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MULTIPLE MYELOMA (R NIESVIZKY, SECTION EDITOR)

Management of Double-Refractory Multiple Myeloma

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Abstract Widespread use of the novel agents bortezomib and lenalidomide has improved outcomes in multiple myeloma (MM). Despite remarkable progress, patients will eventually relapse after exhausting treatment with these drugs. Management of myeloma that is refractory to both bortezomib and lenalidomide (double-refractory MM, DRMM) is complicated due to disease, patient, and treatment-related factors and new therapies for these patients are required. A review of the unique challenges of treating DRMM, recently FDA-approved therapeutic agents, and selected novel drugs under active clinical investigation, is presented below.

Keywords Myeloma · Multiple myeloma · Relapsed · Refractory · Double-refractory · Carfilzomib · Pomalidomide · Bortezomib · Lenalidomide · Panobinostat · Daratumumab · Elotuzumab · Ixazomib

Introduction

Multiple myeloma (MM) comprises 1 % of all cancers and 10 % of newly diagnosed hematologic malignancies in the United States. It is the second most common hematologic malignancy with 21,700 new cases diagnosed and 10,900 deaths in 2012 [1]. Treatment of MM has changed dramatically, starting with the discovery of the anti-myeloma activity of thalidomide in the late 1990s [2, 3]. The subsequent development of thalidomide analogues as a new class of antineoplastic agents called the immunomodulatory drugs (IMiDs®) led to significantly improved survival in myeloma patients [4]. In June 2006, lenalidomide became the first IMiD® to be FDA approved [5].

Research in the early 1990s demonstrated the increased levels of proteosomal mRNA in cancer [6]. Aiming to exploit this feature, bortezomib was developed as a first-in-class proteasome inhibitor (PI). It was first approved for relapsed/refractory disease in 2003 and later approved for treatment-naïve MM (2008) [7].

Thalidomide, lenalidomide, and bortezomib were called the "novel agents" and have led to significant improvement in survival outcomes and have become a mainstay of myeloma treatment [8–10]. Despite the advances in treatment, MM still is considered an incurable disease and patients eventually become refractory to even the novel agents. After relapse, patients are left with limited options for treatment and face a grim overall prognosis. Retrospective review has shown persons with myeloma that has progressed after prior lenalidomide and bortezomib treatment have a median overall survival of 9 months and an event-free survival of 5 months [11••].

The success of lenalidomide and bortezomib and the need for new treatment options in heavily pretreated MM have led to the development of next-generation IMiDs® and PIs. In July 2012, Carfilzomib became the latest PI to be FDA approved for treatment of relapsed/refractory myeloma [12]. Pomalidomide followed shortly thereafter as the next IMiD® (February 2013) [13]. These two agents have shown efficacy with a good safety profile in heavily pretreated myeloma patients. The evidence supporting their use in these patients is expounded in detail below.

With expanding knowledge of possible molecular targets in MM, a multitude of investigational targeted therapies are also being assessed. As none of these agents are currently approved for use outside of the clinical trial setting, they are discussed below mainly to provide the reader with a sense of the current multi-targeted approach to myeloma treatment.

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This article will review the current and future treatment options for patients with double-refractory multiple myeloma (DRMM), defined as MM that is relapsed and/or refractory to both bortezomib and lenalidomide. The terms "relapsed", "refractory", and "relapsed and refractory" carry the standard definitions as proposed by the International Multiple Myeloma Working Group (IMWG) [14].

Comorbidities of Relapsed/Refractory Myeloma

In choosing treatment options for the relapsed myeloma patient, oncologists are faced with several challenges related to disease and patient factors. Renal insufficiency, peripheral neuropathy and depleted bone marrow reserve often arise as comorbidities and commonly affect the choice of next line therapy in relapsed myeloma.

Renal impairment occurs in 25 – 50 % of myeloma patients at some point in their disease course and confers poor prognosis [15]. It can be the result of myeloma itself or other unrelated medical conditions such as diabetes mellitus or hypertension. Lenalidomide is excreted mostly unchanged into the urine and decreased glomerular filtration in these patients can lead to increased drug exposure and risk of toxicity [16, 17]. In contrast, although a large proportion of pomalidomide is excreted in the urine, it is first metabolized in the liver, via the cytochrome p450 enzymes CYP1A2 and CYP3A4 to inactive metabolites, with only 10 % of the parent drug excreted unchanged in the urine [17]. As a result, the risk of excess toxicity of pomalidomide in patients with renal impairment theoretically is significantly lessened. This aspect of pomalidomide treatment remains to be vetted, however, since the clinical trials for pomalidomide reported thus far excluded subjects with severe renal impairment.

