Sequencing of nontransplant treatments in multiple myeloma patients with active disease

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The approval of several different classes of drugs in recent years has resulted in a dramatic expansion of treatment options for multiple myeloma patients, improving both survival and quality of life. Lenalidomide and bortezomib are now core components of treatment both at time of diagnosis and at relapse. Next-generation immunomodulatory drugs, like pomalidomide, and newer proteasome inhibitors like carfilzomib and ixazomib are available for use at relapse. Drugs with novel mechanisms of action such as the histone deacetylase inhibitor panobinostat and the monoclonal antibodies targeting SLAMF7 (elotuzumab) and CD38 (daratumumab) are significant steps forward. Recent clinical trials describing novel combinations of these drugs have demonstrated unprecedented improvements in efficacy while maintaining tolerability. All of these options provide not only a challenge for choice of therapy, but also the opportunity to aim for increasing depth of response. This chapter will describe an approach on how to sequence and incorporate these therapies, focusing on patients where high-dose melphalan and autologous stem cell transplant are deferred or not applicable.

Learning Objectives

- Understand the shift toward more active combination therapy in newly diagnosed and relapsed multiple myeloma in patients not eligible for autologous stem cell transplant
- Learn about recently approved drugs in multiple myeloma and their role in combination therapy
- Learn the principles of sequencing these therapies

Introduction

The advent of several classes of drugs recently approved in the treatment of multiple myeloma (MM) provides us a unique opportunity to recalibrate our goals of care. Patients with MM are living longer and better due to more effective and better tolerated drug classes: immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs). These drug classes are now integral components of treatment of all stages of MM. Next-generation IMiDs such as pomalidomide and PIs including carfilzomib and ixazomib are all a part of the antimyeloma armamentarium. Drugs with novel mechanisms of action such as the HDAC inhibitor panobinostat and the monoclonal antibodies elotuzumab and daratumumab have further expanded our tool kit. This chapter will discuss the sequencing of these therapies to optimize outcomes for older patients who are typically not a candidate for high-dose therapy with autologous stem cell transplant.

Goal of treatment: depth of response

The goal of treatment upfront is to achieve the deepest response possible, as outcomes correlate with depth of response. This objective is just as important for older and less fit patients, which comprise the majority of newly diagnosed patients, as MM is a disease of older individuals with a median age at diagnosis of 69 years, and a third of patients are ≥75 years.[1] Moreover, patients at the extremes of age (patients ≥80 years) present with more advanced disease, eg, 50% are International Staging System stage III vs 32% in patients ≤65 years ($P < .001$).[2] These findings further emphasize the need for active and effective therapies for these older patients and, at the same time, meet the challenge of balancing the side effects and burden of treatment, which may be more pronounced in this population. In a retrospective analysis of 3 trials evaluating melphalan-based combinations with thalidomide and/or bortezomib, achievement of complete response (CR) was an independent predictor of longer progression-free survival (PFS) and overall survival (OS), regardless of age, including patients over the age of 75.[3] These observations have been extended beyond CR with assessment of minimal residual disease (MRD) through sequencing for clonal rearrangements. In 1 study, among patients who achieved CR (either through transplant or nontransplant regimens), the time to progression was significantly superior for MRD-negative patients (where the frequency of the clone was $<1 \times 10^{-5}$) compared with MRD-positive patients (131 vs 35 months; $P = .0009$).[4]

Newly diagnosed patients

Deep responses are now routinely achievable with combination regimens (Table 1). The RVD (lenalidomide, bortezomib, dexamethasone) regimen set a new standard for efficacy in induction treatment, with an overall response rate (ORR) of 100% in a phase 2 trial in newly diagnosed patients.[5] SWOG S0777, a phase 3 study, validated this triplet combination (VRd) as first-line treatment in patients where autologous stem cell transplant was deferred, demonstrating superior outcomes compared with the standard of

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Table 1. Selected nontransplant trials for newly-diagnosed patients

Reference	Phase	Name of trial	Arm	N	PFS*	HR	ORR	≥VGPR	≥CR
Benboubker et al[64]	3	FIRST	MPT	547	21.2		62%	28%	9%
			Rd 18	541	20.7		73%	43%	14%
			Rd cont.	535	25.5	0.72†	75%	44%	15%
Durie et al[6]	3	SWOG S0777	VRd	264	43	0.712	81.5%	43.5%	15.7%
			Rd	261	30		71.5%	31.8%	8.4%
O'Donnell et al[8]	2	RVD lite	RVd	50			90%‡	60%	25%
Niesvizky et al[13]	3B	UPFRONT	Vd	168	14.7		73%	37%	3%
			VTd	167	15.4		80%	51%	4%
			VMP	167	17.3		70%	41%	4%
Mateos et al[14]	3	GEM2005	VMP	130	34		80%		20%
			VTP	130	25		81%		28%
#NCT02252172	3	MAIA	Rd-dara				Ongoing		
			Rd						
#NCT01850524	3	TOURMALINE-MM2	IRd				Closed to accrual		
			Rd						

