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REVIEWS

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IN THIS ISSUE

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It takes a village (of therapies) to achieve optimal long-term outcomes for multiple myeloma
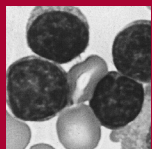
Jan S. Moreb and John R. Wingard

During the last two decades, the treatment of multiple myeloma (MM) has produced significant improvements in overall survival and quality of life. This can be attributed to the use of autologous stem cell transplantation, novel drugs in combination with old drugs, bisphosphonates, improved supportive care, and, importantly, dissemination of knowledge about the disease and treatments through multiple societies and medical centers. Despite the overall improvement, according to National Cancer Institute, there will be an estimated 24,050 new myeloma patients diagnosed (this number keeps going up), and 11,090 deaths from myeloma in 2014. Thus, our work has just begun and more need to be done.

Progress is continuing by adding new drugs to our armamentarium, such as the approval of carfilzomib and pomalidomide in the last 2 years. Looking at the Multiple Myeloma Research Foundation website, there are 13 ongoing clinical trials for newly diagnosed MM, 127 clinical trials for relapsed MM, and 117 trials for refractory MM. According to the NCCN 2.2014 guidelines, 6 different drug combinations are listed for induction therapy in newly diagnosed MM patient with another potential 4 alternate combinations. These promising therapies are great news for multiple myeloma patients. Clearly, there is no curative combination as yet and no one treatment fits all. Thus the challenge is how (and when) to use these resources in order to produce the best outcomes for patients. This is indeed the main theme for the multidisciplinary topic in this issue.

This issue contains highlights of a symposium presented at the 2014 BMT Tandem Meeting in Grapevine, Texas. The panel included myeloma and stem cell transplant experts, as well as nurse practitioner and clinical pharmacist. Dr. Sergio Giralt reviews the tools available for risk adjusted approach to the treatment of MM, and how one can modify the risk effect on disease response and toxicities. Ms. Beth Faiman, Advanced Oncology Nurse Practitioner, focuses on the daily care of MM patients and prevention of serious therapy related complications such as peripheral neuropathy, venous thromboembolism, infections, bone complications, gastrointestinal and renal toxicities. Dr. David Vesole reviews incorporating the newly approved drugs into the treatment of relapsed and refractory myeloma with a look at the new promising drugs on the horizon being tested now in clinical trials. Dr. A. Donald Harvey, Clinical pharmacist, describes drug metabolism and clearance of the major MM medications, focusing on drug metabolism, drug interactions and prevention of drug toxicities, especially when administering drugs together.

Thus, with the range of treatment options currently available, the challenge for clinicians is choosing the appropriate treatment regimen that fits the patient's specific characteristics. Other challenges include timing and length of treatment. With the addition of new drugs, creating new combination therapies, the task of doing that keeps getting more complex and the need for better coordination and monitoring of the treatments increases exponentially, and that is where multidisciplinary approach will be helpful.

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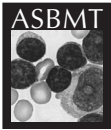
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Symposium Report

Risk-Stratification and Management of Multiple Myeloma: The Multidisciplinary Team Approach in Managing Patients

Adapted from a continuing medical education symposium presented at the 2014 BMT Tandem Meetings on February 26, 2014, in Grapevine, Texas. This publication is supported by educational grants from Celgene and Onyx.

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Program Overview

Multiple myeloma (MM) is a plasma cell malignancy and the second most common hematologic malignancy. The American Cancer Society estimates that in 2013, 22,350 new cases of MM will have been be diagnosed, and 10,710 deaths will occur as a result of the disease in the U.S. While MM was an intractable disease for many years, recent clinical advancements have dramatically changed its therapeutic landscape.

Indeed, due to the introduction of several new effective therapeutic agents, MM is one of the most active and changing fields in clinical oncology. The recent development of novel agents, such as the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide and the proteasome inhibitor bortezomib, have increased response rates and prolonged patient survival.

Additionally, histone deacetylase inhibitors (HDACIs) represent a novel class of drugs targeting enzymes involved in epigenetic regulation of gene expression, which have been evaluated for the treatment of MM. HDACIs appear to be synergistic both in vitro and in vivo when combined with other anti-MM agents, mainly proteasome inhibitors. Despite these advancements, however, MM remains incurable in the majority of patients.

Due to the recent nature of clinical developments, as well as the continued urgency to identify optimal therapeutic approaches for this patient population, it is imperative that oncologists, hematologists, and other healthcare professionals involved in the treatment of MM have access to the most up-to-date information. It is the aim of this accredited educational program to provide access to relevant and topical data in the field of MM.

Learning Objectives

Upon completion of the program, participants should be able to:

- Employ up-to-date strategies to accurately risk-stratify multiple myeloma patients
- Summarize existing and emerging first-line therapies for multiple myeloma
- Describe current treatment approaches for relapsed/refractory disease
- Practice management strategies for multiple myeloma-related bone disease

Target Audience

The program will be oriented to a targeted audience of physicians and medical care professionals specializing in oncology, hematology, immunology, and microbiology.

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Introduction

Multiple myeloma is characterized by widespread molecular, genetic, and clinical heterogeneity that influences treatment response and long-term outcomes. The challenge for clinicians is to identify which treatments are best suited to individual patients. New risk stratification tools can inform the selection of optimal treatment to extend survival and protect quality of life for patients with multiple myeloma. The use of risk-adapted therapy involves multidisciplinary collaboration at each stage of myeloma management, from diagnosis and upfront therapy through relapse. Aggressive management of comorbidities and treatment-emergent adverse events can further improve outcomes via improved treatment adherence. Novel agents and combination regimens are providing clinicians and patients with new opportunities to improve treatment response and long-term disease control.

Risk Stratification in Myeloma

Sergio A. Giralt, MD

Risk stratification has now taken a prominent role in the management of multiple myeloma. The first goal of risk stratification is to identify patients who have worse outcomes with current treatments and to encourage the development of new treatment strategies for them. One example is the patient with poor prognostic features, such as deletion of 17p [del(17p)], that suggest a low likelihood of achieving long-term disease control with the traditional approach of induction, consolidation, and maintenance.

Risk stratification is also used to identify patients for whom current treatments are associated with excellent outcomes. In this subgroup of patients, it is reasonable to evaluate whether the standard of care has approach overtreatment, and to examine ways to reduce the burden of treatment. Between these two extremes, risk stratification can be used to identify patients who are most likely to benefit from current treatment strategies.

In clinical practice, risk-stratification tools can be used to predict a range of clinical outcomes. For instance, some risk algorithms may assess short-term outcomes, such as the likelihood of responding (or not) to treatment. Others risk models may predict the chances of achieving long-term disease control, including a sustained major response and the prevention of end-organ damage. Risk-assessment algorithms may also be used to predict the likelihood of developing serious toxicities from therapy, such as bortezomib-related neuropathy. Such risk-prediction tools can inform clinical decisions, such the use of dose modification to reduce the risk of serious toxicities or the choice to avoid particular therapies altogether. Importantly, risk stratification is a dynamic process that changes during the continuum of the disease.

Mayo Stratification for Myeloma And Risk-adapted Therapy (mSMART)

Over the past 3 decades, there has been increasing recognition that multiple myeloma is
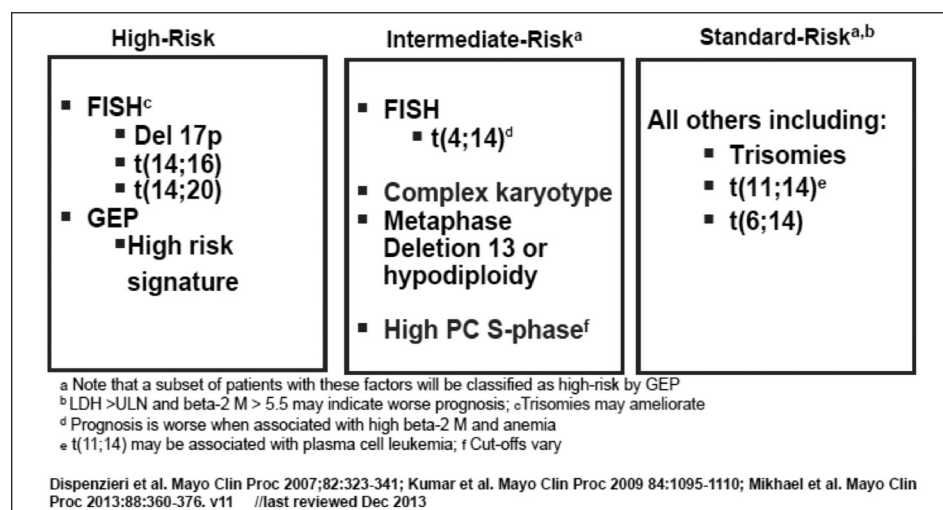

Figure 1. mSMART risk classification of active multiple myeloma [3].

not a single disease entity, but instead consists of a spectrum of disorders characterized by multiple cytogenetic abnormalities. Despite an improved understanding of the heterogeneity of multiple myeloma, however, most patients continue to be treated with the standard paradigm of induction therapy, autologous transplant with high-dose melphalan, and post-transplant maintenance with lenalidomide.