Peripheral neuropathy (PN) is also frequently encountered in myeloma patients. It can be related to the disease process itself in up to 20 % of patients or emerge as a result of treatment in an additional 75 % [18, 19]. The most common MM treatments associated with PN are thalidomide and bortezomib [18, 19]. Unlike bortezomib, the next-generation proteasome inhibitor carfilzomib does not seem to cause significant neuropathy [20–22]. Similarly, in the registration trial for pomalidomide, MM-002, no grade 3 or higher PN was seen in a heavily pre-treated population, thereby suggesting that pomalidomide also does not exacerbate pre-existing neuropathy [23].

Heavily pretreated MM patients, particularly those treated with cytotoxic chemotherapy [24], have decreased bone marrow reserve [25] which can make them more susceptible to myelosuppression from future treatment. Cytotoxic chemotherapy may also promote clonal evolution of myeloma cells and progression towards more aggressive, treatment resistant disease [26, 27]. Choice of later-line chemotherapy must thus take into account the potential for long term immunosuppression and cytopenias that can result from further myelosuppresion.

Re-treatment with Bortezomib and Lenalidomide

While the majority of recent studies focus on treatment of DRMM with pomalidomide, carfilzomib, and other novel agents, re-treatment with bortezomib and/or lenalidomide in DRMM has been evaluated. Notable regimens include DVD-R (pegylated liposomal doxorubicin, bortezomib, dexamethasone, and lenalidomide), BLD (bendamustine, lenalidomide, dexamethasone), and BBD (bendamustine, bortezomib, and dexamethasone).

A recent phase 2 study assessed the DVD-R regimen in a heavily pretreated population (median of three prior lines of treatment). Eighty-two percent of patients were previously treated with bortezomib and 47.5 % were previously treated with lenalidomide [28•]. The objective response rate [ORR, partial response (PR) + very good partial response (VGPR) + complete response (CR)] was 48.7 %. Clinical benefit response [ORR + minimal response (MR)] was seen in 84.6 %.

For patients previously treated with bortezomib (n=33) and lenalidomide (n=19) the clinical benefit rate was 81.8 % and 63.1 %, respectively. Even among patients who had failed prior treatment with both DVD and a lenalidomide-based regimen (n=10), the clinical benefit rate was 60.0 %. Durable responses were achieved, with a median duration of response and progression free survival of 11 and 9 months, respectively.

BLD was evaluated on a on a similarly pretreated (median= 3) population of relapsed and/or refractory MM patients [29•]. History of bortezomib (n=19, 66 %) or lenalidomide (n=13, 45 %) was common but the number of patients with DRMM was not disclosed. The ORR (≥PR) was 76 % (PR 52 %, VGPR 24 %, CR 0 %) with an additional 24 % of patients achieving MR. After 13 months of follow-up, the median PFS and OS were 6.1 months and not reached, respectively.

Another bendamustine-containing regimen, BBD, has shown promising results, albeit in a less heavily pretreated population (most patients received 1 – 2 prior lines of therapy) [30•]. The ORR was 65.2 % with more near complete responses (nCR) and CR (16.7 %) than were seen in BLD. The investigators reported a PFS 12.9 months for the subjects with 1 – 2 prior lines of therapy as compared to 7.8 months in more heavily pre-treated patients.

Recently Approved Agents

Pomalidomide

Pomalidomide is a next-generation immunomodulatory drug that has shown safety and efficacy in the treatment of heavily

pretreated MM [31–33, 34••, 35••, 36••, 37••, 38].. It has three primary effects: potent direct anti-myeloma activity, inhibition of stromal cell-support, and immune modulation [39]. As of February 2013, it is approved by the United States Food and Drug Administration (FDA) for treatment of patients with MM who have received lenalidomide and bortezomib and were refractory to the last therapy [13].

Numerous phase 1 and 2 studies have investigated the safety and efficacy of pomalidomide and a phase 3 study comparing pomalidomide + dexamethavsone versus dexamethasone alone for the treatment of relapsed myeloma is currently underway.(40•) The results of selected recent trials are summarized in Table 1. Most common grade 3 / 4 adverse events seen in the phase 1 trials were neutropenia (53 % in all dose cohorts combined), anemia (21 %), thrombocytopenia (18 %), sepsis (11 %), and pneumonia (8 %). Back pain, muscle weakness, renal failure and DVT each occurred in 5 % of patients. The maximum tolerated dose (MTD) of pomalidomide was established at 4 mg daily with the dose limiting toxicity of neutropenia. Peripheral neuropathy and venous thromboembolism (VTE) were uncommon AEs, at≤5 % each [23].