d, dexamethasone; dara, daratumumab; FIRST, Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide; GEM, Grupo Español de Mieloma; I, ixazomib; M, melphalan; P, prednisone; R, lenalidomide; T, thalidomide; V, bortezomib; VTP, bortezomib, thalidomide, and prednisone.
*Median PFS in months.
†HR of Rd continuous vs MPT.
‡Response rates are after four cycles of treatment in 40 patients.

lenalidomide and dexamethasone (Rd).[6] VRd resulted in a significant gain in median PFS (43 vs 30 months; $P = .0018$) and OS (75 vs 64 months; $P = .025$).

To increase the accessibility of combination therapy for older patients, modifications in dosing and schedule are key. The International Myeloma Working Group (IMWG) have created a geriatric assessment tool based on age, comorbidities, cognitive condition, and physical condition and identified 3 groups: fit, intermediate, and frail.[7] Frail patients had significantly worse OS, with 3-year OS of 57% vs 84% in fit patients, and experienced more toxicity from treatment, with an incidence of grade 3 or higher nonhematologic adverse events at 12 months of 34% vs 22.2%. O'Donnell et al thus adapted RVD, "RVD lite," to make it more user friendly for older, nontransplant eligible patients in a phase 2 study of 53 patients.[8] The treatment cycle is extended from the standard 21-day schedule to a 35-day schedule, with a reduction in lenalidomide dose from 25 to 15 mg given on days 1 to 21; bortezomib is given weekly at 1.3 mg/m^2 subcutaneously on days 1, 8, 15, and 22; and dexamethasone 20 mg is given on the day of and day after bortezomib. For patients over the age of 75, dexamethasone is given only on the days of bortezomib. This study builds on modifications that have significantly improved the tolerability of treatment over the years, such as giving bortezomib subcutaneously to minimize risk of peripheral neuropathy,[9] as well as giving it weekly.[10] The median age was 72 (range, 65-91 years) on this trial. The ORR with modified RVD was 90% at the end of 4 cycles, with a very good partial response (VGPR) or better of 60%, and the 1-year PFS was 95%. Importantly, adverse events were in keeping with other trials in transplant-ineligible patients. This study therefore demonstrates how to adapt the traditional RVD schedule for the more commonly seen older patient population, with excellent efficacy and tolerability.

Conventionally, choice of treatment reflects a balance between priorities of efficacy vs tolerability, although newer combinations and schedules increasingly allow patients to benefit from the efficacy of treatment without compromising tolerability. For nontransplant eligible patients, the FIRST trial showed that continuous lenalidomide-dexamethasone (Rd) therapy was superior to 18 cycles of melphalan-prednisone-thalidomide (MPT) with longer PFS (25.5 vs 21.2 months; $P < .001$) and was better tolerated with less grade 3 to 4 neutropenia and peripheral neuropathy. The FIRST study thus established continuous Rd as 1 standard treatment of older patients and may be relevant in a subset of patients, especially elderly patients at the extremes of age or the very frail. In a subset analysis of the FIRST trial, over half of patients, 54%, were categorized as "frail" according to the IMWG geriatric assessment, and continuous Rd improved PFS and OS in these frail patients compared with MPT (hazard ratio [HR], 0.79 and 0.8, respectively), although the magnitude was less compared with "fit" patients (HR, 0.56 and 0.52 for PFS and OS, respectively).[11] In the FIRST study, lenalidomide was given at 25 mg with dexamethasone 40 mg weekly. For patients who are frailer or the "very" elderly (eg, patients ≥80 years), we modify the FIRST regimen with a dose reduction in lenalidomide to 15 mg to improve tolerability (dose reductions occurred in 52% of patients treated with continuous Rd in the FIRST study). In our practice, for patients who defer high-dose therapy with stem cell transplant and who are fit, we use the RVD lite regimen as described above by O'Donnell et al.[8]

