting of central venous catheters.⁶⁶ The risk of these events with thalidomide therapy may be attributed to the finding that thalidomide significantly increases thrombin generation in patients with MM, as a measure of hypercoagulability.⁶⁷

Peripheral neuropathy has been reported to affect between 1% and 50% of patients in clinical trials.⁶⁶

Figure 2 Effect of thalidomide (Thal) and immunomodulatory drugs (IMiDs) on the myeloma cell and its bone marrow microenvironment. Thalidomide and IMiDs affect multiple cellular pathways, causing MM cell apoptosis and growth arrest. These compounds directly and indirectly affect the host microenvironment by blocking the secretion of growth, survival, and migratory factors (IL-6, IGF-1, SDF-1 α , VEGF, bFGF, TNF- α and TGF- β), angiogenic factors (VEGF and bFGF), and cell adhesion molecules (ICAM-1 and VCAM-1). Thalidomide and IMiDs expand natural killer cell and T-cell numbers and enhance myeloma cell susceptibility to ADCC in vivo. Legend: $\perp$ and $\downarrow$ = inhibition; $\rightarrow$ and $\uparrow$ = stimulation; $\downarrow$ = downregulation. Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; bFGF, basic fibroblast growth factor; BM, bone marrow; BMSC, bone marrow stromal cells; ICAM, intracellular adhesion molecule; IGF, insulin-like growth factor; IFN, interferon; IL, interleukin; MM, multiple myeloma; NF- κ B, nuclear factor κ B; SDF, stromal-derived factor; TGF, transforming growth factor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor. Modified from Richardson et al.,⁵⁴ with permission.

Symptoms may improve when thalidomide is discontinued; however, recovery may not be total and symptoms may also progress after discontinuation of therapy.⁶⁶ In one retrospective analysis of a phase II study, researchers found that 56% of patients developed symptoms of peripheral neuropathy and suggested that the incidence and severity of peripheral neuropathy are likely related to dose and duration of therapy.⁶⁸ In another study of thalidomide in patients with relapsed or refractory disease, 41% of patients and 81% of responding patients were seen to develop peripheral neuropathy, with the actuarial incidence among patients remaining on therapy increasing from 38% at 6 months to 73% at 12 months; 15% of patients discontinued thalidomide because of this toxicity.⁶⁹ Based on these results, the researchers recommended that thalidomide therapy should be limited to less than 6 months to minimize the risk of neurotoxicity.⁶⁹

Because of the dose-linked toxicity profile of thalidomide, lower doses than the median of 300 to 400 mg used in most studies have been explored. A recent prospective study in 400 patients with relapsed or refractory MM has shown that a 100 mg daily dose of thalidomide is comparable in terms of overall survival to a dose of 400 mg daily and is better tolerated.⁷⁰

The clinical benefit of thalidomide increases when it is combined with other agents, although the elevated risk of deep vein thrombosis is an important safety consideration.^{71,72} The risk increases substantially when thalidomide is combined with corticosteroid therapy^{73,74} or other therapeutic agents, such as anthracyclines.⁷⁵ Prophylaxis with warfarin or low molecular weight heparin (LMWH) should be used to manage this risk.^{72,76} Although the use of low-dose aspirin may help reduce the incidence,⁷⁵ researchers have suggested that aspirin should only be used in patients unable or unwilling to take warfarin or LMWH.⁷⁶

Thalidomide in combination with dexamethasone therapy is a commonly-used first-line regimen for MM in the United States and has also shown efficacy in relapsed disease in a number of phase II studies.^{31,77–80} A recent retrospective analysis of studies of patients with relapsed or refractory MM reports that thalidomide plus dexamethasone may be superior to thalidomide alone in this group of patients, with response rates (M-protein reduction > 50%) of 51% and 29%, respectively.⁸¹ The addition of cyclophosphamide to thalidomide and dexamethasone (CTD) appears to

further increase activity in the relapsed or refractory setting, with response rates (using various criteria) of up to 83% and complete response rates of up to 17% reported.^{32,82–84}