The two largest phase 2 trials for pomalidomide, MM-002 and IFM 2009-02, evaluated the safety and efficacy of pomalidomide with (POM+LoDex) or without (POM) low-dose dexamethasone [34••, 36••]. All patients were previously treated with bortezomib and lenalidomide-based regimens, and the majority of subjects had DRMM [34••]. Patients were randomized to one of the two regimens, with pomalidomide 4 mg daily given on days 1 – 21 of 28-day cycles. The IFM 2009-02 trial also included a group taking pomalidomide all 28 days of the cycle [36••].

Overall, 34 – 37 % of patients achieved PR or better in the two studies (including the 28/28 days of pomalidomide group). Patients had received a median of 5 – 6 prior treatments although number of treatments did not seem to affect response to POM+LoDex [36••]. Median PFS was 4.6 months in both studies and OS was 14.9 – 16.5 months.

A Mayo Clinic-based series of studies examined six different dose cohorts of pomalidomide combined with fixed-dose dexamethasone [37••]. Cohorts 3 and 4 (n=35 for each) comprised patients with DRMM. These groups were treated with pomalidomide 2 mg and 4 mg, respectively. Patients with DRMM had inferior response rates (30.6 vs. 34 %). This is illustrated further by patients in Cohort 1 (n=60), defined as not refractory to either lenalidomide or bortezomib with a 65 % overall response rate.

Two phase 2 studies have evaluated three drug combinations with pomalidomide + dexamethasone. In the ClaPD

Table 1 Selected phase 1 and 2 studies of pomalidomide and carfilzomib

Phase	Study	Regimen	N	Schedule	Doses	ORR / CBR	PFS / DOR / OS, months
1	Richardson et al. Blood 2013	Pom +/- dex	38	21/28d	2, 3, 4, or 5 mg	21 % / 42 %	4.6 / 4.6 / 18.5
2	Jagannath et al. Blood 2012	Pom +/- dex	113	21/28d	4 mg	34 % / 45 %	4.6 / 8.3 / 16.5
2	Leleu et al. Blood 2013	Pom+dex	66	21/28d or 28/28d	4 mg	41 % / –	4.6 / 7.3 / 14.9
2	Lacy et al. Blood 2012	Pom+dex	70	28/28d	2 mg or 4 mg	26 % / – (2 mg) 29 % / – (4 mg)	6.4 / 15.6 / 16 3.3 / 3.1 / 9.2
2	Mark et al. Blood 2012	ClaPD	97	21/28d	4 mg	54 % / 59 %	8.2 / – / NR
2	Rossi et al. JCO 2012	ClaPD	66	21/28d	4 mg	56 % / 68 %	5 / – / –
2	Ludwig et al. Blood 2012	PCP	11	21/28d	2.5 mg	63 % / 81 %	64 % / – / 69%[a]
3	San-Miguel et al. JCO 2013	Pom+LoDex	455	21/28d	4 mg	21 % / –	3.6 / – / NR
2	Vij et al. BJH 2012	Carfilzomib	35	d1, 2, 8, 9, 15, 16 / 28d	20 mg/m^2	17 % / 31 %	4.6 / >10.6 / 29.9
2	Lendvai et al. Blood 2012	Carfilzomib	34	d1, 2, 8, 9, 15, 16 / 28d	56 mg/m^2	58 % / –	4.6 / – / NR
1/2	Shah et al. Blood 2012	Car-Pom-d	27	Car: d1, 2, 8, 9, 15, 16 / 28d Pom: 21/28	Car: 20/27 mg/m^2 Pom: 4 mg	33 % / 56 %	70 % / – / –[b]

a: 1-year PFS and OS reported

b: 6-month PFS reported

MTD: maximum tolerated dose

DLT: most common dose limiting toxicity

ORR: overall response rate

CBR: clinical benefit response

PFS: progression-free survival

DOR: duration of response

OS: overall survival

NR: not reached

(Clarithromycin 500 mg BID, Pomalidomide 4 mg QD on d1 – 21 of a 28 day cycle, dexamethasone once weekly) phase 2 study, 100 subjects with a median of five prior lines of therapy underwent treatment [41, 42]. Seventy-four percent had DRMM. The ORR and PFS were approximately double those seen with Pom+LoDex alone at 57 %, with a PFS of 8.4 months. Prior history of DRMM or high-risk cytogenetics made no impact on response. Overall survival after 9.6 months of follow up was 72 %.