For patients where lenalidomide is not available, treatment options include bortezomib-based combinations such as bortezomib and dexamethasone, bortezomib with thalidomide and dexamethasone (VTD), or bortezomib with melphalan and prednisone (VMP).[12] The UPFRONT study randomized transplant-ineligible patients to these combinations and found similar PFS and OS across the 3 arms (Table 1).[13] Notably, unlike current practice, bortezomib in this study was given intravenously according to the conventional 21-day schedule in this trial, and peripheral neuropathy was the most common reason for discontinuation. The shorter than expected PFS in these arms (median, 14.7-17.3 months) may reflect a high proportion of patients discontinuing treatment due to adverse events (22-28%) such as peripheral neuropathy, emphasizing the importance of improving the tolerability of treatment to maintain dosing exposure. Similarly, in the phase 3 GEM2005 trial comparing VMP with VTP in older transplant-ineligible patients, there were more serious adverse events (31% vs 15%; $P = .01$) and treatment discontinuations (17% vs 12%; $P = .03$) in the VTP arm than in the VMP arm.[14] An

updated analysis of the trial showed superior OS with VMP compared with VTP (63 vs 43 months; HR, 0.67; $P = .01$), and some of this was attributed to lower dosing exposure for VTP, particularly in patients over the age of 75.[15]

Maintenance therapy

An important shift in myeloma treatment is the movement toward increasing duration of treatment as maintenance therapy following induction treatment. This is best described following high-dose melphalan and autologous stem cell transplant, which showed maintenance lenalidomide improving PFS.[16] Similar gains in PFS were also seen for maintenance lenalidomide in patients who did not undergo high-dose therapy in a landmark analysis of lenalidomide maintenance following induction with melphalan, prednisone, and lenalidomide (26 vs 7 months; $P < .001$).[17] Motivated by these findings along with the benefit shown with continuous therapy in the FIRST trial, our practice is to offer lenalidomide maintenance (eg, 10-15 mg for 21 of 28 days, without dexamethasone) after completion of induction treatment in patients who do not proceed to autologous stem cell transplant.

With longer use of lenalidomide, there is increasing risk for developing a second primary malignancy. This risk appears to be mainly in patients undergoing autologous stem cell transplant or those receiving melphalan-based treatment and was not seen in the lenalidomide arms in the FIRST trial. A meta-analysis of 9 randomized trials found that the cumulative incidence of all secondary malignancies was 6.9% in the lenalidomide arm vs 4.8% in the control arm ($P = .037$).[18] In aggregate, the risk of dying from relapse of MM is higher than the risk of dying of a secondary malignancy, which thus favors the use of lenalidomide maintenance.

Bortezomib may also be used for maintenance. Various schedules have been described including a 21-day cycle of bortezomib every 3 months with prednisone or thalidomide[14]; weekly bortezomib for 4 of 5 weeks[13]; or bortezomib every other week.[19] Thalidomide has also been used for maintenance, although adoption of this has been limited due to cumulative neuropathy, as well as the finding that maintenance thalidomide in high-risk patients was associated with worse survival.[20]

Relapsed disease

Although significant gains have been made with upfront treatment, disease relapse continues to be a central issue in myeloma. A challenge in sequencing myeloma treatment is the diminishing effectiveness of each successive line of treatment, with a shorter period of disease response with each line of therapy.[21] Furthermore, patients who are refractory to newer agents such as lenalidomide and bortezomib have historically had a poor prognosis, with a median event-free survival of 5 months and median OS of 9 months.[22] A better understanding of the molecular architecture of myeloma may help explain the difficulties with relapsed disease. Comprehensive molecular profiling of myeloma samples show multiple heterogeneous clonal populations that evolve with treatment.[23,24] Varying clones may alternate dominance over time, also known as "clonal tiding."[25] Overall, the presence of this striking clonal heterogeneity and clonal evolution with every relapse reinforces the importance of achieving deep responses both upfront and at time of relapse.

The availability of several novel classes of drugs has allowed us to obtain deep responses even in the relapsed setting. Several randomized trials demonstrating the efficacy and tolerability of triplet combinations will be discussed in greater detail below (Table 2). These approaches are relevant to both patients who have had or were ineligible for an autologous stem cell transplant.

Timing of treatment

For patients who have a clinical relapse with symptoms related to disease progression, the decision to treat is relatively straightforward. However, what is challenging is the common clinical scenario for patients with an asymptomatic rise in monoclonal protein following initial treatment. The IMWG provides guidance for the timing of starting the next line of treatment based on the criteria for significant paraprotein relapse in patients who do not have a clinical relapse (Table 3), although there is variation in practice in when to start or change treatment.

Carfilzomib

Carfilzomib is a second-generation PI that received accelerated approved in July 2012 for patients with relapsed disease based on a phase 2 study of carfilzomib as a single agent showing an ORR of 23.7%.[26] In the initial studies, unlike bortezomib, treatment-emergent peripheral neuropathy was uncommon, with grade 3 to 4 neuropathy occurring in 1.1% of patients. However, toxicities unique to carfilzomib included cardiac failure in 7% of patients. Dyspnea was reported in 35% of patients, including 5% experiencing grade 3 dyspnea. In our practice, we found that lengthening the infusion time from the initially described 2 to 10 minutes to, eg, 30 minutes, has decreased the rate of some of these side effects.