Investigators at the Mayo Clinic in Rochester, Minnesota, introduced the Mayo Stratification for Myeloma And Risk-Adapted Therapy (mSMART) algorithm to differentiate between different levels of risk in patients with multiple myeloma on the basis of cytogenetic, molecular, and clinical features [1-3]. The mSMART algorithm was most recently updated in 2013 (Figure 1) [3]. The mSMART algorithm takes into account genetically determined risk status to guide the selection of treatments that are best suited to patients with standard, intermediate, and high risk (Figure 2).

In addition to cytogenetic criteria, however, clinicians should also consider patient factors, disease stage, and other prognostic features when developing an individualized treatment plan. The mSMART investigators recommend that all patients with newly diagnosed multiple myeloma been seen by a referral center with expertise in myeloma, at least once, to offer input on optimal treatment [3]. Moreover, participation in clinical trials is preferable for all risk categories and should be considered for all patients. Treatment decisions for multiple myeloma may also vary depending on factors such as renal function and the presence or absence of amyloidosis [3].

The clinical rationale for evaluating molecular characteristics in addition to ISS stage is strong. In 2009, investigators from the International Myeloma Working Group (IMWG) described the prognostic implications of cytogenetic abnormalities in a multicenter, international study of 9,897 patients with multiple myeloma [4]. Cytogenetic and/or FISH abnormalities were common. The most frequent abnormalities were del(13) by FISH (n = 3,226); cytogenetic del(13) (n = 2,309); any cytogenetic abnormality (n = 2,295); hypodiploidy (n = 1,713); hyperdiploidy (n = 1,673); and the FISH abnormalities t(4;14) (n = 1,573); del p17 (n = 1,486); t(11;14) (n = 1,683); and t(4;16) (n = 366). At each ISS stage, the presence of any cytogenetic abnormality, t(4;14), del 17p, hypodiploidy, and/or cytogenetic del 13q was associated with worse 4-year OS. By comparison, hyperdiploidy and/or t(11;14) predicted better 4-year survival outcomes.
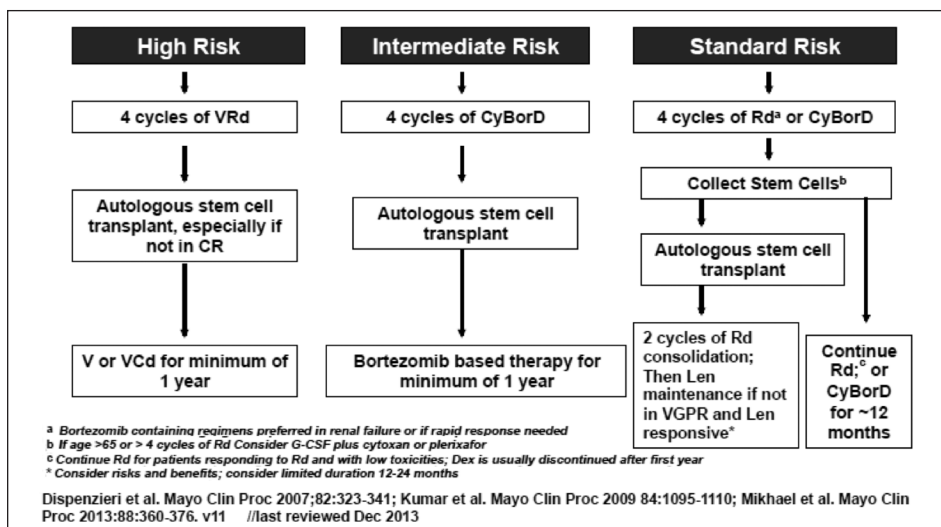
Figure 2. mSMART treatment algorithm for transplant-eligible patients with newly diagnosed multiple myeloma [3].

Can We Modify Risk?

Yes. Several studies suggest that that advent of novel therapies has improved the prognosis for patients with multiple myeloma, even in the presence of poor risk characteristics [5,6]. In a recent meta-analysis, Wang and colleagues demonstrated that induction therapy with bortezomib or thalidomide prior to autologous stem cell transplantation (ASCT) improves outcomes across all subgroups of patients with multiple myeloma, regardless of the presence of cytogenetic abnormalities [5]. The meta-analysis included 3 clinical trials of bortezomib and 2 clinical trials of thalidomide that enrolled a total of 2,316 patients with multiple myeloma. No trials of lenalidomide were included. Compared with control groups that did not include novel agents, the risk ratios for complete response (CR) were 4.25 for bortezomib (95% CI, 2.44-7.41; P < .001) and 1.66 for thalidomide (95% CI, 1.15-2.38; P =.007). The upfront use of novel agents also improved progression-free survival (PFS). The hazard ratios for PFS were 0.73 for bortezomib (95% CI, 0.59-0.89; P = .002) and 0.68 for thalidomide (95% CI, 0.59-0.79; P < .001).

Achieving complete remission (CR) also improves patient prognosis in multiple myeloma. In an analysis of the Intergroupe Francophone du Myelome (IFM) 99 trials, investigators examined the quality of response as a predictor of long-term outcomes [6]. In the risk-adapted trials, treatment was based on the presence of 2 adverse prognostic factors: beta-2 microglobulin > 3 mg/L and del(13) by FISH analysis.

Patients with 0 or 1 adverse prognostic factor(s) were considered to have standard-risk myeloma, while those with 2 adverse prognostic factors had high-risk myeloma. After an induction therapy with 3-4 courses of vincristine, adriamycin, and dexamethasone (VAD), all patients aged < 65 years received a double transplantation. Those with standard-risk multiple myeloma underwent double ASCT followed by randomization to no further treatment, pamidronate, or thalidomide plus pamidronate (IFM 99/02). Patients with high-risk multiple myeloma received a first ASCT after melphalan 200 mg/m2 followed by a reduced-intensity allogeneic SCT if an HLA-identical sibling was available (IFM 99/03), or a second ASCT after melphalan 220 mg/m2 with or without an anti IL-6 antibody (IFM 99/04).

Among those assessed for best response to treatment following double transplant (n = 849), 32% achieved a CR and 22.5% achieved a very good partial response (VGPR). By comparison, 37% had only a partial remission (PR) and 8.5% had stable disease (SD) or progressive disease (PD). Clinical outcomes were significantly better for patients who achieved at least 90% reduction of their M-component. Indeed, the median event-free survival (EFS) was significant better for patients who achieved CR or VGPR than for those who achieved only PR or SD (40 months versus 28 months, respectively; $P = 7.10 \times 10^{-6}$). Five-year OS was also significantly better in the CR+VGPR group compared with the SD+PD group (72% versus 52%, respectively; $P = 6.10 \times 10^{-6}$). Therefore, findings from the combined IFM 99 trials illustrate

the prognostic impact of CR + VGPR in the context of a double transplantation program.

Additional measures of CR also provide valuable prognostic information for patients with multiple myeloma. Hoering and colleagues examined various patterns of CR as a time-dependent variable in the Total Therapy (TT) trials [7]. Achieving a sustained CR over 3 years significantly correlated with improved survival. Conversely, failure to achieve CR (non-CR) and loss of CR independently predicted worse survival in the TT1, TT2, and TT3 trials. In the subgroup of patients with cytogenetic abnormalities associated with poor prognosis, non-CR and loss of CR retained their value as independent predictors of worse survival. These findings underscore the prognostic importance of achieving sustained CR, especially in patients with high-risk multiple myeloma.

Can We Risk Stratify for Treatment Toxicities?

Yes. Several emerging strategies may facilitate the identification of patients at an increased risk for developing treatment toxicities. Pasquini and colleagues described the use of the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) to evaluate the prognostic impact of comorbidities before and after transplantation [8]. The prospective multicenter study included 11,652 patients undergoing ASCT for malignant diseases, including multiple myeloma (49%) and lymphoma (41%). The HCT-CI instrument identified comorbidities in 49% of patients, mostly commonly pulmonary conditions (21%), psychiatric diagnoses (11%), and insulin-dependent diabetes mellitus (8%).

