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The use of novel agents in the treatment of relapsed and refractory multiple myeloma

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Abstract

Although outcomes for patients with multiple myeloma (MM) have improved over the past decade, the disease remains incurable and even patients who respond well to induction therapy ultimately relapse and require additional treatment. Conventional chemotherapy and high-dose therapy with stem cell transplantation (SCT) have historically been utilized in the management of relapsed MM, but in recent years the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, as well as the proteasome inhibitor bortezomib, have assumed a primary role in this setting. This review focuses on the role of thalidomide, lenalidomide and bortezomib in relapsed and refractory MM, with additional discussion dedicated to emerging drugs in relapsed MM that may prove beneficial to patients with this disease.

Keywords

multiple myeloma; chemotherapy; lenalidomide; thalidomide; bortezomib

Introduction

Although patients with multiple myeloma (MM) often respond to initial therapy, the disease ultimately recurs and over the course of time becomes refractory to further treatment. Historically, conventional or high-dose therapy has been used in relapsed MM. Conventional chemotherapeutic regimens used in this context have included high-dose dexamethasone;[1,2] vincristine, doxorubicin and dexamethasone;[3–7] vincristine, melphalan, cyclophosphamide, prednisone/vincristine, carmustine, doxorubicin and prednisone;[8] and doxorubicin, vincristine, dexamethasone, etoposide and cyclophosphamide.[9] The use of high-dose melphalan in relapsed MM, meanwhile, was introduced over 20 years ago by Barlogie *et al*.[10,11], who showed that myeloablative doses of melphalan with stem cell

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Conflict of interest

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support could overcome resistance to conventional-dose chemotherapy in this group of patients.

The emergence of the immunomodulatory drugs thalidomide and lenalidomide, as well as the proteasome inhibitor bortezomib has changed the therapeutic landscape for relapsed MM. The ability of these agents to overcome drug resistance was shown in preclinical models and confirmed in the context of clinical trials, leading to FDA-approval of thalidomide, lenalidomide and bortezomib in the treatment of relapsed MM. This review focuses on the role of these agents in relapsed MM and also discusses emerging drugs that have yielded promising results in early-phase clinical trials involving patients with relapsed MM.

At the onset of this discussion, it is emphasized that definitions of relapsed and refractory MM are understood in the broader context of disease progression. Relapse from a complete response (CR) is defined as reappearance of the serum or urinary paraprotein, ≥5% bone marrow plasma cells, new lytic bone lesions/soft-tissue plasmacytomas, an increase in the size of residual bone lesions and/or development of hypercalcemia (corrected serum calcium>11.5 mg per 100 ml) not attributable to another cause.[12] Criteria for progressive disease when a CR has not been achieved include new or expanding bone lesions, hypercalcemia and a >25% increase in either serum monoclonal paraprotein concentration, 24 h urinary light-chain excretion, or plasma cells within a bone marrow. Relapsed MM refers to a scenario wherein a patient treated to the point of maximal response experiences progressive disease, whereas refractory MM refers to one in which a patient is either unresponsive to current therapy or progresses within 60 days of last treatment. Meanwhile, relapsed and refractory MM describes an individual who previously achieved at least a minimal response (MR), experiences progressive disease, receives salvage therapy and is either unresponsive to salvage therapy or progresses within 60 days of last treatment.

Thalidomide

The antiangiogenic properties of thalidomide[13] initially led to the consideration of its use in MM based on the premise that myeloma is associated with both elevated levels of circulating angiogenic cytokines such as vascular endothelial growth factor and increased bone marrow vascularization.[14,15] A more detailed understanding of the relationship between MM cells and the bone marrow microenvironment has highlighted other more important biological properties of thalidomide that contribute to its anti-MM activity.[16] In addition to its angiogenic activity, thalidomide enhances T-cell- and NK-cell-mediated immunological responses, induces caspase-8 mediated apoptosis, downregulates IL-6 production within the bone marrow microenvironment and sensitizes MM cells to other agents used in treatment of the disease[17–19] Selected clinical trials involving thalidomide in relapsed MM are summarized in Table 1.

Single-agent thalidomide

The clinical activity of thalidomide was highlighted by a phase II trial in which 84 individuals with relapsed and refractory MM received single-agent thalidomide at doses ranging from 200 to 800 mg/day.[20] In this heavily pre-treated group, the overall response (OR) rate was 32%. The 2-year event-free survival (EFS) and OS were 20 and 48%, respectively,[21] with 10-year EFS and OS rates of 6 and 10%.[22] Lambda light-chain isotype and the presence of chromosomal abnormalities were identified through multivariate analysis of pre-treatment characteristics as predictors of less favorable outcome in this trial.[22] The results of this study have been confirmed by several other clinical trials of single-agent thalidomide in MM wherein response rates ranged from 14 to 48%.[23–30] Based on a systemic review of phase II trials involving 1674 patients with relapsed or refractory

MM, the OR rate associated with single-agent thalidomide therapy is 29% and the median OS 14 months.[31] Grade 3/4 somnolence and constipation occurred in 11 of 16% of patients in these trials, respectively, with peripheral neuropathy (PN) both cumulative and dose-limiting.