Another three-drug pomalidomide-based regimen, PCP (pomalidomide 2.5 mg, cyclophosphamide 50 mg QOD and prednisone 50 mg QOD), also showed some promise in DRMM [43]. These patients (n=11) achieved an ORR of 63 % and a clinical benefit rate of 81 %. After 1 year of follow-up, 69 % of patients were still alive, with 64 % being free from disease progression. These numbers compare favorably with those from the entire study (including non-DRMM patients) where PFS and OS were 52 % and 78 %, respectively.

Results from MM-003, the first phase 3 trial of POM+LoDEX (arm A) versus high-dose dexamethasone (HiDEX; arm B) were recently reported [40••]. Patients who showed progression on HiDEX were allowed to receive POM in a companion trial, MM-003C. Patients in treatment arm A received pomalidomide 4 mg on days 1 – 21 and weekly dexamethasone 40 mg (20 mg if age>75 years) while arm B received dexamethasone 40 mg (or 20 mg) on days 1 – 4, 9 – 12, and 17 – 20 in the 28-day cycle. Seventy-two percent of the 455 patients (median of five prior treatments) had DRMM at randomization. After a median of only 18 weeks, PFS was already significantly greater in POM+LoDEX group (15.7 vs. 8.0 weeks). OS was not reached in the POM+LoDEX group but was 34 weeks in the HiDEX group.

The most common grade 3 to 4 adverse events in the phase 2 and 3 studies were related to bone marrow suppression – neutropenia 13 – 42 %, anemia 16 – 25 %, thrombocytopenia 12 – 21 %, leukopenia 10 %, and fatigue 6 – 14 %.(26, 29, 47, 48, 91) An increased rate of respiratory infections was also seen, with some studies reporting grade 3 / 4 pneumonias in 8 – 22 % of patients [34••, 37••].

Venous thromboembolism, a known adverse effect of lenalidomide, was noted in only 1 % of patients in phase 3 study; however, all patients where on thromboprophylaxis with either aspirin or anticoagulated with warfarin or low molecular weight heparin. Emergence of peripheral neuropathy was seen in only 1 % of patients [40••].

Carfilzomib

Carfilzomib is a proteasome inhibitor that was approved by FDA in July 2012 for treatment of patients with myeloma who have received at least two prior therapies including bortezomib and an immunmodulatory drug (thalidomide or lenalidomide) [12]. It is a selective proteasome inhibitor that, unlike bortezomib, binds irreversibly to its target of the 26S proteasome, forming two covalent bonds. As a result, carfilzomib causes a longer duration of proteasome inhibition than does bortezomib [20, 44••].

Several phase 1 and 2 studies have examined treatment with single-agent carfilzomib (Table 1). Although earlier data from the PX-171-001 study used a 14-day cycle with carfilzomib given on days 1 – 5 (MTD=15 mg/m^2) [21], more recent reports (PX-171-002) used a 4-week treatment cycle with carfilzomib being given on days 1, 2, 8, 9, 15, and 16 (doses up to 27 mg/m^2, MTD not reached). Carfilzomib was dosed at 20 mg/m^2 on days 1 and 2 with 27 mg/m^2 given thereafter. The rationale for lower dosing on the first 2 days was that carfilzomib was noted to cause acute infusion reactions in some patients on the initial dose [20].

A single-agent phase 2 study of carfilzomib in patients with relapsed myeloma previously treated with bortezomib patients with at least one prior bortezomib-based regimen were enrolled and received carfilzomib 20 mg/m^2 twice weekly on consecutive days [44••]. The best ORR was 17.1 % (1 CR, 1 VGPR, and 4 PR) and clinical benefit response (ORR + minimal response) was 31.4 %. Median duration of response was 10.6 months and median TTP was 4.6 months. Median OS was calculated to be 29.9 months.

In a phase 2 investigation, Lendvai et al. used high-dose single-agent carfilzomib, up to 56 mg/m^2, given over a longer infusion time (30 minutes rather than the usual 10 minutes) [45••]. Preinfusion dexamethasone 8 mg was given to minimize infusion reactions. Dexamethasone 40 mg/week was added to the regimen of all patients who did not show improve or had progressive disease (PD) within the first two cycles. In this study, 78 % of patients were refractory to bortezomib. Overall response after four cycles in bortezomib-refractory patients was 57 %, thus suggesting that higher doses of carfilzomib may be more efficacious. Median PFS was 4.6 months and median OS had not been reached after median follow-up of 9.6 months.