Based on the presence and severity of comorbidities, the total HCT-CI score ranged from 0 to 15. Patients were classified into risk groups based on total scores of 0 (n = 5,851), 1-2 (n = 3,089) and ≥3 (n = 2,645). The HCT-CI risk group significantly correlated with treatment-related mortality (TRM) and OS. The 3-year cumulative incidence of TRM in patients with HCT-CI scores of 0, 1-2 and ≥3 were 5%, 6% and 9%, respectively (P < .001). The corresponding 3-year OS rates for patients with HCT-CI scores of 0, 1-2 and ≥3 were 79%, 73%, and 70%, respectively (P < .001). Additional subgroup analyses found similar correlations between HCT-CI score and 100-day mortality in patient subgroups defined by Karnofsky performance score (KPS < 80 versus KPS ≥ 80, respectively; P < .001) or disease indication (myeloma versus lymphoma; P < .001). In summary, the HCT-CI is a validated tool that can be used to predict TRM and OS outcomes

after autologous HCT based upon the presence of patient comorbidities. In the clinical setting, the HCT-CI tool can be used for risk-stratification when counseling patients about outcomes of HCT.

In current clinical practice, patients with a greater comorbidity burden may not be given high-dose melphalan (200 mg/m2) due to the perceived risk of treatment toxicity. Instead, these patients may be treated with melphalan 140 mg/m2 or 180 mg/m2 as an alternative dosing strategies. However, some evidence suggests that exposure to high levels of melphalan is necessary to improve OS. The Australian Melphalan Pharmacokinetics Trial examined the correlation between melphalan exposure and clinical outcomes in patients with multiple myeloma ASCT (N = 115) [9]. For the pharmacodynamic analysis, plasma melphalan concentrations were measured across 6-11 blood samples per patient after patients were treated with a median melphalan dose of 192 mg/m2 (range, 136-450 mg/m2). Results of the pharmacodynamic analysis showed a 5-fold variation in total melphalan exposure, as measured by area-under-the-concentration-versus-time curve (AUC). The median melphalan

AUC was 12.85 mg/Lh (range, 4.9-24.6 mg/Lh). Patients with higher melphalan exposure were more likely to develop grade 3 or higher mucositis (HR, 1.17; P = .03). Higher melphalan exposure also predicted better clinical outcomes. Patient with melphalan AUC above the median had prolonged time to progression (HR, 0.56; P < .02) and improved OS (HR, 0.35; P = .006), and showed a trend toward improved PFS (HR, 0.64; P = .08) [9]. These findings support targeting a higher melphalan AUC to achieve better clinical outcomes in myeloma patients undergoing ASCT.

Among many common comorbidities, obesity is another source of potential variability in treatment response, toxicity, and clinical outcomes. Vogl and colleagues examined the effects of obesity on clinical outcomes among 1087 patients with multiple myeloma who received high-dose melphalan conditioning, with or without total body irradiation (TBI), followed by ASCT [10]. All patients were classified as normal, overweight, obese, or severely obese on the basis of baseline body mass index (BMI). Overall, there was no correlation between BMI and PFS, OS, or nonrelapse mortality (NRM). However,

in the subgroup of patients who received both melphalan and TBI conditioning, PFS and OS was superior among patients who were obese or severely obese compared with those who were normal or overweight. Although higher BMI was associated with reduced melphalan dosing, there was no interaction between either melphalan or TBI dosing and PFS. These findings suggest that obesity should not exclude patients from consideration for ASCT. In addition, these findings suggest that current melphalan dosing strategies will not impair outcomes for patients who are obese or severely obese.

Summary

Clinicians now have access to a range of risk-stratification tools that can classify patients into different risk groups according to the likelihood of treatment response, long-term disease control, and treatment-related toxicity. The time has come to incorporate these risk-stratification algorithms into clinical decision-making to improve survival, enhance the quality of life, and minimize the burden of treatment for patients with multiple myeloma.

Goals of Induction Therapy in Multiple Myeloma Transplant Candidates and Treatment Associated Side Effects

Beth Faiman PhDc, MSN, APN-BC, AOCN

With the advent of improved risk stratification, as well as better ways of incorporating novel therapies across the treatment spectrum, patients with multiple myeloma are living longer [11]. Over the past 2 decades, the median OS for multiple myeloma has more than doubled, from 36.9 months among those diagnosed between 1995 and 2000 to more than 72 months for those diagnosed between 2006 and 2010 [11,12]. The median OS for patients who are treated with thalidomide, lenalidomide, or bortezomib now exceeds 7.3 years, with many younger patients living longer than 10 years from the time of diagnosis [11].

Despite progress in the development of antimyeloma regimens, however, no standard of care has been defined for the treatment of multiple myeloma at diagnosis or relapse. There is no 'one size fits all' regimen that improves survival for all patients, such as the R-CHOP (rituximab, cyclophosphamide, doxorubicin,

vincristine, prednisone) combination in the lymphoma setting. Clinical trials remain an important option that should be offered to all patients and at all stages, from newly diagnosed disease through post-transplantation.

Goals for Induction Therapy

For the patient with symptomatic, newly diagnosed multiple myeloma, the primary goal of induction therapy is to achieve disease control [13-15]. Ideally, the choices of upfront therapy should not limit future treatment options. To avoid any future limitations on peripheral blood stem cell (PBSC) mobilization, induction therapy should limit the use of melphalan and avoid overtreatment with lenalidomide [13-15].

Additional benchmarks for induction therapy include rapid responses, the depth of response, and the duration of response. Induction therapy can also improve performance status and, with the addition of maintenance therapy, prolong PFS and OS [13-15]. Overall, the aim of treatment in multiple myeloma is to extend survival while maintaining quality of life. Toward this goal, the prevention and management of side effects is critical.

Considerations for Selected Induction Therapies

Patient considerations will dictate the choice of induction therapy that may be most

appropriate. Each agent is associated with side effects that may require special management considerations, which are described in greater detail below (Table 1) [16-18]. The use of recommended adjunctive therapies can minimize the risk of complications related to multiple myeloma and its treatment [19].

Peripheral Neuropathy

Peripheral neuropathy arises from damage to the peripheral nervous system caused by injury, inflammation, or degeneration of peripheral nerve fibers. Approximately 20% of patients with multiple myeloma have peripheral neuropathy at the time of diagnosis, and as many as 75% will experience peripheral neuropathy as a result of myeloma treatment [20]. The risk of treatment-emergent peripheral neuropathy is influenced by the dose, schedule, and combinations of potentially neurotoxic agents.

To date, no effective preventive strategies have been identified. Therefore, it is critically important to assess patients for the presence of neurotoxicity at each treatment [21]. To facilitate early recognition, infusion nurses should be trained to identify the signs and symptoms of neurotoxicity [20]. In addition, patient should be educated about the risk of peripheral neuropathy, and counseled to report any new symptoms [20]. Specific recommendations for dose modification

and treatment discontinuation vary by agent and by the grade and severity of symptoms [20,21].

The differential diagnosis of neuropathy in patients undergoing induction therapy can include treatment-induced neuropathy secondary to bortezomib or thalidomide, as well as symptoms arising from uncontrolled diabetes, steroid-induced hyperglycemia, excessive alcohol use, and/or vitamin B6 or B12 deficiencies [20]. If needed, newer options are available for dose modifications and schedule adjustments [20]. For example, reduction to once weekly bortezomib dosing is recommended for patients who develop grade 2 or 3 peripheral neuropathy [18]. Subcutaneous bortezomib is also an option for patients with newly diagnosed multiple myeloma [22].

Several pharmacologic and non-pharmacologic interventions have been examined to reduce the incidence and severity of peripheral neuropathy. Examples of pharmacologic therapy include duloxetine, gabapentin, and pregabalin. Non-pharmacologic interventions include glutamine, alpha-lipoic acid, and acetyl carnitine [20,21].

Life-Threatening Infections

Infections are a leading cause of death in patients with multiple myeloma. The risk of infection appears to stem from impaired antigenic stimulation and deficient antibody production. The risk of infections is further increased by cytotoxic therapy, transplantation, and steroid use [23]. Educating patients about the signs and symptoms of infection and encouraging prompt reporting are essential for reducing the risk of infection.