Because these trials used different doses of thalidomide, a uniform treatment dose has not been established. However, insight regarding the issue of dosage can be derived from a study by Yakoub-Agha *et al*. in which patients were randomized to 100 or 400 mg/day thalidomide, with the addition of dexamethasone after 3 months if no response was achieved with single-agent thalidomide.[32] Although patients who received 100 mg/day more frequently required dexamethasone, the 1-year survival rate associated with the two treatment arms was equivalent. Furthermore, individuals who received 100 mg/day tolerated therapy better, with fewer instances of high-grade treatment-related side effects. The rate of deep venous thrombosis (DVT) was similar in the two treatment arms. On the basis of these results, lower doses of thalidomide are preferred, particularly for individuals who may poorly tolerate thalidomide-related side effects, such as the elderly and those with pre-existing PN.

Thalidomide plus dexamethasone

Preclinical investigation showed that thalidomide enhances the anti-MM effect of dexamethasone.[17] This observation was followed by results from several phase II studies showing the clinical activity of the combination.[33–35] In one study, 44 patients with refractory MM (77% resistant to dexamethasone based therapy and 32% previously treated with HDT) received thalidomide 200 mg/day with dose escalation to 400 mg/day along with pulsed dexamethasone.[33] The combination produced a partial response (PR) rate of 55%, with comparable activity among patients resistant to previous dexamethasone-based therapy and those who were not. Responses tended to be rapid, with a median time to response of 1.3 months. The efficacy of low-dose thalidomide (100 mg/day) plus pulsed dexamethasone was evaluated in 77 patients with relapsed or refractory MM.[35] In this trial, a 41% OR rate was noted. Thalidomide plus dexamethasone have also proven to be effective as salvage therapy in patients who relapse following autologous stem cell transplantation (SCT). In a retrospective comparison, thalidomide plus dexamethasone produced superior PFS and OS in comparison with conventional chemotherapy and a second autologous SCT among patients who relapsed following autologous SCT.[36]

Thalidomide plus chemotherapy

Thalidomide has also been used in combination with other chemotherapeutic agents in the management of relapsed and refractory MM. In a trial involving 236 individuals with relapsed MM, 63% of whom had progressed on standard chemotherapy and 23% of whom had chromosome 13 abnormalities, a regimen of dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide produced an OR rate of 32%, with comparable response rates among patients with and without chromosome 13 abnormalities.[37] Neutropenic fever occurred in 12% of patients, and venous thromboembolic (VTE) disease in 15%. Thalidomide is also active in combination with liposomal doxorubicin. Specifically, thalidomide, liposomal doxorubicin and dexamethasone led to an OR rate of 76% and CR rate of 26% in a study involving 50 patients with advanced MM, 40% of whom had previously received HDT and 54% of whom had received more than two lines of previous therapy.[38] VTE disease occurred in 12% of study participants, with severe infection in 15%. An oral regimen of thalidomide, cyclophosphamide and dexamethasone has also proven to be both well tolerated and active, with the OR rate ranging from 57 to 79% in these studies.[39–41]

Important side effects

Owing to the association between thalidomide and severe birth defects noted in the 1960s, access to the compound is restricted to individuals who participate in the System for Thalidomide Education and Prescription Safety Program, which was developed and implemented by the drug's manufacturer, Celgene Corporation (Summit, NJ, USA). VTE is an important thalidomide-related toxicity in MM, particularly when the compound is administered in conjunction with dexamethasone or chemotherapy. The incidence of thromboembolic events in clinical trials of MM patients receiving thalidomide plus dexamethasone and/or chemotherapy is 3–34% among individuals with newly diagnosed disease and 2–15% among those with relapsed/refractory disease.[42] A dose and time-dependent PN can also occur in association with thalidomide and is believed to be the result of axonal injury with progressive loss of large-diameter myelinated fibers.[43,44] Other side effects associated with thalidomide include bradycardia, hypothyroidism, hepatotoxicity and skin reactions ranging from mild muculo-papular rash to Stevens Johnson syndrome.

Lenalidomide

Lenalidomide is a thalidomide analog in which the structural backbone of its parent compound has been modified through elimination of a carbonyl group and addition of an amine. Although the initial intent of these modifications was to more effectively inhibit TNF-α, other mechanisms underlying the anti-MM effect of lenalidomide have been identified, including modulation of the immune response, inhibition of angiogenesis, induction of apoptosis, decreased binding of MM cells to the endogenous bone marrow stromal cells and modulation of cytokines in the bone marrow.[18,19,45–47] Selected clinical trials involving lenalidomide in relapsed MM are summarized in Table 2.

The first clinical study of lenalidomide in MM was a phase I study in which 27 patients with relapsed and refractory MM (median of three previous regimens) received escalating doses of lenalidomide ranging from 5–50 mg/day.[48] All 13 patients who received the 50 mg/day dose developed grade 3 myelosuppression after the first cycle, whereas the 25 mg/day dose was well tolerated in 12 patients and was therefore selected as the optimal dose for a subsequent phase II study. A response rate of 70% (minimal response (MR) or better) was observed, suggesting significant anti-MM activity. In a subsequent multicenter phase II study, 70 patients with relapsed and/or refractory disease were randomized to receive either 30 mg once-daily or 15 mg twice-daily oral lenalidomide for 21 days of every 28-day cycle to better define dose and schedule.[49] The 15 mg twice-daily dose was associated with increased grade 3/4 myelosuppression compared with daily dosing. The OR rate to lenalidomide monotherapy was 25% with a median OS of 28 months in the 30 mg once-daily group.[49] Importantly, non-hematological toxicity was minimal, with DVT occurring in 3% and significant PN in 2% of the study participants. The addition of dexamethasone was associated with increased response in 29% of the study participants.

