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How I treat myeloma with new agents

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At present, multiple classes of agents with distinct mechanisms of action are available for the treatment of patients with multiple myeloma (MM), including alkylators, steroids, immunomodulatory agents (IMiDs), proteasome inhibitors (PIs), histone deacetylase inhibitors (DACIs), and monoclonal antibodies (mAbs). Over the last 5 years, several new agents, such as the third-generation IMiD pomalidomide, the second-generation PIs carfilzomib and ixazomib, the DACI panobinostat, and 2 mAbs, elotuzumab and daratumumab, have been approved, incorporated into clinical guidelines, and have transformed our approach to the treatment of patients. These agents may be part of doublet or triplet combinations, or incorporated into intensive strategies with autologous stem cell transplantation. In this review, I discuss the different treatment options available today for the treatment of MM in frontline and relapse settings. (*Blood*. 2017;130(13):1507-1513)

Introduction

Multiple myeloma (MM) accounts for 1% of all cancers and ~10% of all hematologic malignancies.[1] The treatment of this malignancy has changed dramatically in the past decade with the introduction of new drugs to therapeutic strategies both in frontline and relapse settings. This has led to a significant improvement in median overall survival (OS), which now approaches 6 to 10 years, depending on the age of the patient at diagnosis.[1-3] Over the last 5 years, several new agents, such as the third-generation immunomodulatory agent (IMiD) pomalidomide, the second-generation proteasome inhibitors (PIs) carfilzomib and ixazomib, the histone deacetylase inhibitor (DACI) panobinostat, and 2 monoclonal antibodies (mAbs), elotuzumab and daratumumab, have been approved. These drugs have been incorporated into clinical guidelines and have transformed our approach to the treatment of MM patients.[1,4] With the availability of at least 6 different classes of agents (ie, alkylators, steroids, PIs, IMiDs, DACIs, and mAbs) that can be combined in doublet or triplet regimens, the choice of the optimal strategy at diagnosis and at relapse represents a therapeutic challenge for physicians. There is consensus that treatment should be initiated in all patients with MM according to the updated definition developed by the International Myeloma Working Group in 2014.[5] In this review, I provide an overview of possible treatment choices (listed in Table 1) for both frontline and relapse settings using patient cases, based on my experience with the various classes of agents and based on the latest results from clinical trials.

Case 1: frontline therapy in a 60-year-old patient

Case presentation

A 60-year-old female was diagnosed with immunoglobulin G (IgG)-κ MM in 2014. At that time, she presented with symptomatic myeloma-related bone lesions, and a bone marrow aspirate confirmed the presence of 33% plasma cells. The International Staging System[6] (ISS) score was low (I), and fluorescence in situ hybridization (FISH) analysis did not reveal any adverse cytogenetic factors [no t(4;14) translocation, 17p deletion, or t(14;16) translocation]. The first line of therapy consisted of 4 cycles of bortezomib-cyclophosphamide-dexamethasone (VCD), followed by high-dose melphalan and autologous stem cell transplantation (ASCT). The patient achieved complete remission (CR) after ASCT. Lenalidomide maintenance (10 mg/day continuously) was started 2 months after ASCT. In 2017, the patient was still receiving lenalidomide maintenance, with a sustained CR.

Comments on patient 1

For patients in good clinical condition, induction followed by ASCT is the standard treatment.[1,3,4] Two recent phase III trials comparing front-line ASCT vs ASCT at the time of first relapse showed that progression-free survival (PFS) was improved in the front-line ASCT arm with the use of triplet, novel agent–based induction.[7,8] Nevertheless, especially in the French trial that compared frontline ASCT vs lenalidomide-bortezomib-dexamethasone (RVD) and delayed ASCT, OS was similar in the 2 treatment groups, suggesting that delayed transplantation is feasible and does not have a detrimental effect on OS.[7] There is an ongoing cure vs control debate as to whether patients should receive an aggressive multidrug strategy with the aim of achieving CR, or a sequential disease control approach that emphasizes quality of life (QOL) as well as OS. These objectives are not mutually exclusive. Nevertheless, recent data show that minimal residual disease (MRD)-negative status has a favorable prognostic impact, and it is known that frontline ASCT is associated with the higher rate of MRD negativity.[7,9]