The combination of thalidomide with liposomal doxorubicin and high-dose dexamethasone has also been investigated in a phase II study.³³ The overall response rate was 76%, and 32% of patients experienced a complete or near complete response. Median progression-free and event-free survival times were 22 and 17 months, respectively.³³ This triplet regimen was compared with thalidomide plus dexamethasone in a case-matched study in patients with advanced MM, and resulted in a higher response rate (76% vs. 60%), and rate of complete or near complete responses (30% vs. 11%).⁸⁵ Median progression-free survival was also significantly longer with the triplet combination (22 vs. 12 months). However, the incidence of vascular events was also greater with the triplet regimen (13% vs. 6%).⁸⁵

Thalidomide has also been combined with liposomal doxorubicin, vincristine, and dexamethasone (DvD-T). An overall response rate of 76% was seen, but toxicities included 25% grade 3 or 4 thromboembolic events and 22% grade 3 or 4 peripheral neuropathy.³⁴ Finally, a small study investigating the combination of thalidomide, melphalan, and prednisone in patients with refractory and relapsed myeloma showed a response rate of 42%, including 13% near complete responses, with acceptable levels of toxicity.³⁵

Lenalidomide

Thalidomide has shown great promise in the treatment of MM; however, its toxicity profile has spurred the development of thalidomide-derived analogues, also known as immunomodulatory drugs (IMiDs), with the potential of improved potency and reduced toxicity. Like thalidomide, the other IMiDs inhibit angiogenesis, induce both apoptosis and growth arrest in resistant myeloma cells, and inhibit myeloma cell adhesion to bone marrow stromal cells (Figure 2).³³ Furthermore, this inhibition of cell adhesion leads to a blockade of myeloma cell growth, survival, and migratory factor secretion. These compounds expand natural killer cell and T-cell numbers and function against human myeloma cells and enhance their susceptibility to antibody-dependent cell-mediated

cytotoxicity *in vivo*.^{53,55,86–89} Lenalidomide is the most advanced IMiD in terms of clinical development, and has been investigated in relapsed and first-line settings.

Lenalidomide as a Single Agent and in Combination

As with thalidomide, lenalidomide as a single agent is active in the relapsed setting, with significant responses seen in approximately one fourth of patients.^{36,90,91} However, again as seen with thalidomide, activity is greatly increased in combination with dexamethasone (Table 1). The combination regimen was compared with dexamethasone alone in 2 phase III trials in North America (MM-009)²⁰ and Europe (MM-010).²¹ In the North American study, a response rate of 59% was seen with lenalidomide plus dexamethasone, including 13% complete responses. This was significantly greater than the 21% response rate and 1% complete response rate seen with dexamethasone alone in this study.²⁰ The combination regimen also resulted in a significantly longer median time to progression of 11.1 months compared with 4.7 months with dexamethasone, and an extended median survival of 29.6 versus 20.2 months with dexamethasone.²⁰

A response rate of 59% was also seen with lenalidomide plus dexamethasone in the European phase III study, compared with 24% with dexamethasone. Complete response rates were 15% and 3%, respectively.²¹ Time-to-events data were also similar to those seen in the North American study; median time to progression was 11.3 months with the combination compared with 4.7 months with dexamethasone. After 27.9 months of follow up, median survival had not been reached in patients receiving lenalidomide plus dexamethasone, compared with 20.6 months in those receiving dexamethasone.²¹

A pooled analysis of these 2 studies examined the efficacy of lenalidomide plus dexamethasone in patients who had received 1 or more prior line of therapy.⁹² The results showed that the combination retained its greater efficacy in response rate, time to progression, and overall survival compared with dexamethasone alone in each subgroup of patients. In addition, lenalidomide plus dexamethasone appeared to be more active in patients with only 1 previous line of therapy than in those with more than 1 previous line.⁹² This supports its use at first relapse as opposed to later as salvage therapy.