Treatment with intravenous immunoglobulin is an effective strategy for reducing the risk of life-threatening infection [19]. Patients who are treated with bortezomib or carfilzomib can benefit from herpes zoster oral prophylaxis [19]. In addition, patients should receive immunization against pneumococcal disease with the pneumococcal conjugate vaccine (PCV13) or pneumococcal polysaccharide vaccine (PPSV23), as well immunization against influenza, in accordance with current CDC guidelines [24,25].

Venous Thromboembolic Events

Multiple myeloma is an intrinsically hypercoagulable disease associated with a higher risk of thromboembolism. Prophylactic anticoagulation is recommended for patients undergoing treatment with thalidomide-based therapy or lenalidomide plus dexamethasone [19]. Research is ongoing to improve risk stratification and expand options for thromboprophylaxis.

Table 1. Considerations for Selected Induction Therapies [16-19]

Side Effect	Thalidomide	Lenalidomide	Bortezomib	Cyclophosphamide (standard dose)	High-dose melphalan, busulfan + cyclophosphamide
Peripheral neuropathy	√		√		√
Deep vein thrombosis	√ More with dex	√ More with dex			
Myelosuppression	√ Neutropenia	√ Neutropenia, thrombocytopenia, anemia	√ Thrombocytopenia	√ Neutropenia, thrombocytopenia, anemia	√ Neutropenia, thrombocytopenia, anemia
Hypotension			√		
Fatigue, weakness	√	√	√	√	√
Sedation	√				
Rash	√	√			√
Viral reactivation of herpes zoster			√		√
Gastrointestinal disturbance	√ Constipation	√ Constipation, diarrhea	√ Nausea and vomiting, diarrhea	√ Nausea and vomiting, diarrhea, constipation, mucositis/stomatitis	√ Nausea, diarrhea, constipation, vomiting, mucositis
Renal/Hepatic		√ Reduce dose for decreased CrCL		√ Hepatic	√ Reduce dose for decreased CrCL

CrCL = creatinine clearance; dex = dexamethasone.

Renal Complications

Renal complications are common in patients with multiple myeloma [26]. At the time of diagnosis, 30% to 40% of patients have elevated serum creatinine levels, indicating early renal dysfunction [27]. Approximately 25% to 50% of patients will have renal impairment during the course of their disease [27]. Furthermore, patients who have light chain (Bence Jones protein) proteinuria can experience renal failure or progress to end-stage renal disease (ESRD). These patients may require dialysis due to light chain cast nephropathy [28].

If not adequately treated and reversed, renal complications can adversely effect survival and quality of life in patients with multiple myeloma [27]. Strategies for managing renal health include appropriate hydration and the avoidance of dehydration, as well as correction of hypercalcemia [19,27]. Specific agents such as NSAIDs and IV contrast media should also be avoided in patients with renal impairment [19]. For patients with diabetes, tight glycemic control is essential to protect the kidneys from damage [27].

For patients with renal insufficiency, bortezomib with high-dose dexamethasone is considered the treatment of choice for multiple myeloma [26]. Alternatives include lenalidomide, thalidomide, pomalidomide, and carfilzomib (in relapsed disease) [26]. Treatment with glucocorticoids may improve renal function in patients with multiple myeloma who develop renal failure [29].

Myelosuppression, Gastrointestinal, and Bone Complications

Myelosuppression is common in patients undergoing treatment with novel therapies, and may include grade 3-4 anemia (8-16%), neutropenia (13-21%), and thrombocytopenia (4-29%) [30]. Because hematologic toxicities are expected side effects of thalidomide, lenalidomide, and bortezomib, patients should be monitored closely and educated about signs and symptoms [30]. Monitoring for myelosuppression should include a complete blood count (CBC) with differential on an ongoing basis. Specific recommendations for the management of myelosuppression vary by agent, but may include the use of growth factor support, dose reductions, and RBC transfusions [30].

Treatment with lenalidomide, thalidomide, and bortezomib can cause serious gastrointestinal side effects in patients with multiple myeloma, including constipation, diarrhea, nausea, and vomiting [31]. Effective management of GI complications is necessary to improve patient adherence to treatment, decrease the risk of psychological impairment such as anxiety and depression, and improve the quality of life of

patients and caregivers [31]. The use of proton pump inhibitors (PPIs) and antiemetic therapy can reduce the risk and severity of nausea and vomiting for some patients. Diarrhea is a side effect of long-term treatment with lenalidomide. Dietary adjustments and increased fluid intake can be effective in managing symptoms. However, antidiarrheal agents should be used with caution. A stool culture for Clostridium difficile may be necessary if infection is suspected [31].

Up to 90% of patients will develop the bony manifestations of myeloma, including diffuse osteopenia and/or osteolytic lesions [32]. In addition, pathologic fractures and other skeletal events can lead to poor circulation, blood clots, muscle wasting, reduced performance status, and poor survival [32]. Therefore, patients should be assessed routinely for bone involvement [33]. Treatment with bisphosphonate therapy can decrease pain and bone-related complications, improve performance status, and preserve quality of life [19]. Therefore, bisphosphonates can be considered for all patients after baseline and ongoing dental examination to identify risk factors for osteonecrosis of the jaw (ONJ), a rare but devastating complication of bisphosphonate therapy [19,33]. Throughout treatment with bisphosphonates, patients should be assessed for proteinuria and ONJ [19,33].

Summary

Effective management of the patient with newly diagnosed multiple myeloma begins with risk-adapted induction therapy that incorporates appropriate novel agents. Patients should also receive recommended prophylaxis against infections, VTE events, myelosuppression, and bone complications, as needed. Patients and caregivers should be educated about what to expect during and after treatment, with guidance to enhance self-management and early reporting of adverse events. Patients should be monitored for side effects with each dose of induction therapy. Effective health maintenance and routine preventive screening are critical to extending survival and protecting quality of life in patients with multiple myeloma. The International Myeloma Foundation, Multiple Myeloma Research Foundation, and Lymphoma & Leukemia Society are excellent resources for additional support to address survivorship concerns.

Current Treatment Approaches for Relapsed/Refractory Multiple Myeloma

David H. Vesole, MD, PhD

Until recently, few options have been available for patients with refractory or relapsed/refractory multiple myeloma who do not respond to treatment with bortezomib and lenalidomide. However, several new and emerging treatment options with novel mechanisms of action are showing potential for the management of these patients (Table 2).

Pomalidomide

The randomized phase II MM-002 trial evaluated pomalidomide alone or in combination with low-dose dexamethasone in patients with relapsed/refractory multiple myeloma (N = 221) [34]. Patients were randomly assigned to treatment with pomalidomide 4 mg on days 1-21 of each 28-day cycle alone (n = 108) or in combination with dexamethasone 40 mg/week (n = 113). Anticoagulants and granulocyte colony-stimulating factor (G-CSF) were started with the first cycle. In addition, erythroid growth factors, bisphosphonates, platelet, and/or red blood cell (RBC) transfusions were allowed as clinically indicated. All patients were treated until disease progression. Those initially assigned to the pomalidomide monotherapy group had the option of adding low-dose dexamethasone in cases of progressive disease or no response after 4 treatment cycles (n = 61). The primary endpoint was PFS.

After a median follow-up of 14.2 months, both ORR and PFS significantly favored treatment with pomalidomide/dexamethasone compared with pomalidomide alone (Table 3). The ORR was 33% with combination therapy and 18% with pomalidomide alone (OR, 2.28; P = .013). The median PFS in the pomalidomide/dexamethasone was 4.2 months, compared with 2.7 months with single-agent pomalidomide (HR, 0.68; P = .003). In a subgroup analysis, refractoriness to prior treatment did not diminish the response to combination therapy. The pomalidomide/dexamethasone combination was effective in patients who were refractory to both lenalidomide and bortezomib, with an ORR of 30% and a median PFS of 3.8 months.

Treatment with pomalidomide and low-dose dexamethasone was generally well tolerated. The rate of pomalidomide discontinuation due to treatment0related adverse events was 3%. The most common adverse event was grade 3-4 neutropenia, which occurred in 41% of patients in the pomalidomide/dexamethasone group and 48% of patients treated with pomalidomide alone. The risk of grade 3-4 febrile neutropenia was low, occurring in 3% and 5% of patients, respectively. There were no reports of grade 3-4 peripheral neuropathy.