Although there is currently no phase 3 data published on carfilzomib, Hajek et al. recently published the study design and rationale for a randomized, open-label, phase 3 study (PX-171-011) comparing single-agent carfilzomib to corticosteroid treatment with optional cyclophosphamide. This trial is currently ongoing and has finished recruiting [46, 47]. This study and other ongoing phase 3 trials of other carfilzomib-based regimens should help to more clearly delineate the efficacy of carfilzomib [47–49].

Carfilzomib is a well-tolerated drug in most patients with an adverse event profile distinct from bortezomib. Unlike bortezomib, emergent peripheral neuropathy was not common for patients treated with carfilzomib, even in patients with baseline neuropathy at the start of treatment [20–22]. Manifestations of bone marrow suppression (grade ≥3) including anemia (14 %), thrombocytopenia (20 %), neutropenia

(11 %), and lymphopenia (6 %) were noted. Dyspnea, pneumonia, and other infections were also noted and were sometimes severe. Of note, symptoms of congestive heart failure were seen in up to 7 % of patients.

Pomalidomide and Carfilzomib in Combination

Thus far, only one phase 1 trial has reported results of combining carfilzomib and pomalidomide for the treatment of double-refractory MM [50•]. Patients had received a median of six prior lines of therapy. All were refractory to lenalidomide and 11 of 12 patients had a history of bortezomib treatment. MTDs were carfilzomib 20/27 mg/m^2 and pomalidomide 4 mg. Grade≥3 neutropenia and febrile neutropenia occurred in two patients each.

Fifty percent of patients achieved at least PR (2 VGPR, 4 PR). Clinical benefit response was 67 %. While survival was not the primary outcome of interest, 6-month PFS was calculated at 70 % (95 % CI: 37 to 90 %). An expansion cohort of 20 patients (total n=32) was added after the dose escalation phase. Twenty-seven patients were evaluable for response: 2 VGPR, 7 PR, 6 MR, 8 SD, 4 PD. This brought ORR and clinical benefit response down to 33.3 % and 55.6 %, respectively.

Selected Investigational Agents

The treatment landscape of multiple myeloma is rapidly evolving and there are many new agents in current clinical trials that are selective for molecular targets not previously exploited by other drugs. A discussion of some of the more significant emerging therapies is presented here.

Ixazomib

Ixazomib (MLN9708) is the first oral proteasome inhibitor to enter clinical investigation. Phase 1 studies seem to suggest a somewhat low rate of response of<10 % in heavily pretreated myeloma patients (median prior therapies 4 – 6); however, there is a remarkable 88 % overall response rate when combined with lenalidomide and dexamethasone in previously untreated MM [51, 52]. Like carfilzomib, ixazomib does not seem to cause severe peripheral neuropathy. Still, 52 – 63 % of studied patients experienced grade ≥3 adverse events including thrombocytopenia, neutropenia, fatigue and rash [51, 52]..

Panobinostat

Histone deacetylases are enzymes that remove acetyl groups from histones, the structure around which strands of DNA wind. They have become a significant target for cancer therapies as they play a role in DNA transcription, repair, recombination and replication [53, 54]. Panobionstat is a novel pan-deacetylase inhibitor (pan-DACi) [53, 55] and it has been associated with accumulation of cytotoxic misfolded protein aggregates which may lead to MM cell death [56, 57]. It has been evaluated as a single agent [55] as well as in combination with MPT, a well-established regimen for relapsed myeloma [53, 58].

In single-agent use, patients received panobinostat 20 mg three times a week for a 21-day treatment cycle [55]. Of 38 patients studied, 63 % had received prior bortezomib, lenalidomide and thalidomide-based treatments (median of five prior treatment lines). Response rates were modest, with only one patient achieving PR and one achieving MR [53].

Investigation of escalating doses of panobinostat in combination with fixed-dose MPT (melphalan, prednisone, thalidomide) [53] showed better response rates. Seventy-seven and 47 % of patients had received bortezomib and lenalidomide-based prior therapy, respectively. Overall response rate was 38.7 % (12 of 31 patients) with two patients each achieving CR and VGPR [55].