Based on response rates, depth of response, and PFS as surrogate markers for outcome, 3-drug combinations, including bortezomib and dexamethasone, are currently the standard of care as induction therapy prior to ASCT, but only limited data from prospective phase III trials are available to demonstrate that one combination is superior to the other.[1,4,10,11] Four to six courses of induction are recommended before proceeding to stem cell collection.[1] The preferred regimens consist of VCD, RVD, or bortezomib-dexamethasone plus thalidomide or doxorubicin.[1,4] RVD is widely used in the United States [12] and will probably become standard of care in the European Union as soon as it is approved. Carfilzomib-lenalidomide and dexamethasone (KRd) has also been investigated as induction therapy prior to ASCT, and is associated with high response rates and MRD negativity.[13] This triplet

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Table 1. Major treatment regimens in MM

Regimen	Usual dosing schedule
Frontline	
VMP	Bortezomib: 1.3 mg/m^2 IV, days 1, 8, 15, 22; melphalan: 9 mg/m^2 oral, days 1-4; prednisone: 60 mg/m^2 oral, days 1-4; repeated every 35 d
Rd	Lenalidomide: 25 mg oral days 1-21 every 28 d; dexamethasone: 40 mg oral days 1, 8, 15, 22 every 28 d; repeated every 4 wk
MPT	Melphalan: 0.25 mg/kg oral, days 1-4 (use 0.20 mg/kg per day oral, days 1-4 in patients >75 y of age); prednisone: 2 mg/kg oral, days 1-4; thalidomide 100-200 mg oral, days 1-28 (use 100-mg dose in patients >75 y of age); repeated every 6 wk
VCD	Cyclophosphamide: 300 mg/m2 orally on days 1, 8, 15 and 22; bortezomib 1.3 mg/m2 intravenously on days 1, 8, 15, 22; dexamethasone 40 mg orally on days 1, 8, 15, 22; repeated every 4 wk
VTD	Bortezomib: 1.3 mg/m^2 IV, days 1, 8, 15, 22; thalidomide: 100-200 mg oral, days 1-21; dexamethasone: 20 mg on day of and day after bortezomib (or 40 mg on days 1, 8, 15, 22); repeated every 4 wk × 4 cycles as pretransplant induction therapy
VRd	Bortezomib: 1.3 mg/m^2 IV days 1, 8, 15; lenalidomide: 25 mg oral, days 1-14; dexamethasone: 20 mg on day of and day after bortezomib (or 40 mg on days 1, 8, 15, 22); repeated every 3 wk
Relapsed/refractory disease	
KRd	Carfilzomib 20 mg/m2 (cycle 1) and 27 mg/m2 (subsequent cycles) intravenously on days 1, 2, 8, 9, 15, 16; lenalidomide 25 mg oral days 1 to 21; dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22); repeated every 4 wk
VD-Pano	Bortezomib: 1.3 mg/m^2 IV, days 1, 8, 15, 22; dexamethasone: 20 mg on day of and day after bortezomib; panobinostat: 20 mg oral, days 1, 3, 5, wk 1 and 2; repeated every 3 wk (cycles 1-8)
Kd	Carfilzomib: 56 mg/m^2 IV, days 1, 2, 8, 9, 15, 16 (20 mg/m^2 d 1, 2, cycle 1 only); dexamethasone: 20 mg, days 1, 2, 8, 9, 15, 16, 22, 23; 28-d cycles
Rd-Elo	Lenalidomide: 25 mg oral, days 1-21; dexamethasone: 40 mg/wk; elotuzumab: 10 mg/kg IV per week cycle 1 and 2, every other week cycles 3+; repeated every 28 d
IRd	Lenalidomide: 25 mg oral, days 1-21; dexamethasone: oral 40 mg, days 1, 8, 15, 22; ixazomib: 4 mg oral, days 1, 8, 15; repeated every 28 d
DVd	Bortezomib: 1.3 mg/m^2 subcutaneous, days 1, 4, 8, 11 (cycles 1-8); dexamethasone: 20 mg oral, days 1, 2, 4, 5, 8, 9, 11, 12 (cycles 1-8); daratumumab: 16 mg/kg IV every week (cycles 1-3), every 3 wk (cycles 4-8), every 4 wk (cycles 9+); cycles 1-8: repeated every 21 d; cycles 9+: repeated every 28 d
DRd	Lenalidomide: 25 mg oral, days 1-21; dexamethasone: 40 mg oral, every week; daratumumab 16 mg/kg IV every week (cycles 1-2), every other week (cycles 3-6), q4w cycles 7+; cycles: 28 d