The favorable side effect profile and efficacy of lenalidomide led to two large, randomized, multicenter, double-blind, placebo-controlled studies in patients with relapsed or refractory MM—the MM-009 North American trial and the MM-010 European/Israeli/Australian trial.[50,51] In both studies, patients were randomly assigned to receive 25 mg of oral lenalidomide or placebo on days 1–21 of a 28-day cycle. All patients received dexamethasone on days 1–4, 9–12 and 17–20 for the first four cycles and subsequently, after the fourth cycle, only on days 1–4. The median time to progression (TTP) was significantly longer in the lenalidomide/dexamethasone combination (MM-009: 11.1 months; MM-010: 11.3 months) compared with placebo/dexamethasone (4.7 months in both trials). Similar superiority was seen for the lenalidomide/dexamethasone combination in terms of OR

(MM-009: 61%; MM-010: 60.2%) compared with placebo/dexamethasone (MM-009: 19.9%; MM-010: 24%).

Lenalidomide has also been used in conjunction with both alkylating agents and anthracyclines in the treatment of relapsed/refractory MM. In a phase II study involving 21 patients with relapsed/refractory disease, lenalidomide (25 mg, days 1–21), cyclophosphamide (500 mg, days 1, 8, 15 and 21) and dexamethasone (40 mg, days 1–4, 12–15) produced an OR rate of 65%, including a CR in 5% and very good partial response (VGPR) in 15%.[52] The combination of lenalidomide, doxorubicin and dexamethasone, meanwhile, was evaluated in a recently published study involving 69 individuals with relapsed and refractory MM.[53] In this extensively pre-treated group of patients, the regimen produced an OR rate of 73%. At the highest dose level (lenalidomide 25 mg, days 1–21/28-day cycle; doxorubicin 9 mg/m^2 days 1–4; and dexamethasone 40 mg days 1–4 and 17– 20), the OR rate was 77% and the rate of VGPR or better, 74%. The median TTP in the study was 45 weeks. Deletion 17p and an elevated β2-microglobulin were associated with inferior response rate and shorter TTP.

Important side effects

Unlike thalidomide, lenalidomide is rarely associated with PN. Myelosuppression was the most common high-grade toxicity in phase III trials of lenalidomide.[50,51] Neutropenia was the most frequent manifestation of myelosuppression in these studies. Single-agent lenalidomide has not been associated with an increased risk of VTE.[48] In phase III trials, lenalidomide plus dexamethasone was associated with VTE in 15 and 8.5% of patients compared with rates of 3.5 and 4.5% with dexamethasone alone.[50,51] Rash occurs in approximately 30% of patients who receive lenalidomide.[54] The teratogenic effects of lenalidomide in humans are unknown, but based on the teratogenicity of thalidomide, access to the compound is restricted to individuals who participate in the RevAssist program. Administered by the drug's manufacturer, Celgene, the RevAssist program was designed to prevent fetal exposure to lenalidomide and thus minimize the risk of birth defects associated with the drug. During the first year of lenalidomide's availability in the United States, 15 584 patients registered in the RevAssist program and there were no pregnancies in female patients or female partners of male patients.[55] Other important side effects include fatigue myalgia, and diarrhea.

Bortezomib

Bortezomib is a first-in-class boronic acid dipeptide small molecule that reversibly inhibits the proteasome. By regulating protein degradation, the proteasome has a critical role in such diverse processes as cell cycle regulation and antigen processing. Protein degradation occurs through a 2-step process in which proteins destined for removal first undergo ATP-dependent ubiquitination followed by a second step of proteolysis within the proteasome.[56] Proteolysis takes place within the 20S subunit of the proteasome, which possesses chymotryptic-like, tryptic-like and post-glutamyl peptide hydrolyzing activity. Bortezomib specifically blocks the chymotryptic-like activity of the 20S subunit. Accumulation of undegraded proteins interferes with processes required for MM cell survival such as tumor-stromal cell adhesion, cytokine production and angiogenesis, thus leading to tumor cell death.[57] Selected clinical trials involving bortezomib in relapsed MM are summarized in Table 3.

Bortezomib in relapsed and refractory MM

Initial evidence of bortezomib's clinical activity in MM came from a phase I trial of patients with refractory hematological malignancies.[58] A CR was achieved by one of nine MM

patients in this study, whereas a reduction in either serum M-protein or marrow plasma cell content occurred in the other eight patients. Two phase II trials followed, the Study of Uncontrolled Myeloma Management with proteasome Inhibition Therapy (SUMMIT) and Clinical Response and the Efficacy Study of bortezomib in the Treatment of refractory myeloma (CREST) trials. In SUMMIT, 202 patients with relapsed and/or refractory MM received bortezomib 1.3 mg/m^2 twice weekly for 2 weeks followed by 1 week without treatment, with the addition of dexamethasone after two cycles for progressive disease or after four cycles for patients with stable disease.[59] The OR rate was 35%, with a 10% rate of complete or near complete response (CR/nCR) and an encouraging median OS of 16 months. In the 54-patient CREST study, bortezomib was administered at a dose of 1.0 or 1.3 mg/m^2 twice weekly for 2 weeks of each 3-week cycle as in SUMMIT, with addition of dexamethasone for progressive or stable disease after two or four cycles, respectively.[60] The OR rate was 30 and 38% in the 1.0 and 1.3 mg/m^2 treatment groups, with durable responses observed as in SUMMIT. A subset analysis of SUMMIT and CREST underscored the ability of bortezomib to overcome poor prognosis conferred in MM by chromosome 13 deletion (del(13)), as bortezomib produced comparable response rates and survival among patients with and without del(13) by metaphase cytogenetics.[61] This finding has been supported by other studies showing that response to bortezomib in patients with relapsed and/or refractory MM is independent of chromosomal abnormalities such as del(13) and t(4;14).[62,63] It is interesting to note that the number and type of previous therapy, performance status, β_2 microglobulin and other adverse prognostic factors were not shown to adversely affect a response in another subset analysis.[64]