Unfortunately severe adverse effects were frequent in these patients. In both single-agent and combination therapy, patients treated with panobinostat had frequent grade ≥3 neutropenia (71.0 % of patients treated with PAN + MPT) and thrombocytopenia (35.5 %) [53, 55]. Other panobinostat-based combination regimens are currently being investigated.

Elotuzumab

Elotuzumab is a humanized monoclonal IgG1 antibody that targets CS-1, a cell surface glycoprotein that is highly expressed in myeloma cells but minimally expressed in other tissues, and may lead to natural killer cell mediated antibody dependent cellular toxicity [59, 60].

This drug has been examined in several trials in combination with lenalidomide and weekly dexamethasone [60–63]. It was generally well tolerated, with no dose-limiting toxicities observed in phase 1 study [61]. After a median 16.4 months of follow-up, median TTP was not reached for patients in the highest dose category (20 mg/kg).

The efficacy of elotuzumab (10 mg/kg or 20 mg/kg) in combination with lenalidomide and dexamethasone (Elo + Len/Dex) in a moderately pretreated population [60, 62] has been examined in recent phase 2 study. Greater than 90 % of patients (median follow-up 18.1 – 20.8 months) had at least a partial response and lived without progression of disease (PFS) for greater than 2 years. The response was still encouraging when patients who received only one prior therapy were excluded (ORR=78 %, PFS 21.3 months). For comparison, lenalidomide and high dose dexamethasone alone have previously demonstrated an ORR of 61 % and median PFS of 11.1 months in a similar patient population [62].

Notable grade 3 or greater adverse effects mostly included bone marrow suppression (neutropenia, thrombocytopenia, etc.) which occurred in less than 20 % of patients [60, 62]. Infusion reactions were seen in 12 % of patients in one study [62].

A phase 3 trial of Elo + Len/Dex is currently underway and should be completed in 2017 [63]. Interestingly, the 10 mg/kg dosing level has shown the greatest efficacy and this was the dose chosen for this study [60, 62, 63].

Elotuzumab has also been examined in combination with bortezomib [59]. Jakubowiak et al. combined fixed doses of bortezomib (1.3 mg/m^2) with escalating doses of elotuzumab (2.5, 5.0, 10.0, and 20 mg/kg). The maximum tolerated dose was not achieved and the most common grade≥3 toxicities were lymphopenia (25 %), fatigue (14 %), thrombocytopenia, neutropenia, hyperglycemia, pneumonia, and peripheral neuropathy (11 % each). Partial response or better was observed in 48 % of patients.

Other studies with this regimen are currently underway [64].

Daratumumab

Daratumumab is a humanized monoclonal antibody against CD38, which is a cell surface glycoprotein that is highly expressed in multiple myeloma [65, 66]. Daratumumab recently received breakthrough therapy designation from the FDA for highly encouraging early results. In a phase 1 study daratumumab, at doses ranging from 0.005 mg/kg up to 24 mg/kg, was found to induce PR in 42 % of patients with relapsed/refractory multiple myeloma who had been exposed to six prior lines of therapy [67]. Further study of daratumumab, alone and in combination with other agents, will further elucidate the clinical potential of this immunologic approach to myeloma treatment.

Conclusion

The average survival for persons with myeloma has nearly tripled since the use of high-dose chemotherapy with autologous stem cell rescue and the novel agents thalidomide, bortezomib, and lenalidomide became widespread [8]. Yet, even with these advances, the disease remains incurable and patients are left with significant morbidity related to their disease and the adverse effects of treatment. After relapse patients typically have more resistant disease which complicates further treatment. Patients with DRMM are at the greatest risk, with a median survival of less than one year [11••].

The next generation of proteasome inhibitors, carfilzomib and ixazomib, as well as the newest IMiD® pomalidomide, have shown efficacy and tolerability in the treatment of patients with DRMM. These drugs represent an opportunity to improve overall survival in DRMM although the optimal combinations and sequencing of these drugs remain to be determined.

Immunologic therapy with elotuzumab and daratumumab is a novel therapeutic approach that may herald a new revolution in myeloma treatment. These drugs may have a role in augmenting the activity of the novel agents, as effective single-agent therapy (in the case of daratumumab), and as maintenance therapy for persons in the future.

All of the treatment options reviewed above represent new avenues of hope that we may convert myeloma from a uniformly fatal malignancy to a curable disease.

Compliance with Ethics Guidelines

Conflict of Interest J. Meadows: none; T. Mark: Speakers Bureau: Celgene, Millennium, Onyx; Research Funding: Celgene, Onyx; Advisory Board Member: Celgene, Millennium.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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