q4w, every 4 weeks; Rd-Elo, lenalidomide/dexamethasone/elotuzuman; VD-pano, bortezomib/dexamethasone/panobinostat; VTD, bortezomib/thalidomide/dexamethasone.

regimen, potentially the most active combining a PI and an IMiD, is currently being evaluated as induction therapy in phase III trials prior to ASCT. Other ongoing studies are investigating the impact of adding mAbs, either elotuzumab or daratumumab, to a triplet induction combination to further increase the MRD negativity rate prior to ASCT.

Patient 1 did not receive any consolidation after ASCT, and this is an issue that remains a matter of debate in 2017. Conflicting data from 2 recent randomized trials, not yet fully published, are available. The Stamina study, conducted in the United States, prospectively compared no consolidation following ASCT vs tandem ASCT vs 4 cycles of RVD.[14] Subsequently, patients in all 3 arms of the trial received maintenance therapy. With a short follow-up, on an intent-to-treat basis, there were differences regarding PFS or OS. In contrast, the European Myeloma Network 2 trial evaluated 2 cycles of RVD vs no consolidation, and in this study, the RVD arm was associated with a better PFS rate.[15] The latter trial also included a comparison of single vs tandem ASCT prior to RVD consolidation, and PFS was found to be longer in the group of patients who underwent the tandem ASCT procedure, especially among those with high-risk cytogenetics.

This leads to the issue of a risk-adapted strategy in patients eligible for ASCT. Some experts, especially in the United States, suggest that patients with standard-risk disease can benefit from ASCT either upfront or at a later stage in the disease course.[3] For the treatment of patients with high-risk disease outside clinical trials, many experts, especially those in Europe, recommend tandem stem cell transplantation.[16,17] For this subgroup of patients, KRd is also frequently proposed in the United States.[3] Nevertheless, in 2017, there is no prognostic factor or staging system, such as Revised-ISS or gene-expression profiling, that is routinely used to define a risk-adapted strategy.

Following ASCT, patient 1 received long-term maintenance therapy with lenalidomide. This drug is approved in this setting, and a recent meta-analysis based on individual patient data of >1200 cases demonstrated that lenalidomide maintenance following ASCT is associated with an overall OS benefit of >2 years.[18] We have to recognize that the 3 individual studies included in the meta-analysis were not planned or powered for OS because the primary endpoint and the OS data were not mature at the time of their initial publications. Nevertheless, lenalidomide maintenance is standard practice, although the optimal duration of maintenance remains to be defined. Bortezomib maintenance has also been evaluated in a 2-year study and was associated with a survival benefit over thalidomide maintenance, especially in patients with high-risk disease, but induction therapy was not identical in the 2 arms of this prospective trial, making a comparison of the 2 arms difficult.[16] Ongoing phase III trials are evaluating the role of other novel agents, such as ixazomib or daratumumab, in the maintenance setting following ASCT. Combinations of drugs are also undergoing evaluation: for example, carfilzomib-lenalidomide vs lenalidomide alone in the FORTE study, lenalidomide-dexamethasone-ixazomib vs lenalidomide-dexamethasone in the GEM14 trial, or elotuzumab-lenalidomide-dexamethasone vs lenalidomide-dexamethasone in the GMMG-HD6 trial. For patient 1, outside a clinical trial, my approach is triplet induction therapy followed by ASCT and lenalidomide maintenance.