Findings from the MM-002 trial support the use of pomalidomide in combination with low-dose dexamethasone in patients with relapsed/refractory multiple myeloma, including patients who have received multiple prior therapies [34]. Together, findings from the MM-002 and MM-003 trials also support the synergy of pomalidomide in combination with low-dose dexamethasone [34,35]. The MM-003 trial examined the combination of pomalidomide (4 mg/day on days 1-21 of each 28-day cycle) and low-dose dexamethasone (40 mg/day on days 1, 8, 15, and 22) compared with high-dose dexamethasone alone (40 mg/day on days 1-4, 9-12, and 17-20) [35]. The pomalidomide/low-dose dexamethasone combination was associated with better PFS than high-dose dexamethasone (4.0 months versus 1.9 months, respectively; HR, 0.50; P < .001). The PFS benefit was consistent across patient subgroups, including those with high-risk cytogenetics such as del(17p) and t(4;14). The pomalidomide/low-dose dexamethasone combination also significantly improved OS compared with high-dose dexamethasone alone (13.1 months versus 8.1 months, respectively; HR, 0.72; P = .009). The most common grade adverse event was grade 3-4 neutropenia, which occurred in 48% of patients in the combination group and 16% of patients treated with high-dose dexamethasone alone.

Carfilzomib

Carfilzomib is a next-generation proteasome inhibitor that has shown antitumor activity in the treatment of relapsed/refractory multiple myeloma. The phase II PX-171-003A1 trial evaluated treatment with single-agent carfilzomib in 257 patients with relapsed/refractory multiple myeloma [36]. The ORR was 23% (n = 61) for all patients, and 3% (n = 21) in the subgroup of patients with unfavorable cytogenetics and FISH prognostic markers (n = 71). The median duration of response was 7.8 months for all patients, and the median OS was 15.6 months.

The phase II PX-171-006 trial examined carfilzomib in combination with lenalidomide and low-dose dexamethasone (CRd) in patients with

Table 2. Classes of Drugs With Anti-Myeloma Activity

Drug Classes	Examples
Steroids	Prednisone, dexamethasone
Immunomodulatory agents	Thalidomide, lenalidomide, pomalidomide
Proteasome inhibitors	Bortezomib, carfilzomib, ixazomib, oprozomib, marizomib
Cytotoxic chemotherapy	Melphalan, cyclophosphamide, PLD, DCEP, BCNU, bendamustine
HDAC inhibitors	Vorinostat, panobinostat, romidepsin, ACY-1215
Signal induction inhibitors	Arry 520, diniciclib, afuresertib, KPT-330
Monoclonal antibodies	Elotuzumab, daratumumab, SAR 650984, indatuximab

BCNU = carmustine; DCEP = dexamethasone, cyclophosphamide, etoposide, and cisplatin; PLD = pegylated liposomal doxorubicin.

Table 3: MM-002 Trial of Pomalidomide Alone or in Combination with Low-Dose Dexamethasone in Relapsed and Refractory Multiple Myeloma [34]

Outcome	Pomalidomide + Low-Dose Dex	Pomalidomide	P Value
Overall population	(n = 113)	(n = 108)	
ORR, %	33	18	.013
Median PFS, months	4.2	2.7	.003
Median OS, months	16.5	13.7	.709
Lenalidomide- and bortezomib-refractory population	(n = 69)	(n = 64)	
ORR, %	30	21	.243
Median PFS, months	3.8	2.2	.150
Median OS, months	16	12	.814

PFS = progression-free survival; ORR = overall response rate; OS = overall survival.

relapsed or progressive multiple myeloma [37]. Patients received up to 12 cycles of CRd on the following schedule of 28-day cycles: carfilzomib 20 mg/m2 on days 1 and 2 of cycle 1 and 27 mg/m2 on days 8, 9, 15, 16, and thereafter; lenalidomide 25 mg days 1 to 21; and dexamethasone 40 mg once weekly. Among 52 patients who received the maximum planned dose and were evaluable for response, the ORR (defined as partial response or better) was 76.9%. Responses were both rapid and durable, occurring with a median time to response of 0.95 months and a median duration of response of 22.1 months. In a subgroup analysis, the ORR was 69.2% in bortezomib-refractory patients (n = 13) and 69.6% in lenalidomide-refractory patients (n = 23). The median PFS for all patients was 15.4 months. The CRd combination had acceptable toxicity, with grade 3-4 hematologic adverse events that included lymphopenia (48.1%), neutropenia (32.7%), anemia (19.2%), thrombocytopenia (19.2%), and leukopenia (11.5%).

On the basis of these promising phase II results, the phase III ASPIRE trial is comparing CRd with Rd in approximately 780 patients with relapsed multiple myeloma and 1-3 prior therapies [38]. The trial has completed accrual and is awaiting results.

Other dosing schedules for IV carfilzomib have also been evaluated. The phase I, dose-escalating CHAMPION-1 trial examined the combination of once-weekly carfilzomib (20-88 mg/m2 on days 1, 8, and 15) plus IV or oral dexamethasone (40 mg on days 1, 8, 15, and 22) in patients with relapsed/refractory multiple myeloma [39]. The ORR was 63% across all dosing cohorts. The most common grade 3-4 adverse events were increased blood creatinine, dyspnea, hyperglycemia, and thrombocytopenia, occurring in 7% of patients each. The maximum tolerated dose (MTD) was once-weekly carfilzomib 70 mg/m2 given over 30 minutes IV plus dexamethasone 40 mg.

Pomalidomide-Based Combination Regimens

At the 2013 American Society of Hematology (ASH) annual meeting, several groups presented preliminary efficacy findings on a range of pomalidomide-based combination regimens relapsed or in relapsed/refractory multiple myeloma (Table 4) [40-42]. The pomalidomide-based combinations are showing deeper and more durable responses than single-agent therapy due to enhanced efficacy and manageable overlapping toxicity.

In a phase I/II trial, Shah and colleagues evaluated the combination of carfilzomib and pomalidomide with dexamethasone (Car-Pom-d) in 79 patients with relapsed/refractory MM [40]. All patients were refractory to previous treatment with lenalidomide and had a median of 5 prior lines of therapy. Following a phase I dose-escalation analysis, in the phase II analysis patients were treated with induction therapy (cycles 1-6) every 28 days as follows:

- Carfilzomib 20 mg/m2 on days 1 and 2 of cycle 1; 27 mg/m2 on days 8, 9, 15, and 16 of cycle 1 and on all days of following cycles
- Dexamethasone 40 mg on days 1, 8, 15, and 22
- Pomalidomide 4 mg on days 1-21

Eligible patients also received maintenance therapy until disease progression. Beginning with cycle 7, patients received carfilzomib 27 mg/m2 on days 1, 2, 15, and 16 of each 28-day cycle; dexamethasone and pomalidomide dosing remain unchanged. All patients also received antiviral therapy administered with treatment, as well as thromboprophyaxis prophylaxis with aspirin 81 mg QD (or low-molecular weight heparin in aspirin-intolerant patients).

The Car-Pom-d combination regimen was associated with high rates of response in this heavily pretreated patient population. The ORR was 70%, including a VGPR or better in 27% patients. In patients with high-risk FISH/cytogenetic status (n = 18), the ORR was 78%. Although 49% of patients had high- or intermediate-risk status at baseline, treatment with Car-Pom-d was associated with prolonged disease control, with a median response duration of 17.7 months. The median PFS was 9.7 months and the median OS was 18 months [40].

The Mayo-PVD and MM-005-PVD trials examined the combination of pomalidomide, bortezomib, and dexamethasone (PVD) in patients with lenalidomide-refractory multiple myeloma (Table 4) [41,42]. The ORRs were 94% and 71%, respectively, demonstrating high levels of activity with pomalidomide-based combination therapy in patients with lenalidomide-refractory disease [41,42].

Next-Generation Proteasome Inhibitors

Until 2012, bortezomib was the only proteasome inhibitor available for the treatment of multiple myeloma. The approval of carfilzomib in 2012 provided a new option for proteasome inhibition [43], although both approved

Table 4. Pomalidomide-Based Combinations in Relapsed/Refractory Multiple Myeloma

Outcomes	Car-Pom-d[40] (N = 79)	Mayo-PVD[41] (N = 16)	MM-005: PVD[42] (N = 22)
Median prior therapies, N (range)	5 (1-12)	3 (1-6)	2 (1-4)
Prior lenalidomide, %	100 (ref)	100 (res/ref)	100 (ref)
Prior bortezomib, %	89	50	100
Efficacy			
ORR, %	70	94	71
≥ VGPR	27	56	38
Median response duration	NR	NR	11 cycles
Median PFS, months	9.7	NR	NR

Car-Pom-d = carfilzomib, pomalidomide, and dexamethasone; NR = not reported; PFS = progression-free survival; ORR = overall response rate; PVD = pomalidomide, bortezomib, and dexamethasone; VGPR = very good partial response.