The ENDEAVOR trial directly compared carfilzomib and dexamethasone with bortezomib and dexamethasone in patients with relapsed disease after 1 to 3 prior lines of treatment.[27] This phase 3 study showed that median PFS was nearly double with carfilzomib (18.7 vs 9.4 months; $P < .0001$), and this benefit extended to patients who were bortezomib naïve. The dosing of carfilzomib was much higher in this trial (56 mg/m^2), demonstrating a dose response.

Carfilzomib, lenalidomide, and dexamethasone (ASPIRE trial). The ASPIRE trial was a randomized, phase 3 study that examined the combination of carfilzomib with lenalidomide and dexamethasone (KRd) compared with lenalidomide and dexamethasone in relapsed MM.[28] Patients were eligible to participate if they received 1 to 3 prior lines of therapy. Prior lenalidomide and bortezomib treatment was permitted if there was no disease progression on these drugs. Notably, the majority of patients (80.2%) were lenalidomide naïve. Also of note is that the dosing of carfilzomib in ASPIRE (20 mg/m^2 with increase to 36 mg/m^2) was higher than the initial approved dose (20 mg/m^2 with increase to 27 mg/m^2). The ORR was significantly higher in the carfilzomib arm compared with the control arm (87.1% vs 66.7%; $P < .001$), and similarly, the carfilzomib arm had a higher complete response rate (31.8% vs 9.3%). The median PFS was 26.3 vs 17.6 months ($P = .001$). The depth and duration of response in the treatment arm were unprecedented (although the control group also had a high response rate compared with previous trials in relapsed disease), and serious adverse events were uncommon. Overall, this is a pivotal trial as it is the first randomized study to demonstrate the superiority and the tolerability of a PI and IMiD combination in relapsed disease.

Ixazomib

Ixazomib (previously known as MLN9708) is a new, oral boronic acid PI. The TOURMALINE-MM1 study compared the combination

Table 2. Selected phase 3 trials in relapsed disease

Reference	Name of trial	No. prior lines	Arm	N	PFS*	HR	ORR	≥VGPR	≥CR
Dimopoulos et al[27]	ENDEAVOR	1-3	Kd	464	18.7	0.53	77%	54%	13%
			Vd	465	9.4		63%	29%	6%
Moreau et al[29]	TOURMALINE-MM1	1-3	IRd	360	20.6	0.74	78%	48%	12%
			Rd	362	14.7		72%	39%	7%
Lonial et al[42]	ELOQUENT-2	1-3	Elo-Rd	321	19.4	0.7	79%	33%	4%
			Rd	325	14.9		66%	28%	7%
Stewart et al[28]	ASPIRE	1-3	KRd	396	26.3	0.69	87%	70%	32%
			Rd	396	17.6		67%	40%	9%
San Miguel et al[36]	PANORAMA 1	1-3	Pano-Vd	387	11.99	0.63	61%		11%
			Vd	381	8.08		55%		6%
San Miguel et al[30]	NIMBUS (MM-003)	≥2†	Pd	302	4.0	0.48	31%	6%	1%
			D	153	1.9		10%	1%	0%
Palumbo et al[48]	CASTOR	≥1	Vd-dara	251	NE	0.39	82.9%	59.2%	19.2%
			Vd	247	7.2		63.2%	29.1%	9%
Dimopoulos et al[49]	POLLUX	≥1	Rd-dara	286	NE	0.37	93%	76%	43%
			Rd	283	18.4		76%	44%	19%

D, high-dose dexamethasone; d, low-dose dexamethasone; dara, daratumumab; I, ixazomib; K, carfilzomib; NE, not estimable; P, pomalidomide; Pano, panobinostat; R, lenalidomide; V, bortezomib.
*PFS is in months.
†Refractory to prior therapy; ≥2 cycles of bortezomib and lenalidomide, alone or in combination; adequate alkylator treatment (or as part of stem cell transplant).

of ixazomib with lenalidomide and dexamethasone (IRd) vs lenalidomide and dexamethasone (Rd) in a phase 3, double-blind, randomized study of 722 patients with relapsed disease and 1 to 3 prior lines of treatment.[29] The majority of patients (69%) had prior bortezomib treatment, and only 12% had prior lenalidomide treatment. The median PFS was significantly longer in the IRd arm (20.6 vs 14.7 months in the Rd arm), with an HR of 0.74 ($P = .01$), and the ORR was higher with IRd (78% vs 72%; $P = .04$). The toxicity profile between both arms was generally similar, including peripheral neuropathy, although grade 3 to 4 rash occurred in 5% of patients vs 2% in the control arm. Based on these encouraging findings in the TOURMALINE-MM1 study, the US Food and Drug Administration (FDA) approved ixazomib in November 2015 as part of a combination with lenalidomide and dexamethasone in patients with relapsed disease who have received ≥1 prior therapy. This was an important advance as an all-oral triplet combination for relapsed disease. As treatment duration becomes longer (especially given the tolerability and efficacy of treatment), convenience for patients will also become increasingly important, and the availability of a PI as an oral agent may be an important factor.