Case 2: frontline therapy in a 75-year-old patient

Case presentation

A 75-year-old male was diagnosed with IgA-κ myeloma in 2014. The patient presented with myeloma-related anemia and bone lesions. Renal

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function was normal, performance status was good, and no genetic abnormalities were seen using FISH. The monoclonal spike (M-spike) at the onset of therapy was 3.5 g/dL. The patient was treated with 25 mg lenalidomide/day for 21 days out of 28-day cycles plus low-dose dexamethasone at a dose of 40 mg/week (Rd). A partial response was achieved after 3 cycles of Rd, and a very good partial response (VGPR) was achieved after 6 cycles of Rd. However, after the sixth cycle, neutropenia and fatigue required dose reduction. Therefore, the lenalidomide dose was reduced to 15 mg/day, and dexamethasone was reduced to 20 mg/week. Twenty-eight months after the start of therapy, the patient is still in VGPR and therapy with Rd is ongoing.

Comments on patient 2

Rd is one of the standard frontline therapies for patients who are not eligible for ASCT.[1,4,19] According to its approval status, it may be administered until progression of the disease.[19] The final OS analysis of the 3-arm FIRST/MM020 trial that prospectively compared Rd until progression vs melphalan prednisone thalidomide (MPT) vs Rd for 18 cycles showed that PFS was significantly improved in the treatment arm, in which patients received Rd continuously.[19,20] In addition, OS was superior with continuous Rd vs MPT, but was identical in the 2 Rd arms of the study.[20] Therefore, some experts are questioning the role of continuous Rd administration, and instead support a fixed duration (eg, 18 months) of initial treatment to avoid toxicity, save costs, and improve QOL. Patient 2 achieved a VGPR with continuous Rd. The updated analysis of the MM020 trial showed that time-to-next therapy is prolonged in patients who have reached at least a VGPR with continuous Rd, and these patients may benefit most from the long-term administration of this combination.[20] Rd is also feasible in frail patients or patients >75 years of age.[3,21]

In the recently conducted, prospective SWOG0777 trial, which enrolled patients with newly diagnosed MM who were not intended to undergo immediate ASCT, Rd was compared with Rd plus bortezomib (VRd).[22] The addition of bortezomib resulted in significantly improved PFS and OS, and the combination had an acceptable risk-benefit profile. This triplet combination is recommended as upfront therapy for transplant-ineligible patients in several guidelines,[1,4] but it has to be emphasized that only 43% of the patients enrolled in the SWOG0777 trial were >65 years of age, and that all patients received ongoing maintenance treatment with Rd after completion of the induction therapy.

The triplet combination bortezomib-melphalan-prednisone (VMP) is another standard-of-care therapy based on data from the randomized phase III VISTA trial, which showed PFS and OS benefit over melphalan-prednisone.[23] This regimen is mostly used in Europe. VCD is also a valuable option.[1,4]

Patient 2 presented with standard-risk myeloma at diagnosis, and Rd, VRd, VMP, or VCD are all feasible options in this setting. For patients with high-risk disease who are not eligible for ASCT, some experts recommend the use of KRd; however, limited data are available to support this choice.[3] Rd may be suboptimal for this subgroup of patients.[19] Very few patients enrolled in the SWOG0777 trial had a cytogenetic evaluation at diagnosis, and although the median PFS was higher with the triplet VRd combination as compared with Rd, the difference was not statistically significant.[22]

Patient 2 had adequate performance status at diagnosis and was able to stay on treatment for a long period of time. Patients who are not eligible for ASCT represent a very heterogeneous population, and frailty is one of the most important prognostic factors for OS besides ISS and cytogenetics. A geriatric assessment is recommended for all elderly patients at diagnosis and may guide treatment choices.[24] Dose reduction and doublet combinations should be favored for patients considered frail or not fit.

Several important phase III trials are ongoing that may change the landscape of frontline therapy in the near future. Rd is currently being compared with Rd plus elotuzumab, with Rd plus daratumumab, and with Rd plus ixazomib in what may become the first all oral, triplet regimen combining a PI plus an IMiD for the treatment of patients not eligible for ASCT. The triplet combination VMP is also currently being tested vs VMP plus daratumumab.

For patient 2, outside a clinical trial, I would recommend Rd until progression or unacceptable toxicity.