Table 5. Trials of HDAC Inhibitors in Combination with New Therapies in Relapsed/Refractory Multiple Myeloma

Author/Trial	Combination Regimen	N	Overall Response Rate (%)	
			All patients	Bortezomib-refractory patients
Harrison 2008 [45]	Romidepsin + bortezomib	18	67	
VANTAGE PN095 [46]	Vorinostat + bortezomib	142	18	100
VANTAGE 088 [47]	Vorinostat + bortezomib vs. Bortezomib	317 320	56 41	0
Richardson 2010 [48]	Vorinostat + lenalidomide	30	63	NA
San Miguel 2010 [49]	Panobinostat + bortezomib	47	70	60
PANORAMA 2 [50]	Panobinostat + bortezomib + dexamethasone	55	29	100
PANORAMA 1 [51]	Panobinostat + bortezomib + dexamethasone	768	61	NA

regimens require parenteral administration. [Kumar Abs 1944] The development of oral proteasome inhibitors may expand treatment options and improve the ease of administration for patients with multiple myeloma [43]. At the 2013 ASH annual meeting, investigators provided updates on 2 novel oral proteasome inhibitors, ixazomib citrate and oprozomib [43,44].

Ixazomib citrate is an oral proteasome inhibitor that rapidly hydrolyzes to ixazomib, its biologically active form. A phase II study examined single-agent ixazomib citrate in 32 patients with relapsed MM who were not refractory to bortezomib.[43] All patients received ixazomib 5.5 mg on days 1, 8, and 15 of each 28-day cycle for 2-4 cycles. Dexamethasone 40 mg/week was added for patients who failed to achieve a minimal response (MR) after 2 cycles or a PR after 4 cycles, or for PD at any time during treatment. In total, 19 patients (59%) started dexamethasone, including 16 patients who had not reached the desired response and 3 patients with progression. Five patients had a PR or better to single-agent ixazomib within 4 cycles. Six additional patients who had either an MR (n = 2) or SD (n = 4) achieved a PR after the addition of dexamethasone. Thus, the ORR was 34% (n = 11). The median event-free survival was 12.4 months and the 6-month OS rate was 96%. Additional clinical trials comparing lenalidomide/dexamethasone with or without ixazomib citrate have completed accrual in the upfront and relapsed settings.

Oprozomib is an oral, irreversible, second-generation proteasome inhibitor that is a structural analog of carfilzomib. In a phase I/II study, oprozomib demonstrated promising activity in 57 patients with hematologic malignancies, including MM (n = 37).[44] In the entire study group, 61% of patients had prior exposure to bortezomib, and 54% were refractory or relapsed/refractory to bortezomib. Additional dose-finding phase I trials have examined different dosing schedules for oprozomib in MM, and phase II studies of oprozomib are ongoing. All patients were treated with oprozomib 150 mg/day on days 1, 2, 8, and 9 of a 14-day cycle (2/7 schedule) or days 1-5 of each 14-day cycle (5/14 schedule). The median treatment exposure was 15.3 weeks. Among patients with multiple myeloma, the ORR was 13.3% for the 2/7 dosing schedule and 23.3% for the 5/14 dosing schedule. Overall, the 5/14 doing schedule of oprozomib 150 mg/day represents a promising new therapy for patients with multiple myeloma, including those who are relapsed or relapsed/refractory to bortezomib.

HDAC Inhibition

Several histone deacetylase (HDAC) inhibitors, including romidepsin, vorinostat, and panobinostat, have been evaluated in combination with novel therapies for the treatment of relapsed/refractory multiple myeloma (Table 5) [45-51].

At the 2014 American Society for Clinical Oncology (ASCO) annual meeting, investigators presented results from the phase III PAN-ORAMA 1 trial of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed or relapsed/refractory MM (N = 768) [51]. Patients were randomly assigned to oral panobinostat 20 mg (n = 387) or placebo (n = 381) 3 times per week plus IV bortezomib (1.3 mg/m2 on days 1, 4, 8, and 11) during weeks 1 and 2 of each 21-day cycle for 8 cycles. All patients also received oral dexamethasone 20 mg on the days of and the days after bortezomib treatment. After a median follow-up of 125 weeks, panobinostat delayed disease progression by 3.9 months compared with the placebo group (12.0 months versus 8.1 months, respectively; HR, 0.63; P < .0001). The panobinostat group showed a nonsignificant trend toward an improved ORR compared with placebo (60.7% versus 54.6%, respectively; P = .087), and a significant improvement in CR/near CR compared with placebo (27.6% versus 15.7%, respectively; P = .00006). The OS data were not yet mature, but interim analysis showed a nonsignificant trend toward improved survival with panobinostat plus bortezomib/dexamethasone compared with bortezomib/dexamethasone alone (33.6 months versus 31.4 months; HR, 0.87; 95% CI, 0.69-1.10).

ACY-1215 is a first-in-class selective oral HDAC-6 inhibitor. In 2013, Raje and colleagues reported preliminary findings from a phase I/II trial of ACY-1215 in patients who had prior proteasome inhibitor and/or immunomodulatory agent therapy for multiple myeloma [52]. In the phase Ib dose-escalation phase of the trial, 22 patients were treated with the following combination regimen in 21-day cycles:

- Oral ACY-1215 (40, 80, 160, 240 mg) on days 1-5 and 8-12
- IV bortezomib (1.0, 1.3 mg/m2) on days 1, 4, 8, and 11
- Oral dexamethasone 20 mg on days 1, 2, 4, 5, and 8, 9, 11, 12

ACY-1215 combination therapy was well tolerated in doses up to 240 mg QD (days 1-5, 8-12) and 160 mg BID. Grade 3/4 adverse events were rare and hematologic adverse events were management. The ORR was 25% and the clinical benefit rate (CBR) was 60%, suggesting promising activity in patients with multiple myeloma refractory to bortezomib.

Kinesin Spindle Protein Inhibitors

Kinesin spindle protein (KSP) inhibition is a novel mechanism of action that disrupts the division of myeloma cells.[53] Filanesib (ARRY-520) is a first-in-class KSP inhibitor with preliminary results in multiple myeloma.[53,54] In a phase II study, Lonial and colleagues evaluated treatment with filanesib 1.5 mg/m2 given on days 1 and 2 every 2 weeks, either alone (n = 32) or in combination with dexamethasone 40 mg (n = 55), in patients with relapsed/refractory multiple myeloma.[53] The trial also evaluated the potential role of alpha 1-acid glycoprotein (AAG), which binds to filanesib, as a selection marker for treatment. In the overall study population, the ORR was similar with filanesib alone (15%) or in combination with dexamethasone (16%). However, single-agent filanesib was associated with a longer duration of response than combination therapy (8.6 months vs. 5.1 months), as well as prolonged OS (19.0 months vs. 10.5 months). High pretreatment AAG levels appeared to decrease the therapeutic benefit of filanesib. No patients with high pretreatment levels of AAG responded to therapy, compared with 19-24% of those with low AAG levels. Therefore, low AAG may serve as a biomarker to identify patients who are more likely to respond to treatment with filanesib.

Preliminary phase I results also showed promising activity with filanesib 1.5 mg/m2/day in combination with carfilzomib 27 mg/m2 in relapsed/refractory multiple myeloma (N = 20) [54]. The ORR was 37% and the CBR was 63% in the study population of patients who received prior treatment with lenalidomide and were refractory or intolerant to bortezomib. On the basis of these early findings, a phase II trial of filanesib/carfilzomib is currently underway, and a phase III trial of the filanesib/carfilzomib combination is being planned.[53]

Anti-CD138 Therapy

Indatuximab ravtansine is an investigational antibody-drug conjugate that delivers the cytotoxic agent DM4 specifically to targets CD138-expressing tumor cells. In a phase I/IIa study, Kelly and colleague evaluated the combination of indatuximab, lenalidomide, and dexamethasone in patients with relapsed/refractory multiple myeloma [55]. The phase I dose-escalation portion of the trial identified the dose-limiting toxicities (DLTs) and MTD of indatuximab ravtansine (80, 100, and 120 mg/m²). The MTD was defined as indatuximab 100 mg/m², with anemia and mucositis as the DLTs at higher doses.

In the phase IIa portion of the trial, 37 patients were treated with indatuximab ravtansine on days 1, 8, and 15, lenalidomide 25 mg/day for 21 days, and dexamethasone 40 mg/day on days 1, 8, 15, and 22 every 28 days [55]. Of 15 evaluable patients, 100% achieved SD or better, including CR (n = 2), VGPR (n = 4), and PR (n = 5). The ORR is 73% for the overall study population, 75% for patients who were refractory to lenalidomide and dexamethasone (n = 8), and 89% for patients treated at the MTD (n = 9).