Pomalidomide

Pomalidomide is a third-generation IMiD that importantly is effective in disease refractory to lenalidomide or bortezomib. MM-003 was a phase 3 study comparing pomalidomide and dexamethasone to high-dose dexamethasone.[30] This study enrolled patients with refractory disease who received ≥2 previous consecutive cycles of bortezomib and lenalidomide, alone or in combination, and who had adequate alkylator treatment (eg, as part of an autologous stem cell transplant). Patients in the trial had received a median of 5 prior lines of treatment. The ORR was significantly higher in the pomalidomide-dexamethasone arm (31% vs 10% in the high-dose dexamethasone arm; $P < .0001$). The median PFS with pomalidomide plus low-dose dexamethasone was 4 vs 1.9 months ($P < .0001$). Based on these findings, pomalidomide with low-dose dexamethasone was approved by the FDA in February 2013 for patients with refractory disease and who have received ≥2 prior therapies including lenalidomide and a PI.

Similar to lenalidomide, myelosuppression is a common characteristic of pomalidomide, with 48% of patients experiencing grade 3 to 4 neutropenia in the MM-003 trial. On the other hand, unlike lenalidomide, dosing of pomalidomide is not as dependent on renal function as lenalidomide, and adverse events such as myalgias (16%) and skin rash (<10%) were seen less frequently with pomalidomide than with lenalidomide.

Although the doublet of pomalidomide and dexamethasone is effective, our practice increasingly has been to combine pomalidomide with a PI to increase depth of response, similar to the rationale behind RVD. The following trials illustrate this approach.

Pomalidomide, bortezomib, and dexamethasone. The MM-005 study evaluated in a phase 1 study the combination of pomalidomide, bortezomib, and dexamethasone (PVD) in patients who had 1 to 4 prior lines of treatment and ≥2 cycles of lenalidomide plus a PI.[31] Patients had to be refractory to lenalidomide but not refractory to bortezomib. Treatment was given on a 21-day cycle on a schedule similar to RVD. The study enrolled 34 patients. There were no dose-limiting toxicities at the maximum planned dose of pomalidomide 4 mg and bortezomib 1.3 mg/m^2. The ORR was 65%, with 2 patients achieving CR. The Mayo Clinic has also evaluated PVD given on a 28-day schedule with weekly bortezomib, with similar findings.[32] An ongoing phase 3 trial, the OPTIMISMM study (#NCT01734928), is testing this combination in relapsed/refractory MM after 1 to 3 prior lines of treatment.

Additional combinations. A phase 1 study of carfilzomib, pomalidomide, and dexamethasone in patients with disease refractory to prior lenalidomide treatment has been reported.[33] A total of 32 patients were enrolled; they had received a median of 6 prior lines of treatment (range, 2-12), and 100% were refractory to lenalidomide and 97% were refractory to bortezomib. The ORR was 50% with a median PFS of 7.2 months, which is notable given that all patients were refractory to lenalidomide and nearly all were refractory to bortezomib. This trial showed that this regimen had

significant activity in a heavily pretreated, double refractory cohort, with a side effect profile typical for an IMiD and PI combination. Similarly, a phase 1/2 study evaluated the all oral combination of pomalidomide, ixazomib, and dexamethasone.[34] Patients who had ≥2 lines of therapy and who were refractory to lenalidomide and PIs were eligible to participate. Pomalidomide 2 to 4 mg was given for 21 of 28 days with ixazomib (2.3-4 mg) on days 1, 8, and 15, with weekly dexamethasone, on a 28-day schedule. The trial enrolled 22 patients with a median of 3 prior lines of treatment. The ORR was 55%, including an ORR of 50% who were dual refractory to the combination of lenalidomide with a PI.

Histone deacetylase inhibitors, a new class of therapy

Histone deacetylase (HDAC) inhibitors such as vorinostat and now panobinostat are an important new class of cancer therapeutics.[35] By increasing the acetylation of histones, HDAC inhibitors modulate the transcriptional profile of cells and affect nuclear events. There are also other non-histone substrates of HDACs in the cytoplasm through which HDAC inhibitors have various effects, such as protein degradation.