These results were confirmed in the international, multicenter phase III Assessment of Proteasome Inhibition for EXtending remissions trial, in which 669 patients, more than 50% of whom had undergone two or more previous lines of therapy, were randomized to either bortezomib or high-dose dexamethasone.[65] The OR rate among individuals in the bortezomib group was 38%, with a CR rate of 6%, whereas the OR and CR rates in the dexamethasone group were 18 and 1%, respectively. Superior median TTP (6.22 versus 3.49 months) and 1-year OS (80 versus 66%) were observed in the bortezomib as compared with dexamethasone-treated patients. Important grade 3/4 treatment-related toxicities included anemia (10%), neutropenia (14%), thrombocytopenia (26%), fatigue, diarrhea (7%) and PN (7%). In an updated analysis, the OR and CR rates in the bortezomib arm were 43 and 9%, respectively.[66] The median survival for bortezomib-treated patients in this analysis was 29.8 versus 23.7 months in the dexamethasone group. Results of a multicenter phase IIIb study involving 638 patients who received bortezomib for relapsed or refractory disease were also recently published.[67] Study participants received dexamethasone for progressive disease after at least two cycles and for stable disease after at least four cycles. The OR rate was 67%, with 11% of patients achieving a CR and 22% a VGPR.

Combinations of bortezomib and dexamethasone or conventional chemotherapy

Synergy between bortezomib and dexamethasone observed in preclinical analysis[68] supported the use of this combination for patients in the SUMMIT and CREST trials with stable or progressive disease after several cycles of bortezomib monotherapy. In the SUMMIT trial, 13 (18%) of 78 bortezomib-treated patients with stable or progressive disease achieved a minimal or partial response with the combination.[59] In the CREST trials, meanwhile, the OR rate among patients who received the combination was 50%.[60]

Preclinical studies also showed the potent sensitizing effect of bortezomib on other classes of drugs including alkylating agents and anthracyclines[69,70] and provided rationale for additional bortezomib-containing combinations in the treatment of relapsed and/or refractory MM. Several trials have evaluated bortezomib-based combinations containing liposomal doxorubicin or doxorubicin.[38,71–73] In a phase I trial involving 42 patients with advanced

hematologic malignancies, significant anti-MM activity was observed.[72] Among 22 study participants with MM, including 13 who had received previous anthracycline therapy, eight (36%) patients achieved a CR or nCR and eight (36%) individuals a PR. Bortezomib plus liposomal doxorubicin was subsequently compared with bortezomib alone in a randomized, phase III trial involving 646 with relapsed and/or refractory disease, 66% of whom had received two or more previous lines of therapy and 9% of whom had progressed on treatment preceding enrollment.[73] Although the OR rate (CR+PR) in the two treatment arms was equivalent, bortezomib plus liposomal doxorubicin produced a superior median TTP (9.3 versus 6.5 months) and 15-month OS (76 versus 65%). Combination therapy was more effective than bortezomib monotherapy even in patients with advanced ISS stage, previous thalidomide exposure and multiple previous lines of therapy. Grade 3/4 drug-related adverse events were more common with combination therapy, particularly gastrointestinal symptoms (anorexia, vomiting), neutropenia and hand–foot syndrome. However, cardiac toxicity was only minimally increased with the doublet and rates of PN were similar in both arms.

The combination of bortezomib, doxorubicin and dexamethasone (PAD) has been evaluated in a study involving 64 patients with relapsed and/or refractory MM.[74] Fifty-eight percent had previously undergone autologous SCT, 70% prior anthracycline therapy and 27% prior bortezomib treatment. In this heavily pretreated group, PAD produced a PR or better in 67% of patients and a VGPR in 25%. Common grade III–IV toxicities included thrombocytopenia, neutropenia, anemia and PN.

Important side effects

Frequently observed toxicities associated with bortezomib-based therapy in patients with relapsed and/or refractory MM include PN, thrombocytopenia and gastrointestinal dysfunction. Of the 256 patients enrolled in the SUMMIT and CREST trials, 90 (35%) developed treatment-emergent PN or exacerbation of pre-existing neuropathy.[75] One or more courses of bortezomib was withheld as a result of therapy-related neuropathy in 19/90 (21%) of individuals. The incidence of PN was dose related, being more frequent with a dose of 1.3 versus 1.0 mg/m^2 and peaked at cycle 5 (cumulative dose~30 mg/m^2). Higher-grade PN, meanwhile, was more frequent in patients with pre-existing PN. Importantly, PN associated with bortezomib is reversible in most cases with treatment interruption and/or dose modification.[75,76] A symptom-based dose modification algorithm used in the SUMMIT and CREST trials and validated in Assessment of Proteasome Inhibition for EXtending remissions can be followed to prevent development of this therapy-related adverse event.

Thrombocytopenia occurring as a consequence of bortezomib therapy typically follows a cyclical, biphasic pattern with a predictable decline in the platelet count during the 2-week treatment period followed by platelet recovery during the rest period.[77] Although grade 3/4 thrombocytopenia occurred in 30% of study participants overall, it was uncommon in patients with a baseline platelet count of >200×10^9/l and was not associated with significant bleeding.