Anti-CS1 Therapy

Elotuzumab is a monoclonal antibody directed against the cell surface glycoprotein CS1, which is highly expressed on tumor cells in the vast majority of patients (>95%) with multiple myeloma. The triplet combination of elotuzumab, lenalidomide, and low-dose dexamethasone is associated with a very high response rate in patients with relapsed/refractory multiple myeloma [56]. In a phase II study, 73 patients with lenalidomide-naïve relapsed/refractory multiple myeloma were treated with elotuzumab 10 or 20 mg/kg IV on days 1, 8, 15, and 22 every 28 days for cycles 1-2, and on days 1 and 15 of subsequent cycles. All patients also received lenalidomide 25 mg mg on days 1-21 and oral dexamethasone 40 mg weekly. The ORR was 92% for patients in the elotuzumab 10 mg/kg group (n = 36) and 76% for those in the elotuzumab 20 mg/kg group (n = 37), for a total ORR of 84% when elotuzumab was used in combination with lenalidomide/dexamethasone. In addition, the ORR in the elotuzumab 10 mg/kg group was 100% for patients who received only 1 prior line of therapy, suggesting a role for elotuzumab in combination with lenalidomide/dexamethosone earlier in the course of multiple myeloma treatment. The median PFS was 26.9 months in the elotuzumab 10 mg/kg group and 18.6 months in the elotuzumab 20 mg/kg group. Treatment was well tolerated, grade 1/2 infusion reactions the most common adverse events associated with elotuzumab.

Phase 3 clinical trials of elotuzumab 10 mg/kg in combination with lenalidomide and low-dose dexamethasone are completed and awaiting results relapsed/refractory MM (ELOQUENT2) and in the front-line multiple myeloma setting (ELOQUENT1) [56].

Anti-CD38 Antibodies

CD38 is a transmembrane glycoprotein that is expressed with high receptor density on 80-100% of multiple myeloma cells, making it a promising therapeutic target. Anti-CD38 monoclonal antibodies mediate the eradication of CD38-expressing tumor cells via antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis [Martin 2013 284]. Two monoclonal antibodies that target CD38, daratumumab and SAR650984, have recently been evaluated in relapsed/refractory multiple myeloma.[57-59]

In a phase I study, daratumumab was the first monoclonal antibody to show single-agent antitumor activity in MM, with 67% of patients showing a minimal response (MR) or better [57]. Based on these findings, a phase I/II study was conducted to examine daratumumab in combination with lenalidomide and dexamethasone [58]. The combination was associated with a dose-dependent reduction in paraprotein and bone marrow clearance of myeloma cells. This activity corresponded with response, yielding a PR or better in 8 of 11 evaluable patients (72%). The median time to PR or better was 4.1 weeks. The safety analysis showed a temporary dose-dependent decrease in peripheral blood natural killer cells, but no significant platelet or hemoglobin changes. Overall, treatment was well tolerated, with neutropenia (42%), gastrointestinal (33-42%), and musculoskeletal symptoms (25%) among the most frequently reported adverse events.

Another phase I dose-escalation study examined single-agent SAR650984 in patients with heavily pretreated, CD38-positive hematologic malignancies [59]. Of 39 patients, 34 (87%) had multiple myeloma and had received a median of 6 prior lines of therapy. Treatment doses ranged from 0.0001 mg/kg to 20 mg/kg given either weekly or every 2 weeks. The ORR was 25% for all patients who received single-agent SAR650984 at a dose of 1 mg/kg or greater, and 31% for those who received at least 10 mg/kg. The corresponding CBR was 33% and 38%, respectively, and clinical response appeared to correlate with clearance of plasma cells from the bone marrow. The median time to initial response was 6.1 weeks, and the median duration of response was 5.0 months. The safely analysis found a favorable safety profile across the hematologic malignancies. Infusion reactions were generally mild or moderate, and when given with standard prophylaxis, were observed only with the first dose.
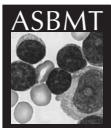
Summary

New agents and novel combination regimens are changing the management of relapsed/refractory multiple myeloma. Pomalidomide-based combination regimens, including pomalidomide combined with carfilzomib/dexamethasone and bortezomib/dexamethasone, showed strong antitumor activity with favorable safety profiles. Ixazomib, an oral protease inhibitor, showed activity used alone as well as in combination with dexamethasone. The oral HDAC-6 inhibitor ACY-1215 showed clinical benefit in patients who were refractory to protease inhibitors and/or immunomodulatory drugs. The KSP inhibitor ARRY-520 (filanesib) showed higher overall survival in patients with lower pretreated AAG levels.

Among antibody-based therapy, the monoclonal antibody daratumumab was well tolerated in combination with lenalidomide and dexamethasone. The CD38 monoclonal antibody SAR650984 showed single-agent clinical responses that correlated with bone marrow plasma cell clearance. The antibody-drug conjugate indatuximab ravtansine, in combination with lenalidomide and low-dose dexamethasone, yielded high levels of response, particularly in patients with few prior therapies. Many novel agents with diverse mechanisms of action have completed phase III trials in combination with lenalidomide/dexamethasone in the relapsed/refractory setting. After demonstrating effective antitumor activity in relapsed/refractory MM, these agents may be incorporated into upfront combination therapies to evaluate their potential efficacy earlier in the disease course. Moreover, based on preliminary findings of single-agent activity, some of the novel monoclonal antibodies (eg, daratumumab and SAR650984) may also demonstrate potential roles in the management of smoldering myeloma, as maintenance therapy after induction, and even as components of transplant regimens.

Practice Management Strategies for Dosing and Drug Administration in Multiple Myeloma

R. Donald Harvey, PharmD, FCCP, BCOP

With the availability of multiple novel therapies for the treatment of multiple myeloma, clinicians and patients have unprecedented options for developing an individualized treatment plan. Multiple patient-specific factors can influence the choice of treatment, and include comorbidities such as diabetes, neuropathy, renal dysfunction, and a history of venous thromboembolism (VTE) or cardiovascular events. A patient's eligibility for transplant will also influence the selection of upfront anti-myeloma therapy. Practical issues such as the patient's distance from the treatment center and access to reliable transportation can affect the treatment plan. The costs and copays for oral medications can also be a barrier to adherence.

Several disease-specific variables should also be considered when selecting optimal anti-myeloma therapy. For instance, patients with relapsed/refractory disease have an increased risk for adverse events such as cytopenia and erosion of performance status. The pace of disease progression may also influence the risk of adverse events and the selection of treatment. Drug-specific variables, such as the requirements for administration (e.g., food effects, timing of dosing), route of elimination, and tolerability profile can also impact treatment choice. These considerations are discussed for each agent in more detail below.

Melphalan

Treatment with melphalan should be avoided in patients who are potential candidates for transplantation. Administration can be cumbersome for some patients, as melphalan is available only as 2-mg tablets. For an 80-kg patient, the recommended dose of 0.25 mg/kg translates to 10 tablets per dose. Melphalan tablets must be refrigerated before use.

The oral bioavailability of melphalan is incomplete and highly variable, ranging from 25% to 89%. Moreover, the bioavailability is reduced when given with food. Therefore, melphalan should be given on an empty stomach.

Melphalan undergoes renal clearance and requires dose reduction in patients with renal insufficiency. It should be given at 75% of the standard dose for patients with creatinine clearance (CrCL) 10-50 mL/min, and at 50% of the standard dose for those with CrCL < 10 mL/min [60].

Thalidomide

The most common adverse events associated with thalidomide are constipation, sedation, neuropathy, and thromboembolism (when used in combination with dexamethasone). Thalidomide should be given on an empty stomach in the evening to minimize sedation during the day. Thalidomide capsules should remain in their packaging until ingested. Because thalidomide undergoes hepatic clearance, no dose reduction is necessary in patients with renal insufficiency [19].

Lenalidomide

Exposure to lenalidomide should be limited prior to transplantation due to concerns of potential impact on future stem cell collection [19]. The most common adverse events associated with lenalidomide are neutropenia, thrombocytopenia, rash, and, when used in combination with dexamethasone, thromboembolism [19].