PANORAMA 1

PANORAMA 1 was a phase 3 trial comparing the combination of the pan HDAC inhibitor panobinostat with bortezomib and dexamethasone vs bortezomib and dexamethasone in patients with 1 to 3 prior lines of therapy.[36] Importantly, patients with disease refractory to bortezomib were excluded. Panobinostat 20 mg was given orally on days 1, 3, 5, 8, 10, and 12, and bortezomib was given intravenously on a conventional 21-day schedule. This study enrolled 768 patients, and the median PFS was significantly longer in the panobinostat arm (11.99 vs 8.08 months in the control arm; $P < .0001$). However, there was more grade 3 to 4 diarrhea in the panobinostat arm (25%) than in the control arm (8%). Panobinostat was re-evaluated as third-line therapy. In a subgroup analysis of patients who received prior treatment with both bortezomib and an IMiD, the benefit of panobinostat was significantly higher in this population. The median PFS was 10.6 months in the panobinostat arm vs 5.8 months in the control arm, and the ORR was also higher (59% vs. 41%), respectively.[37] The FDA approved panobinostat in February 2015 for patients who received ≥2 prior lines of therapy, including bortezomib and an IMiD.[38] However, there is a boxed warning for diarrhea and cardiac events and arrhythmias, given the association between panobinostat and QT prolongation. The ideal way to partner therapies with panobinostat remains to be determined, given the increasing use of bortezomib subcutaneously weekly, rather than twice per week intravenously as studied in the PANORAMA-1 trial.

Monoclonal antibodies: elotuzumab and daratumumab

Monoclonal antibodies designed against cell surface proteins, cytokines, and now immune checkpoints such as PD1 (eg, pembrolizumab) have transformed oncology care and are routinely used across nearly all tumor types. The last year has seen the approval of 2 monoclonal antibodies in MM: elotuzumab and daratumumab.

Elotuzumab. Elotuzumab is a humanized recombinant monoclonal IgG1 antibody that targets signaling lymphocyte activation molecule (SLAMF7), a cell surface glycoprotein that is highly expressed on both normal and MM plasma cells and is also found to a lesser extent, on lymphocytes such as natural killer (NK) cells.[39] Elotuzumab is proposed to have several modes of action: flagging myeloma cells for recognition by NK cells and enhancement of NK cell activity against MM cells by binding to SLAMF7 found on NK cells.[40]

As a single agent, elotuzumab does not show significant clinical activity,[41] but is effective when given in combination. ELOQUENT-2 is a phase 3 study that compared the combination of elotuzumab with lenalidomide, and dexamethasone to lenalidomide and dexamethasone in patients with relapsed disease.[42] Patients with 1 to 3 prior lines of therapy were eligible. Of note, the trial limited enrollment of patients with prior lenalidomide treatment to 10%, and these patients had to previously demonstrate at least a partial response to lenalidomide. Elotuzumab 10 mg/kg was given weekly for the first 2 cycles and then every other week. Lenalidomide and dexamethasone were given according to a conventional 28-day schedule. This trial enrolled 646 patients with a median of 2 prior lines of therapy. The elotuzumab-containing arm had superior PFS (19.4 vs 14.9 months in the control group; HR, 0.7; $P < .001$), and the ORR was also higher (79% vs 66%; $P < .001$). Adverse effects were similar between both arms, aside from infusion reactions with elotuzumab (10% grade 1-2). Taken together, ELOQUENT-2 is the first study to show the benefit of adding a monoclonal antibody to conventional treatment in MM. In November 2015, the FDA approved elotuzumab in combination with lenalidomide and dexamethasone in patients who have received 1 to 3 prior lines of treatment.

Daratumumab. Daratumumab is a human IgG1κ monoclonal antibody that targets CD38, a transmembrane glycoprotein highly expressed in myeloma cells.[43] Recently it was evaluated in a phase 1/2 study where it demonstrated striking effectiveness as a single agent in heavily pretreated patients.[44] In a cohort of 42 patients receiving 16 mg/kg, where 64% of patients were refractory to both bortezomib and lenalidomide, 17% were refractory to carfilzomib, and 36% were refractory to pomalidomide, the ORR in this group was 36%. The most common adverse events were infusion-related reactions (grade 1-2 in 71% of the cohort). These observations were corroborated by the SIRIUS study in a similar refractory MM population,[45] where the median number of prior therapies was 5, and many of these patients were refractory to the latest agents, including carfilzomib (48% refractory) and pomalidomide (63% refractory). The SIRIUS trial found an overall response of 29.2%. These findings establish daratumumab as the first monoclonal antibody with single-agent activity, particularly in a challenging patient population with refractory disease. Based on these findings, the FDA approved daratumumab in November 2015 in patients who had ≥3 prior lines of treatment. Further enhancing the promise of daratumumab therapy is the benefit seen with adding lenalidomide[46] or pomalidomide[47] in early phase studies, with an ORR of 88% and 58.5%, respectively.