There was a higher incidence of herpes zoster reactivation in the Assessment of Proteasome Inhibition for EXtending remissions trial among patients who received bortezomib than among those in the dexamethasone arm (13 versus 5%).[65] The majority of these infections were grade I/II in severity and the incidence of higher-grade herpes zoster infections was similar in the two arms.[78] As a result of this observation and others, viral prophylaxis is strongly recommended for patients receiving bortezomib-based therapy.

Bortezomib has been safely used in MM patients with advanced renal failure, including those undergoing dialysis. A retrospective analysis of MM patients with advanced renal

disease who underwent dialysis at the time of bortezomib-based therapy showed an overall CR rate of 75% and a CR/nCR rate of 30%.[79] The incidence of significant treatment-related toxicities such as PN, thrombocytopenia and infection was similar to that observed in previous studies among patients without renal dysfunction, an observation confirmed in subsequent studies.[80]

Finally, rare instances of lung injury including bronchiolitis obliterans with organizing pneumonia,[81] diffuse alveolar damage[82] and pulmonary fibrosis[83] have been reported in patients receiving bortezomib.

Combinations of novel agents

Bortezomib/thalidomide/dexamethasone

Preclinical studies evaluating synergy among novel agents led to the development of rationally designed combinations of these agents. Bortezomib (1.0–1.3 mg/m^2, days 1,4,8,11), thalidomide (50–200 mg/day) and dexamethasone (20 mg on days of/after bortezomib administration for suboptimal response after three cycles) produced an OR rate of 79% and nCR rate of 22% in a trial involving 85 patients with relapsed and/or refractory myeloma.[84] The most common grade 3 or 4 toxicities were thrombocytopenia and neutropenia. Non-hematological toxicities included neuropathy. Despite concerns related to the development of severe neurotoxicity, the combination of bortezomib and thalidomide was associated with manageable neuropathy, with a cumulative incidence of up to 60%.

Lenalidomide plus bortezomib

Preclinical studies showed that lenalidomide sensitizes myeloma cells to bortezomib, with lenalidomide triggering apoptosis by activation of caspase-8, whereas bortezomib does so in a dual caspase-8- and 9-mediated manner.[57] Although both agents suppress the transcriptional activity of nuclear factor-κB in MM cells, they act at different check points to regulate nuclear factor-κB activity. In a phase I study, lenalidomide plus bortezomib produced an OR rate (CR+PR+MR) of 58% in 36 evaluable patients with relapsed and/or refractory MM, including a CR/nCR rate of 6%.[85] Responses were durable (median 6 months, range: 1–26), and 11 patients remained on therapy beyond 1 year. Dose-limiting toxicity was reached at lenalidomide 15 mg–bortezomib 1.3 mg/m^2 with one episode of grade 3 herpes zoster virus reactivation (successfully treated with acyclovir) and one grade 4 neutropenia. Importantly, the regimen is associated with low rates of DVT (1%) and no significant PN.

Lenalidomide/bortezomib/dexamethasone

In a subsequent phase II study, lenalidomide (15 mg/day, days 1–14), bortezomib (1.0 mg/m^2, days 1,4,8,11) and dexamethasone (40 mg/20 mg, cycles 1–4/5–8) on days of/after bortezomib administration were given to patients with 1–3 previous lines of therapy for up to eight 21-day cycles.[86] After cycle 8, patients with stable or responding disease received maintenance therapy on a 21 day cycle as follows: bortezomib (days 1 and 8), lenalidomide (days 1–14) at the dose levels tolerated at the end of cycle 8, and dexamethasone 10 mg (days 1,2,8,9) until disease progression or unacceptable toxicity. In 63 evaluable patients, the OR rate (CR/nCR+VGPR+PR+MR) is currently 86%, including a CR/nCR rate of 24% and CR/nCR/VGPR/PR of 67%. The regimen is well tolerated with primarily grade 1–2 myelosuppression. Non-hematological toxicities included two episodes of DVT, repeated episodes of atrial fibrillation associated with high-dose dexamethasone and not seen at the lower dose, and one episode of grade 3 PN.

Lenalidomide, melphalan, prednisone and thalidomide

In a phase II trial by Palumbo *et al*.[87], lenalidomide at 10 mg/day on days 1–21, oral melphalan at 0.18 mg/kg on days 1–4, oral prednisone at 2 mg/kg on days 1–4, thalidomide at 50 mg/day (Arm A) or 100 mg/day (Arm B) was administered on days 1–28. Each course was repeated every 28 days for a total of six courses. Among patients who received this regimen as second-line therapy the PR rate was 82%, including VGPR 36%. Among patients who received thalidomide 100 mg, the PR rate was 93% compared to 65% among those who received thalidomide 50 mg. The 1-year progression-free survival was 49%. Grade 3–4 hematological adverse events included neutropenia (67%), thrombocytopenia (36%) and anemia (30%). Grade 3–4 non-hematological adverse events included infections (21%), neurological toxicity and fatigue (9%). No thromboembolic events were reported.