Case 3: relapse treatment in a patient progressing after bortezomib-based induction

Case presentation

A 64-year-old male was diagnosed with symptomatic myeloma in 2014. FISH analysis revealed the presence of t(4;14). The patient received 4 cycles of VCD with the achievement of a VGPR, followed by melphalan 200 mg/m^2 and ASCT. No consolidation therapy and no maintenance therapy were given. Twenty months later, the patient presented with disease progression with anemia and bone pain. Renal function and performance status were good at the time of relapse. The patient was treated with the triplet combination KRd according to the schedule of the ASPIRE study.[25] He responded quickly and achieved a VGPR after the first 2 cycles and CR at cycle 6. He is currently receiving cycle 15 with a sustained CR, without the occurrence of significant toxicity.

Comments on patient 3

The choice of therapy in the relapse setting depends on several parameters, such as age, performance status, comorbidities, the type, efficacy, and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy, the type of relapse (ie, clinical vs biochemical relapse), and cytogenetics.[1,26] In the case of progression after bortezomib induction, as occurred for patient 3, who was lenalidomide naive, Rd is a feasible option.[1,4,26] This doublet combination was standard practice until recently, but it is currently being used less often. Indeed, Rd has been compared with Rd plus another new agent in 4 prospective trials. Elotuzumab (ELOQUENT 2 trial),[27] carfilzomib (KRd, ASPIRE trial),[25] ixazomib (IRd, TOURMALINE 1 trial),[28] and daratumumab (DRd, POLLUX trial)[29] have all been added to Rd and have shown significant improvements in PFS compared with Rd, leading to the approval of these 4 regimens. The choice of the optimal combination out of these 4 agents for a specific patient is not always straightforward.[30] In terms of efficacy, cross-trial comparisons are difficult because of substantial differences in patient populations. However, an evaluation of hazard ratios (HRs) is a reliable method to assess PFS data and can be used to compare the 4 trials (Table 2). For patients who were previously exposed to bortezomib, as is the case for patient 3, the HR is in favor of each of the new triplet combination vs Rd and ranges from 0.37 (POLLUX trial)[29] to 0.73 (TOURMALINE 1 trial)[28] (0.68 in the ELOQUENT 2 trial[27] and 0.70 in the ASPIRE trial[25]). Overall survival data are not yet available. Efficacy has to be balanced with safety. The toxicity profile of each regimen is different, with more cardiac and vascular issues with KRd, infusion-related reactions with mAbs (daratumumab and elotuzumab), and more incidences of rash with IRd. The mAbs are novel drugs in MM that are

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Table 2. Phase III trials in relapsed and/or refractory MM: efficacy

Study (reference)	Regimens	Patients, n	Prior therapies, median, n (range)	Experimental vs placebo arm		
				ORR, %	≥VGPR, %	PFS, mo (HR)
Lenalidomide-based regimens						
ASPIRE (25)	Rd ± carfilzomib	792	2 (1-3)	87 vs 67	70 vs 40	26 vs 18 (0.69)
TOURMALINE-MM1 (28)	Rd ± ixazomib	722	1 (1-3)	78 vs 72	48 vs 39	20.6 vs 14.7 (0.74)
ELOQUENT 2 (27)	Rd ± elotuzumab	646	2 (1-3)	79 vs 66	33 vs 28	19.4 vs 14.9 (0.70)
POLLUX (29)	Rd ± daratumumab	569	1 (1-11)	93 vs 76	76 vs 44	Not reached vs 18.4 (0.37)
Bortezomib-based regimens						
PANORAMA 1 (34)	Vd ± panobinostat	768	1 (1-3)	61 vs 55	Not mentioned	12 vs 8 (0.63)
CASTOR (33)	Vd ± daratumumab	498	2 (1->3)	83 vs 63	59 vs 29	Not reached vs 7.16 (0.39)
Randomized phase II study (35)	Vd ± elotuzumab	150	1 (1-3)	66 vs 63	37 vs 27	9.7 vs 6.9 (0.72)
ENDEAVOR (31)	Kd vs Vd	929	1 (1-3)	77 vs 63	54 vs 29	18.7 vs 9.4 (0.53)

ORR, overall response rate.

attractive partners in combination regimens due to their efficacy and excellent tolerability profile. Improvements in QOL, convenience, and burden to health care providers are also of upmost importance (Table 3). The use of triplet combinations in relapse is particularly important for patients with adverse cytogenetics. Patient 3 has t(4;14), and the HR for this specific subgroup of patients is also in favor of the recently approved triplet combinations vs Rd and ranges from 0.44 (POLLUX trial)[29] to 0.70 (ASPIRE trial)[25] (0.52 in the ELOQUENT 2 trial[27] and 0.64 in the TOURMALINE 1 trial[28]).