Two phase 3 trials evaluating combinations with daratumumab in earlier stages of relapse were just presented and may potentially change practice. The CASTOR study (MMY3004) randomized patients with relapsed disease after ≥1 prior line of treatment to daratumumab with bortezomib subcutaneously and dexamethasone (on a 21-day schedule) vs bortezomib and dexamethasone.[48] The ORR and PFS were significantly higher in the daratumumab arm (82.9% vs 63.2%; $P < .001$; and not estimable vs 7.2 months; HR, 0.39; $P < .001$). The treatment in the daratumumab arm was tolerated well, with similar discontinuation rates due to adverse events (7.4% vs 9.3%) in the control arm. In addition to the expected infusion-related reactions, myelosuppresion was more common in the daratumumab arm, including grade 3 or higher neutropenia (12.8% vs

Table 3. Definitions of disease relapse

Disease progression
Increase of 25% from lowest response value in any of the following
Serum M-component (absolute increase must be ≥0.5 g/dL) and/or
Urine M-component (absolute increase must be ≥200 mg/24 h) and/or
In patients without measurable serum or urine M protein levels:
Difference between involved and uninvolved free light chain values (absolute increase must be >10 mg/dL)
In patients without measurable serum, urine M protein, or free light chain values, bone marrow plasma cell percentage (absolute percentage must be ≥10%)
Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas
Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder
Significant paraprotein relapse
Doubling of the M-component in 2 consecutive measurements separated ≤2 months
Increase in the absolute level of serum M protein by ≥1 g/dL
Increase in urine M protein by ≥500 mg/24 h
Increase in involved free light chain level by ≥20 mg/dL (plus an abnormal FLC ratio) in 2 consecutive measurements separated by ≤2 months

Adapted from Rajkumar et al.[65]

4.2% arm in the control arm). The POLLUX study (MMY3003) randomized patients with ≥1 prior line of therapy to daratumumab with lenalidomide and dexamethasone vs lenalidomide and dexamethasone.[49] Patients with prior lenalidomide exposure who were not refractory were permitted to enroll, although they comprised a small proportion of the trial population (18%). Similar to the CASTOR study, the daratumumab arm had significantly higher ORR and PFS (93% vs 76%, $P < .0001$; not estimable vs 18.4 months; HR, 0.37; $P < .0001$). Grade 3 or higher neutropenia was 52% in the daratumumab arm vs 37% in the control. Both of these trials showed unprecedented improvement in outcomes with the addition of daratumumab and set the stage for using a daratumumab combination earlier in the course of the disease.

Practical considerations

As is true with the initial treatment, multiple factors play into the choice of treatment of relapsed disease. These include host factors, such as the performance status or frailty of the patient, and disease-specific factors. A patient presenting with extramedullary disease or acute onset of hypercalcemia and renal dysfunction may warrant more aggressive treatment than a patient with a slowly rising monoclonal protein, who may be closely observed. The time of the relapse is also important, as patients who relapse early, for example, less than a year after starting treatment, have a worse prognosis. In 1 series, these patients with early relapse after autologous stem cell transplant or induction with novel therapies had a median OS of 21 months vs not reached ($P < .001$).[50]

The prior treatment history also needs to be carefully reviewed to assess exposure history, as well as toxicity to treatments, such as peripheral neuropathy. The treatment schedule also may play a role, depending on the patient's ability to travel for treatment, which in turn may be influenced by the patient's level of fitness and performance status. Related to the schedule is also convenience, eg, the ability to self-administer ixazomib at home.

Given the efficacy of triplet regimens as demonstrated by, eg, the ASPIRE trial and the growing number of trials with 3 drug regimens, the increasing appreciation of intraclonal heterogeneity, as well as the changing treatment landscape with more patients receiving triplet combinations for induction and lenalidomide maintenance, we are using triplet regimens more often given their greater efficacy. An important consideration is that the recent series of phase 3 trials with carfilzomib (ASPIRE), elotuzumab (ELOQUENT-2), or ixazomib (TOURMALINE-MM1) using lenalidomide and dexamethasone as the backbone restricted enrollment to patients who were not refractory to lenalidomide. ELOQUENT-2 capped enrollment of lenalidomide-exposed patients to 10%, and the large majority of patients in ASPIRE and TOURMALINE-MM1 were lenalidomide naïve (80% and 88%, respectively). This is especially relevant given the increasing use of lenalidomide in newly diagnosed patients, as well as maintenance, and as a result, the findings from these trials may not be directly applicable.