Choice of therapy in relapsed MM

A variety of factors are considered in determining appropriate therapy for an individual with relapsed MM. These include co-morbid conditions, previous therapy, time from previous therapy, mode of drug administration, the potential role of autologous or allogeneic stem cell transplantation and risk level. The International Staging system as assessed at the time of initial induction therapy, the plasma cell-labeling index, as well as conventional and FISH-based cytogenetic analysis are used in assessing risk level and influence choice of therapy. It is likely that genomic and proteomic models will increasingly provide beneficial prognostic and predictive information as well. Interestingly, a recent analysis of patients who received bortezomib for relapsed MM showed an association between response to therapy and specific clinical and immunohistochemical characteristics.[88]

Although thalidomide, lenalidomide and bortezomib each have significant activity in relapsed MM, certain clinical scenarios may favor one agent over another. Lenalidomide is preferred for patients with pre-existing PN and for those who based on preference or other circumstances cannot make frequent clinic visits for intravenous therapy. Thalidomide may be selected for patients with significant cytopenias, as it is associated with a mild degree of myelosuppression. Bortezomib is preferred in patients with high-risk disease based on cytogenetic analysis, those with significant underlying renal insufficiency, as well as those with advanced bone disease on the basis of its ability to both inhibit osteoclastogenesis and promote osteoblast differentiation and proliferation.[89,90] As previous discussion underscores, regimens incorporating combinations of these agents have been an important development in the field and are therefore appropriate for certain patients with relapsed MM as well.

Emerging therapies

The successful translation of insights derived from preclinical investigation into effective therapies in MM has stimulated interest in the development of new agents based on a similar paradigm of preclinical laboratory evaluation and clinical investigation of rationally selected candidate drugs. For example, two second-generation proteasome inhibitors and the newest IMiD compound are currently undergoing evaluation in clinical trials involving patients with relapsed and/or refractory disease. In addition, agents from various other drug classes not heretofore used in MM but with demonstrated anti-MM activity in preclinical models are being investigated in clinical trials.

Two second-generation proteasome inhibitors—carfilzomib (PR-171) and salinosporamide (NPI-0052)—have shown significant anti-MM activity in preclinical models[91,92] and are being investigated in early-phase studies. Both agents irreversibly inhibit the proteasome (in contrast to the reversible inhibition of bortezomib) and have the potential for oral

administration. Unlike bortezomib, carfilzomib has activity only against the chymotryptic-like activity of the 20S proteasome,[92] whereas salinosporamide inhibits the tryptic-like and caspase-like activity of the 20S proteasome as well as chymotryptic-like activity.[91] Based on *in vitro* studies, both agents appeared to possess activity against bortezomib-refractory disease.[91,92] Preliminary results of two phase II trials involving carfilzomib therapy for patients with relapsed MM[93] and relapsed and/or refractory MM[94] were recently presented at the 2008 American Society of Hematology Meeting. In relapsed MM, carfilzomib produced a rate of PR or better of 57% among those without previous bortezomib exposure and 18% among individuals who had received previous bortezomib therapy.[93] Only one case of significant PN was reported. Meanwhile, in patients with relapsed and/or refractory MM, many of whom had previously received bortezomib, lenalidomide, thalidomide, alkylating agents and/or SCT, carfilzomib produced rates of PR, MR and stable disease (s.d.) of 13, 13 and 46%, respectively.[94] Although exacerbation of PN was rare in this study, an elevation in creatinine did occur in 33% of study participants and acute renal failure developed in 2%. In addition to reports from these studies of carfilzomib, preliminary results of a phase I dose escalation study involving salinosporamide were also presented recently.[95] Based on the treatment of 10 patients to date, this report provided initial evidence of the compound's tolerability as well as its ability to inhibit the enzymatic activity of the proteasome, but renal toxicity was again seen.

As an analog of the immunomodulatory drugs thalidomide and lenalidomide, pomalidomide exerts anti-MM activity through a variety of mechanisms.[17–19] In two phase I clinical trials involving individuals with relapsed or refractory MM, pomalidomide was well tolerated and produced a PR rate of at least 50%.[96,97] Preliminary results of a phase II trial of pomalidomide in MM have been presented.[98] Thirty-seven patients with relapsed or refractory MM received oral pomalidomide 2 mg daily each day of a 28-day cycle and weekly dexamethasone along with full-dose aspirin as VTE prophylaxis. The rates of PR and VGPR were 38 and 24%, respectively. It is noteworthy that the OR rate among study participants refractory to lenalidomide was 29%. The most common grade 3 toxicity was anemia and no VTE events have been observed to date.

By modulating chromatin conformation, histone acetylation has an important role in the regulation of gene expression.[99] Acetylation of histones is, in turn, controlled by the counter-acting activity of histone deacetylase inhibitors (HDACs) and histone acetyl transferases.[100,101] Identification of an imbalance in enzymatic function favoring HDACs in tumor cells[102] sparked interest in HDAC inhibitors as anti-cancer therapy. Preclinical studies showed the anti-MM of the HDAC inhibitor vorinostat[103] as well as synergy between this agent and bortezomib.[104] The preliminary results of two ongoing multicenter phase I trials of vorinostat plus bortezomib for relapsed and/or refractory MM were recently presented.[105] The combination was active, producing at least a PR in 26% of individuals in one study and 43% of those in the other study. Moreover, the regimen showed significant activity in the treatment of patients with bortezomib-refractory disease, with a rate of PR or better in this group of 33–38%. Dose-limiting toxicities in one study included an episode of grade 3 AST elevation and episode of grade 4 thrombocytopenia, whereas an episode of dose-limiting fatigue and QTc prolongation occurred in the other. Other frequent side effects included nausea, vomiting, diarrhea, anemia and neutropenia. Based on these encouraging results, additional trials involving vorinostat are underway, including a phase II trial of vorinostat plus bortezomib in bortezomib-refractory MM and a phase III trial comparing vorinostat plus bortezomib to bortezomib monotherapy in relapsed and/or refractory MM. In addition, the anti-MM activity of vorinostat has stimulated interest in the development of additional HDAC inhibitors, including LBH 589,[106] depsipeptide,[107] and the HDAC6-selective inhibitor tubacin.[108–110]