For patient 3, outside of a clinical trial, I would recommend DRd.

Case 4: relapse treatment in a patient progressing on IMiD therapy

Case presentation

A 71-year-old female patient presented with anemia and bone pain in 2014 and was diagnosed with MM IgG-λ. FISH did not reveal any adverse cytogenetic abnormalities. In addition, renal function and performance status were adequate. She received Rd as frontline therapy and achieved a partial response following cycle 2, which was associated with clinical improvement. During cycle 22, the M-spike increased from 0.5 to 1.1 g/dL with the reappearance of bone pain. A bone marrow aspirate confirmed the relapse, with 28% plasma cells. The results of another cytogenetic analysis did not differ from those of the initial examination. The patient, who was 73 years old at the time of the relapse, was treated with bortezomib (subcutaneously on days 1-4-8-11 in 21-day cycles) and dexamethasone (20 mg on days 1-2, 4-5, 8-9, and 11-12 of each cycle). She received 6 cycles of therapy and achieved a VGPR. Treatment was discontinued at the end of cycle 6 because of the onset of grade 2 peripheral neuropathy. The patient did not receive any further therapy. Response is ongoing, and grade 2 neuropathy is persisting.

Comments on patient 4

For a patient progressing on Rd as frontline therapy, the logical approach is a switch in the class of agent, or to try to increase the doses of lenalidomide and dexamethasone (in case of a previous dose reduction) and not to add a third agent to Rd. Bortezomib-dexamethasone (Vd) is commonly used in this setting,[26] and VCD may also be used to increase the response rate. No prospective comparison of Vd vs VCD in relapse is available. The toxicity of Vd is well-known, and despite subcutaneous or weekly administration of bortezomib, peripheral neuropathy remains the most important side-effect of this combination.

The phase III randomized ENDEAVOR study prospectively compared Vd vs carfilzomib-dexamethasone (Kd) until progression in the relapse setting.[31] This study, a head-to-head comparison of 2 PIs, demonstrated that both PFS (median: 18.7 vs 9.4 months) and OS (median: 47.6 vs 40 months in the updated analysis presented in 2017) were superior with Kd. The results favor Kd for all subgroups of patients, including first relapse (as is the case in patient 4 described above), prior lenalidomide exposure, and standard-risk cytogenetics. Based on the results of the ENDEAVOR trial and following the approval of this doublet combination, Kd could also have been a feasible option for patient 4. The schedule of Kd, however, is more demanding than that of Vd, with IV administration of carfilzomib at a dose of 56 mg/m^2 on days 1, 2, 8, 9, 15, and 16 of 28-day cycles until progression. The safety profile is also different from that of Vd, with fewer cases of peripheral neuropathy, but higher rates of hypertension, dyspnea, cardiac failure, and acute renal failure. Nevertheless, the rates of treatment discontinuation due to adverse events were identical in the 2 arms of the study. Of note, the phase I/II CHAMPION-1 trial evaluated the more convenient weekly administration of carfilzomib, at a higher dose of 70 mg/m^2 in combination with dexamethasone, and showed promising response rates and PFS that merit additional evaluation.[32]

Recently, Vd was compared with Vd plus daratumumab (DVd) in relapsed MM (CASTOR trial), and the triplet combination was associated with an impressive PFS improvement (HR: 0.39).[33] The benefit of the addition of daratumumab was observed across all subgroups of patients, including those with all the characteristics of patient 4: first relapse, prior IMiD, and >65 years of age. Importantly, the safety profile of the triplet combination is acceptable, and daratumumab was not found to add any significant toxicity to the Vd combination. DVd is now approved and represents another option for patients progressing on Rd.