Myeloma patients with renal insufficiency have a 66% to 75% decrease in lenalidomide clearance, resulting in 1.5-times greater exposure than patients with normal renal function [16, 61]. Therefore, lenalidomide dose adjustments should be considered for patients with renal insufficiency. For patients with CrCL 30-60 mL/min, lenalidomide 10 mg daily is recommended. This represents 40% of the standard recommended starting dose. For patients with severe renal impairment (CrCL < 30 mL/min), the recommended dose is lenalidomide 15 mg every 48 hours. Patients on dialysis should be treated with lenalidomide 15 mg three times per week [61].

Pomalidomide

Pomalidomide should be given on an empty stomach, with the capsules remaining in their packaging until the time of ingestion. Pomalidomide undergoes hepatic clearance and is a substrate for CYP1A2, CYP3A, and p-glycoprotein. Given that smoking induces CYP1A2, smoking may reduce pomalidomide exposure. The most common adverse events associated with pomalidomide are cytopenias and dizziness. Thromboembolism is also a risk when it is used in combination with dexamethasone.

Bortezomib

The subcutaneous route of bortezomib administration decreases the risk of peripheral neuropathy, and therefore should be considered for the majority of patients, particularly those with pre-existing neuropathy. Rotating the abdominal and thigh injection sites can

reduce the risk of injection-site adverse events. Diluting the bortezomib solution from 2.5 mg/mL to 1 mg/mL also reduces the risk of local injection-site reactions [18].

Bortezomib undergoes hepatic clearance, meaning there is no requirement for dose reduction in patients with renal insufficiency. However, bortezomib is a substrate for CYP3A4, suggesting the need for close monitoring for patients undergoing concomitant treatment with strong CYP3A4 inhibitors or inducers[18].

Common adverse events associated with bortezomib include thrombocytopenia and neuropathy. Bortezomib is also associated with increased susceptibility to herpes infections. Therefore, prophylaxis for herpes zoster infections (eg, acyclovir 400 mg PO BID) should be considered [19].

Carfilzomib

The recommended dosing schedule for carfilzomib is 20 mg/m2 over 2-10 minutes on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle of induction therapy, followed by carfilzomib 27 mg/m2 daily for subsequent cycles. Extending the infusion time up to 30 minutes may reduce the risk of infusion-related side effects. Premedication with dexamethasone 4 mg is recommended, as well as pre- and posthydration with 250-500 mL normal saline. The maximum body surface area (BSA) to be used for dose calculations is 2.2 m2 for all patients.

Carfilzomib does not require dose reduction in renal insufficiency due to hepatic clearance. The most common adverse events are fever and cytopenia. Due to an increased risk of infection, prophylaxis for herpes zoster infections is also recommended [19].

Treatment Considerations for End-Organ Dysfunction

To maintain the optimal balance between the safety and efficacy of treatment, patients with renal or hepatic dysfunction may require modifications to standard dosing for anti-myeloma agents (Table 6).

Renal dysfunction is a common complication in patients with myeloma. The first step in patient management is to establish the etiology of renal insufficiency. For example, in contrast to established renal disease secondary to uncontrolled hypertension, myeloma-related renal insufficiency may be reversible with appropriate treatment.

Anti-myeloma interventions should be selected with the goal of optimizing renal function. Dexamethasone is the backbone of many anti-myeloma regimens in patients with newly diagnosed multiple myeloma. Dexamethasone has been shown to rapidly reduce light-chain formation. Reversal of acute paraprotein-induced renal failure has been observed in up to 50% of myeloma patients who are treated with bortezomib-based regimens [62]. Combination therapy with bortezomib, thalidomide, and dexamethasone (BTD) also reduces the risk of renal failure. [63].

Dose-adjusted lenalidomide is another option for anti-myeloma treatment in patients with renal disease. In an analysis of the Eastern Cooperative Group (ECOG) E4A03 study, renal function improved among patients treated with lenalidomide and dexamethasone [64]. Following treatment initiation, the mean serum creatinine (SCr) level improved by 0.23 mg/dL in 81% of patients. In addition, the mean Modification of Diet in Renal Disease (MDRD) CrCL level improved by 24.3 mL/min in 59% of patients. Across 4 cycles of therapy, 44% of patients required dose modification of lenalidomide [64]. Additional options for treatment in patients with renal disease include cyclophosphamide, carfilzomib, and pomalidomide, although long-term outcomes and rates of renal improvement are not well described.

For patients with advanced kidney disease, it is important to consider that renal dysfunction is not a contraindication to ASCT. Patients on dialysis can undergo transplantation safely and effectively. Indeed, clinicians are becoming more comfortable treating myeloma patients with advanced renal failure. Findings from a recent case series demonstrated the feasibility of treatment with melphalan 140 mg/m2 and ASCT in myeloma patients with a single kidney [65].
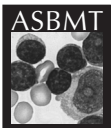
The presence of renal dysfunction may also influence the selection and use of supportive therapy. Bisphosphonates are recommended for all patients with myeloma who have signs of bony involvement, including osteopenia, lytic bone destruction, and other skeletal events [66]. However, dose adjustments are necessary for patients with baseline renal impairment. The standard dose of zoledronic acid is 4 mg delivered over at least 15 min every 3-4 weeks. The recommended modified dosing for zoledronic acid is 3.5 mg for CrCL 50-60 mL/min; 3.3 mg for CrCL 40-50 mL/min; and 3.0 mg for CrCL 30-40 mL/min [66]. No dosing modifications are necessary for pamidronate for patients with CrCL 30-60 mL/min, although pamidronate 60 mg IV over 4-6 hours is recommended for patients with CrCL < 30 mL/min [66].

Patients with myeloma-related hepatic dysfunction can be treated effectively with dose-adjusted bortezomib [67]. Wilson and colleagues recently evaluated the administration of bortezomib in patents with severe hyperbilirubinemia [67]. The findings confirmed the safety and feasibility of treatment with bortezomib 0.7 mg/m2 for cycle 1, followed by dose escalation to 1 mg/m2 or dose reduction to 0.5 mg/m2 based on patient tolerance, for patients with moderate to severe hepatic impairment [67].
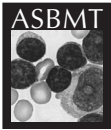
Summary

With the range of treatment options currently available, the challenge for clinicians and patients is determining which treatment regimen is the best fit for the patient's specific characteristics. Each anti-myeloma agent has potential benefits and limitations that must be carefully considered. For patients with renal or hepatic dysfunction, dosing modifications may be necessary to balance the safety and efficacy of treatment. The selection of an individualized treatment regimen that incorporates novel therapies can help patients with multiple myeloma achieve the optimal treatment goal of extended survival.

Table 6. Dose Modifications for End-Organ Dysfunction in Multiple Myeloma

Drug	Primary route of clearance	Recommendations for dosage modification
Melphalan	Hydrolysis; partially renal	Reduce dose in HSCT conditioning to 140 mg/m2
Thalidomide	Hepatic	None
Lenalidomide	Renal	Adjust dose with CrCL < 60 mL/min
Pomalidomide	Hepatic	Avoid with serum creatinine > 3 mg/dL (ongoing studies in renal dysfunction)
Bortezomib	Hepatic	Reduce for elevated bilirubin
Carfilzomib	Peptidase cleavage and epoxide hydrolysis	None
Bisphosphonates	Renal	Reduce in patients with renal insufficiency

CrCL = creatinine clearance; HSCT = hematopoietic stem cell transplantation.

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Release Date:	**June 30, 2014**
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1. **According to the mSMART classification criteria for active multiple myeloma, del(17p) by FISH is a feature of what type of myeloma?**
   A. Low risk
   B. Standard risk
   C. Intermediate risk
   D. High risk

2. **Prophylaxis against herpes zoster is recommended for myeloma patients treated with:**
   A. Bortezomib or carfilzomib
   B. Lenalidomide or pomalidomide
   C. High-dose dexamethasone
   D. Low-dose dexamethasone

3. **In the MM-002 and MM-003 trials, which regimen was associated with the best treatment outcomes in patients with relapsed/refractory multiple myeloma?**
   A. Single-agent pomalidomide
   B. Pomalidomide plus low-dose dexamethasone
   C. Pomalidomide plus high-dose dexamethasone
   D. Single-agent high-dose dexamethasone

4. **Which investigational agent showed an ORR of 100% among patients with relapsed/refractory multiple myeloma who were treated with 1 prior line of therapy?**
   A. Filanesib
   B. Indatuximab
   C. Elotuzumab
   D. Daratumumab

5. **Dose modifications to bisphosphonate therapy are recommended for patients with multiple myeloma and:**
   A. Renal insufficiency
   B. Hepatic dysfunction
   C. A history of thromboembolic events
   D. A history of myelosuppression

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