The phosphatidylinositol 3-kinase/AKT pathway mediates proliferative and anti-apoptotic signals in MM through both cytokine-dependent and cytokine-independent mechanisms [111–114] and as such represents an important therapeutic target in MM. Perifosine is a small molecule inhibitor of AKT that in preclinical study blocked constitutive and cytokine-induced AKT activation and exerted a cytotoxic effect on MM cells.[115] In a phase II study involving a heavily pre-treated population of patients with relapsed and/or refractory MM, perifosine plus low-dose dexamethasone produced an OR rate of 35%.[116] Interim analysis of a phase I study has shown the effectiveness of perifosine plus lenalidomide and dexamethasone, a combination that produced an OR rate of 70%, with a 7% nCR rate and 10% VGPR rate.[117] The most common grade 3/4 toxicities in this trial were neutropenia, hypophosphatemia, thrombocytopenia and anemia. Interim analysis of another phase I/II trial, meanwhile, showed the activity of perifosine plus bortezomib in relapsed and/or refractory MM.[118] Patients in this trial were heavily pre-treated (median number of prior therapies 5) and many (83%) had relapsed and refractory disease at enrollment. The OR rate was 38%, with rates of CR/nCR, PR and MR of 4, 17 and 17%, respectively. Among patients with bortezomib-refractory disease, the OR rate was 15% and improved to 31% with the addition of dexamethasone. Grade 3/4 toxicities included anemia, neutropenia, thrombocytopenia and pneumonia. Grade 3/4 PN occurred in only one study participant.

Heat-shock protein 90 (Hsp90) has also emerged as an important target in the treatment of various cancers, including MM, based on its function as a molecular chaperone for client proteins that are mutated or overexpressed in tumor cells.[119] Several preclinical studies have characterized the cellular repercussions of Hsp90 inhibition in MM[120–124] and have provided a platform for clinical development of Hsp90 inhibitors. In a multicenter phase I/II trial, bortezomib plus the Hsp90 inhibitor tanespimycin showed considerable activity in relapsed and/or refractory MM, with disease stabilization or better response observed in 71% of bortezomib-naive patients, 38% of those who had received prior bortezomib and 33% of those with bortezomib-refractory disease.[125] The most frequently observed treatment-related toxicities included fatigue, diarrhea, constipation, thrombocytopenia and nausea. Dose-limiting toxicities included an episode of grade 3 pancreatitis, an episode of grade 4 metabolic acidosis in the setting of gastrointestinal hemorrhage and an episode of grade 3 muscle cramps. Conversely, lower rates of PN were seen and neutropenia was less pronounced, suggesting a possible protective effect from the combination in this setting. A phase III trial comparing bortezomib plus tanespymcin to bortezomib alone is currently underway.

Summary

Although development of the novel agents thalidomide, lenalidomide and bortezomib has improved outcomes for individuals with MM, the disease remains incurable. As a source of significant morbidity and mortality, relapsed and/or refractory MM represents an important focus of ongoing research efforts. Characterization of the molecular events underlying this disease at the level of the MM cell and the bone marrow microenvironment has provided the platform for development of the novel agents as well as various emerging compounds in MM, including new IMiD and proteasome inhibitors, as well as inhibitors of HDAC, phosphatidylinositol 3-kinase/AKT and Hsp90. It is anticipated that drug combinations that target different oncogenic pathways will possess greater anti-MM activity and add to progress made in the treatment of patients with relapsed and/or refractory disease, for which there remains a clear medical need to improve outcomes.

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Table 1

Summary of selected clinical trials evaluating thalidomide in relapsed/refractory MM

Reference/phase	Treatment	*N*	ORR (CR+CR)	EFS/TTP	Survival
Singhal *et al.*[20]/Phase II	Thal 200 mg/q.d. with dose escalation by 200 mg every 2 weeks to maximum dose 800 mg/day	84	>25% decrease in serum/ urine M-protein: 32	1-year EFS rate: 22%	1-year OS 58%
Dimopoulos *et al.*[33]/phase II	Thal 200 mg/day with dose escalation after 2 weeks to 400 mg q.h.s. Dex 20 mg/m^2 days 1–4, 9–12, 17–20 followed by monthly dex days 1–4 4-week cycles	44	55%	NR	OS 12.6 months
Palumbo *et al.*[35]/phase II	Thal 100 mg/day Dex 40 mg/day, days 1–4 4-week cycles	77	41%	PFS: 12 months	NR
Lee *et al.*[37]/phase II	Dex 40 mg/day, days 1–4 Thalidomide 400 mg/day Cisplatin 10 mg/m^2/day, CI days 1–4 Doxorubicin 10 mg/m^2/day, CI days 1–4 Cyclophosphamide 400 mg/m^2/day, CI days 1–4 Etoposide 40 mg/m^2/day, CI days 1–4 4-week cycles	236	32% (CR/nCR: 15%)	NR	NR
Offidani *et al.*[38]/phase II	Thalidomide 400 mg/day Liposomal doxorubicin 40 mg/m^2 day 1 Dex 40 mg/day, days 1–4, 9–12 4-week cycles	50	76% (CR/nCR 32%, VGPR 6%)	EFS: 17 months	Not reached

Abbreviations: CI, continuous infusion; CR, complete response; Cy, cyclophosphamide; Dex, dexamethasone; DOR, duration of response; Len, lenalidomide; nCR, near complete response; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; Thal, thalidomide; TTP, time to progression; VGPR, very good partial response.