Other combinations based on Vd are available, but will probably be used less frequently in the future, either because of toxicity (panobinostat-Vd)[34] or paucity of results (elotuzumab-Vd).[35]

For patient 4, outside of a clinical trial, I would propose DVd.

Case 5: treatment of lenalidomide- and bortezomib-refractory disease

Case presentation

A 67-year-old female patient with standard-risk MM was treated with frontline Rd in 2013. The initial response was good (VGPR), but she progressed on therapy during cycle 26 in 2015. The salvage therapy

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Table 3. Phase 3 trials in relapsed and/or refractory MM: convenience

Regimen (reference)	Route of administration	Dosing schedule	Hospital/clinic visit	Administration time
KRd (25)	IV	Cycle 1-12: days 1, 2, 8, 9, 15, and 16 of 28-d cycle. Cycle 13-18: days 1, 2, 15, and 16 of 28-d cycle	2/wk (3 wk on/1 wk off)	>30 min + pretreatment hydration
IRd (28)	PO	Days 1, 8, and 15 of 28-d cycle	Every 4 wk	0 h
Rd + elotuzumab (27)	IV	Days 1, 8, 15, and 22 of 28-d cycle (cycles 1 and 2), then days 1 and 15 (cycle 3+)	1/wk for 8 wk, then every 2 wk	5 h; need premedication
DRd (29)	IV	Days 1, 8, 15m and 22 of 28-d cycle (cycle 1 and 2), days 1 and 15 (cycle 3-6), then every 4 wk thereafter	1/wk for 8 wk, every 2 wk for 16 wk, then every 4 wk	6.5 h for the first infusion and 3.5 h for subsequent infusions; need premedication
Vd + panobinostat (34)	PO (+ bortezomib IV)	Panobinostat: days 1, 3, 4, 8, 10, and 12 of 21-d cycle; bortezomib: days 1, 4, 8, and 11	2/wk (2 wk on/1 wk off)	~1 h for bortezomib
DVd (33)	IV (+ bortezomib SC)	Daratumumab: days 1, 8, and 15 of 21-d cycle (cycle 1-3), every 3 wk (cycle 4-8), then every 4 wk; bortezomib: days 1, 4, 8, and 11	4-5 visits by 21-d cycle	6.5 h for the first infusion and 3.5 h for subsequent infusions; need premedication
Kd (31)	IV	Carfilzomib: days 1, 2, 8, 9, 15, and 16 of 28-d cycle	2/wk (3 wk on/1 wk off)	>30 min + pretreatment hydration

PO, per os; SC, subcutaneous.

consisted of Vd. Following the achievement of partial response (PR) after 2 cycles, which was sustained for 3 cycles, the patient progressed again with bone pain, anemia, and an M-spike of >1.5 g/dL. The patient was then treated with pomalidomide-dexamethasone (pom-dex) in 2016. Response to pom-dex lasted for only 5 months before the disease progressed again. At this point, we initiated daratumumab therapy, which induced a PR. The patient is currently still receiving daratumumab single agent at a dose of 16 mg/kg every 4 weeks, according to the design of the SIRIUS trial,[36] with a sustained response, good tolerance, no bone pain, and normal performance status.