Another pooled analysis from the same 2 studies examined the impact of prior thalidomide on outcomes.⁹³ Although lenalidomide plus dexamethasone

retained its superior efficacy compared with dexamethasone alone in both patients who had and those who had not received prior thalidomide,⁹³ data indicated that activity of the combination was reduced in patients who had received prior thalidomide versus those who had not, in terms of response rate (53% vs. 63%), complete response rate (8% vs. 18%), and median time to progression (8.5 vs. 14.2 months).⁹³ These findings suggest that for optimal efficacy, careful consideration of the sequencing of thalidomide versus lenalidomide is required, and in selected patients perhaps lenalidomide plus dexamethasone should be administered before a thalidomide-containing regimen.

Lenalidomide is also being investigated in combination with doxorubicin and dexamethasone,³⁷ as well as with liposomal doxorubicin, dexamethasone, and vincristine (DvD-R) in the relapsed setting.³⁸ Results have shown the DvD-R regimen to produce a 75% response rate (SWOG criteria), with 29% complete or near complete responses and a median progression-free survival of 12 months.³⁸

Compared with thalidomide, some aspects of the toxicity profile of lenalidomide appear reduced. Lenalidomide appears to produce a lower incidence of the characteristic dose-limiting toxicities of thalidomide such as somnolence, gastrointestinal side effects, and neuropathy. The most common grade 3 or higher toxicities are neutropenia and thrombocytopenia, which are manageable via dose reduction.^{36,91} However, as seen with thalidomide, lenalidomide in combination with dexamethasone is associated with an elevated risk of thromboembolic events, particularly in patients receiving concomitant erythropoietin.^{20,21,72,94,95} As with thalidomide, antithrombotic prophylaxis is necessary to manage this risk.^{72,94–96} Moreover, higher rates of thromboses are seen with lenalidomide plus dexamethasone in patients who have been previously exposed to thalidomide,⁹³ suggesting that this may be an important clinical consideration in deciding on sequencing therapies for a patient with relapsed MM.

Other Novel Therapies

A number of other novel therapies have shown anti-myeloma activity, either alone or in combination, in both pre-clinical or clinical studies. These include arsenic trioxide,^{97–103} 2-methoxyestradiol,^{104–106} TRAIL/Apo 2 ligand,¹⁰ cyclic depsipeptides,¹⁰⁷ IL-1 receptor antagonists,¹⁰⁸ Bcl-2 antisense¹⁰⁹ and inhibitors of heat

shock proteins,¹¹⁰ farnesyl transferase,¹¹¹ p38 mitogen-activated pathway kinase,¹¹² and histone deacetylase,^{113,114} as well as monoclonal antibodies. Arsenic trioxide is in relatively advanced stages of development, and researchers have evaluated combinations of arsenic trioxide plus ascorbic acid and melphalan or bortezomib in phase I and II studies.^{97,103} Indeed, other combination regimens incorporating other novel targeted agents with bortezomib, thalidomide, lenalidomide, or other commonly used agents represent a promising future direction for treating relapsed myeloma. Further investigation is needed to evaluate the efficacy and safety of these agents and regimens and the optimal combinations. The outlook for further improvements in response and chemical benefit is encouraging.

Conclusions

Novel therapeutic approaches involving bortezomib, thalidomide, and lenalidomide have shown substantial efficacy with manageable toxicities in a large number of clinical trials in relapsed MM, and their introduction and approval has significantly advanced the management of MM over the past decade. Their use is widening clinically, both alone and in combination regimens. Exploiting our increased understanding of the potential targets for MM therapy and their unique interplay will lead to further advances. The activity demonstrated in patients with disease previously refractory to conventional therapies is especially encouraging and has led to prolonged survival. Ongoing trials currently focus on combining these and other novel therapies with conventional antitumor agents and corticosteroids to identify regimens with the greatest efficacy and most manageable toxicity, with the goal of continued improvements in patient outcome.

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