Table 2

Summary of select clinical trials evaluating lenalidomide in relapsed/refractory MM

Reference/phase	Dosing schedule	*N*	ORR (CR+PR)	EFS/TTP	Survival
Richardson *et al.*[48]/phase I	Len 5–50 mg/day	27	CR+PR: 29	Not reported	Not reported
Richardson *et al.*[49]/phase II	Len 30 mg once daily or 15 mg twice daily, days 1–21 Dex 40 mg for 4 days, every 14 days for suboptimal response 4-week cycles	67 (q.d.) 35 (b.i.d.)	ORR: 24 (once daily) CR/nCR: 6 ORR: 29 (twice daily) CR/nCR: 0	DOR: 19 mo (q.d.) 23 mo (b.i.d.) PFS: 7.7 months (q.d.) 3.9 months (b.i.d.)	OS: 27 months (combined)
Weber *et al.*[50]/phase III	Len 25 mg on days 1–21 Dex 40 mg on days 1–4, 9–12, 17–20 Dex 40 mg on days 1–4 only from cycle 5	170	61 CR/nCR: 13	TTP: 11.1 months	OS: 29.6 months
Dimopoulos *et al.*[51]/phase III	Len 25 mg on days 1–21 Dex 40 mg on days 1–4, 9–12, 17–20 Dex 40 mg on days 1–4 only from cycle 5	176	60.2 CR/nCR 15	TTP: 11.3 months	Not reported
Morgan *et al.*[52]/phase II	Len 25 mg on days 1–21 Cy 500 mg on days 1,8,15,21 Dex 40 mg on days 1–4 and 12–15 4-week cycles for 9 cycles	21	ORR: 65 CR: 5 VGPR: 15	Not reported	Not reported

Abbreviations: CR, complete response; Cy, cyclophosphamide; Dex, dexamethasone; DOR, duration of response; Len, lenalidomide; nCR, near complete response; NR, not reported; ORR, overall response rate; OS, overall survival; PR, partial response; PFS, progression-free survival; Thal, thalidomide; TTP, time to progression; VGPR, very good partial response.

Table 3

Summary of selected clinical trials evaluating bortezomib in relapsed/refractory MM

Reference/phase	Treatment	*N*	ORR (CR+CR)	EFS/TTP	Survival
Orlowski *et al.*[58]/phase I	Bort 0.40, 1.04, 1.20, or 1.38 mg/m^2 days 1, 4, 8, 11, 15, 18, 22, 25 followed by 2-week rest 6-week cycles	9	11% (MR+PR+CR): 33%	Not reported	Not reported
Richardson *et al.*[59]/phase II	Bort 1.3 mg/m^2 days 1, 4, 8, 11 For PD after two cycles or s.d. after four cycles, Dex added 20 mg days 1, 2, 4, 5, 8, 9, 11, 12 3-week cycles	202	35% CR/nCR 10%	DOR: 16 months	Median OS: 16 months
Jagannath *et al.*[60]/phase II	Bort 1.0 or 1.3 mg/m^2 days 1, 4, 8, 11 For PD after two cycles or s.d. after four cycles, Dex added at 20 mg days 1, 2, 4, 5, 8, 9, 11, 12 3-week cycles	54	30% (1.0 mg/m^2) 38% (1.3 mg/m^2) 37% (B 1.0 + dex) 50% (B 1.3 + dex)	Not reported	Not reported
Richardson *et al.*[65]/phase III	Bort 1.3 mg/m^2 days 1, 4, 8, 11 for eight 3-week cycles, then days 1, 8, 15, 22 for three 5-week cycles vs Dex 20 mg days 1–4, 9–12, 17–20 for four 5-week cycles then days 1–4 for five 4-week cycles	669	Bort, 38% (CR, 6%) vs Dex, 18% (CR, 1%)	Bort, 6.2 months vs Dex, 3.49 months	1 year survival: Bort 80% vs Dex 66%
Orlowski *et al.*[73]/phase III	Bort 1.3 mg/m^2 days 1, 4, 8, 11 3-week cycles vs Bort 1.3 mg/m^2 days 1,4, 8, 11 plus liposomal doxorubicin 30 mg/m^2 on day 4 3-week cycles	646	Bort, 41% (CR/nCR 10%) vs Bort plus PLD, 44% (CR/nCR 13%)	Bort, 6.5 months vs Bort plus PLD, 9.3 months	15-month survival: Bort 65% vs Bort plus PLD 76%
Palumbo *et al.*[74]/phase II	Bort 1.3 mg/m^2 days 1, 4, 8, 11 Dex 40 mg days 1–4 and either Doxorubicin 20 mg/m^2 days 1, 4 (34 patients) or liposomal doxorubicin 30 mg/m^2 day 1 4-week cycles	64	67% (VGPR 25%)	1-year EFS 34%	1-year survival 66%

Abbreviations: CR, complete response; CI, Continuous infusion; Cy, cyclophosphamide; Dex, dexamethasone; DOR, duration of response; Len, lenalidomide; nCR, near complete response; NR, not reported; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; Thal, thalidomide; TTP, time to progression; VGPR, very good partial response.