Comments on patient 5

Pomalidomide with low-dose dexamethasone is an approved combination regimen for the treatment of patients with refractory disease, who relapse after at least 2 prior lines of therapy, including lenalidomide and bortezomib. Patient 5 was refractory to both Rd and Vd. In the pivotal MM003 study, in which pom-dex was compared with high-dose dexamethasone, the PFS rate was significantly higher with pom-dex (4 vs 1.9 months), translating into an OS benefit (median 12.7 vs 8.1 months).[37] Recently, Baz et al[38] reported the results of a phase II trial comparing pom-dex with pom-dex plus cyclophosphamide (PCD) in an equivalent patient population and showed that the addition of oral cyclophosphamide (400 mg on day 1, 8, and 15 of a 28-day cycle) to pom-dex was able to increase the PFS from 4.4 to 9.5 months. Patient 5 could have benefitted from the addition of cyclophosphamide, a cheap alkylating agent, to which she had not been exposed previously. In our routine practice, PCD is one of the standard rescue regimens, all oral, effective, and manageable, for those patients who progress after lenalidomide and bortezomib exposure. Patient 5 progressed on pom-dex and subsequently received daratumumab. This mAb, which targets CD38, was approved by the US Food and Drug Administration in 2015 for patients who have received at least 3 prior treatments, based on the results of 2 phase II trials, SIRIUS[36] and GEN501.[39] These trials demonstrated significant single-agent activity of daratumumab in patients who are refractory to all classes of available agents. In the combined analysis of these 2 trials, the median PFS was 3 months overall and 15 months for those reaching PR.[40] Furthermore, for responding patients, OS was found to be prolonged (75% at 2 years). Recently, the data of these 2 trials were used to compare the efficacy of daratumumab monotherapy (148 patients) vs historical controls (658 patients) through an adjusted treatment comparison.[41] This analysis suggests that daratumumab improves OS compared with historical control data in patients with heavily pretreated and highly refractory MM, with an adjusted OS HR of 0.33. Daratumumab, although rarely used as a single agent in the United States, represents a major breakthrough for the treatment of patients with refractory disease. However, the agent will also be used earlier in the course of the disease in combination with PIs and IMiDs, as investigated in the CASTOR and POLLUX trials. The feasibility of retreatment with CD38 mAbs remains to be investigated.

For patient 5, who is refractory to bortezomib and lenalidomide, I would recommend PCD or pom-dex and daratumumab, which was recently approved in the United States.[42]

Final considerations

In the past decade, the treatment of MM has progressed greatly as a result of the introduction of several new active drugs, which have been approved. PFS and OS rates have increased markedly, and recent trials incorporating novel agents and ASCT may lead to a statistical cure fraction of ~15% of patients.[43] In addition, many other new drugs or immune therapies are in advanced stages of investigation, including, for example, isatuximab (CD38 mAb), selinexor (nuclear export inhibitor), venetoclax (oral Bcl2 inhibitor), ricolinostat (oral HDAC6 inhibitor), check-point inhibitors, bispecific T-cell engager antibodies, and chimeric antigen receptor T cells, which will enrich our therapeutic armamentarium.[44,45] Some of these are first-in-class agents and may represent true progress, but a recurrent question is how to design a study to demonstrate the true impact of a specific agent on response, PFS, or OS. For example, the HR for PFS achieved with the DRd combination in relapsed MM in the POLLUX trial (0.37) has set the bar so high that it will be difficult to show the superiority of other combinations over DRd in phase III trials designed for regulatory approvals.

Moreover, MM is a very heterogeneous disease comprised of different genetic entities that differ from each other in evolution, mode

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of presentation, response to therapy, and prognosis.[1,3] Clinical trials seldom target specific genetic subtypes that may benefit most from a new drug. In the future, the use of new agents will probably require the identification of biomarkers to predict response to therapy.[46]

In this article, I have listed numerous possible drug combinations available at diagnosis, in patients with 1 to 3 prior lines of therapy or in very advanced disease. Nevertheless, to date, the optimal strategy for the frontline therapy of MM, the nature and duration of maintenance, or the ideal sequence of therapy at relapse cannot be defined from the available clinical trials. A list of strategic studies that address important questions have been proposed by some investigators to further optimize the management of patients with MM.[46] For example, "Does modifying therapy based on response or MRD detection improve outcome?" Or, "Can limited-duration combination therapy regimens be developed that are as effective as continuous therapy?" Or, "What is the best triplet regimen to use in the most cost-effective way at relapse?" This latter question is of upmost importance because drug access and cost represent the most important challenges for MM patients and physicians worldwide.[47]

The availability of a host of various classes of agents presents both a great opportunity and a great challenge. On the one hand, we are able to achieve unparalleled results regarding improvements in survival, but on the other hand, many issues surrounding the use of these agents remain to be solved. In this review, I have discussed practical patient examples and provided the rationale for the various treatment choices based on our experience and recent data from trials to aid the decision-making process for physicians treating patients with myeloma.

Authorship

Contribution: P.M. wrote the paper.

Conflict-of-interest disclosure: P.M. serves on advisory boards for Takeda, Celgene, Janssen, BMS, Novartis, and Amgen.

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