In our practice, for patients who are experiencing an "aggressive" relapse (eg, with extramedullary disease or skeletal-related events) or "early" relapse (eg, <1 year of lenalidomide maintenance following initial therapy with RVD), we prefer to use a pomalidomide-based regimen, such as carfilzomib with pomalidomide and dexamethasone or pomalidomide with bortezomib and dexamethasone. In patients where the relapse occurs after an extended period of maintenance lenalidomide (eg, over a year) or where it is biochemical only, the addition of ixazomib is a consideration. Alternatively, addition of weekly dexamethasone can be a useful alternative as well.

In patients who have had ≥3 lines of treatment, daratumumab becomes a useful option, either as a single agent, or increasingly in our practice, in combination with lenalidomide or pomalidomide. The recent CASTOR and POLLUX trials of daratumumab with bortezomib and dexamethasone or lenalidomide and dexamethasone, respectively, will likely move daratumumab to earlier lines of treatment. Dose modifications may be helpful to expand the applicability of triplet regimens to the older patient population. We use lower doses of, eg, lenalidomide (eg, 10 or 15 mg instead of 25 mg used in the trials) and dexamethasone (eg, 20 mg instead of 40 mg weekly in patients over 75) to improve tolerability and help prevent treatment discontinuations.

Supportive care with growth factors may also be required in a subset of patients, as neutropenia becomes more prevalent in patients with more advanced disease. Further along the sequence, patients may need to be retreated with components of prior regimens over the course of their illness. The Retreatment after Initial Response to Velcade study showed the efficacy of retreatment with bortezomib,[51] and a similar benefit was seen with retreatment with IMiDs.[52]

Table 4. Therapies under development

Class	Target
Proteasome inhibitors	
Marizomib	Proteasome
Oprozomib	Proteasome
HDAC inhibitors	
Ricolinostat (ACY-1215)	HDAC6
ACY-241	HDAC6
Monoclonal antibodies	
AMG224	BCMA
GSK2857916	BCMA
Isatuximab (SAR650984)	CD38
MOR202	CD38
Indatuximab (BT-062)	CD138
Nivolumab	PD1
Pembrolizumab	PD1
Atezolizumab	PD-L1
Durvalumab (MEDI4736)	PD-L1
Small molecule inhibitors and others	
AMG176	MCL-1
CPI-0610	Bromodomain
Dinaciclib	Cyclin-dependent kinases
Melflufen	Alkylating agent
Selinexor	Exportin 1
Vemurafenib	BRAF
Venetoclax	BCL2

Cyclophosphamide-based combinations also have a place in the sequence, with bortezomib[53] or with carfilzomib.[54] In select patients who are experiencing an aggressive, rapid relapse with eg, a high burden of extramedullary disease and where there is an urgent need for cytoreduction, a salvage infusional regimen combining traditional cytotoxic drugs may be appropriate, such as dexamethasone, cyclophosphamide, etoposide, and cisplatin.[55]

Future directions

Newer treatments on the horizon (Table 4) include next-generation PIs oprozomib (which is given orally)[56] and marizomib.[57] Selective inhibition of specific HDACs is under active investigation, including the selective HDAC6 inhibitor ACY-241, which may be better tolerated than pan HDAC inhibition.[58] Checkpoint inhibitors targeting PD1 restore T-cell activity against tumor cells and have emerged as a vital new therapeutic strategy in oncology. Their role in MM is being developed, and 2 recently presented studies showed promising results for pembrolizumab in combination with lenalidomide (Keynote-023)[59] or pomalidomide.[60] Selinexor is a novel, oral small-molecule inhibitor of exportin 1 that is being studied with dexamethasone or in combination with carfilzomib and dexamethasone.[61] In addition to SLAMF7 and CD38, other targets of monoclonal antibody therapy include B-cell maturation antigen (BCMA). Bispecific T-cell engager antibodies are being developed targeting BCMA.[62] Finally, chimeric antigen receptor T-cell therapy has arrived for MM and may potentially shift the paradigm of treatment.[63]

Conclusions

The treatment options for MM patients have expanded remarkably in the last 4 years, with the FDA approval of carfilzomib in July 2012 followed by pomalidomide in February 2013, panobinostat in February 2015, and recently an unprecedented 3 approvals in November 2015: daratumumab, ixazomib, and elotuzumab. These new additions are effective with very manageable side effects, improving survival for patients and enhancing their quality of life. The field is adopting more active and, equally as important, well-tolerated combinations, both at time of diagnosis and at time of relapse. Ongoing studies will better define the sequence and the components of these regimens.

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