Sequencing of Treatment and Integration of Clinical Trials

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Abstract

This article provides an overview of current approaches for the treatment of newly diagnosed multiple myeloma using approved agents, including bortezomib and lenalidomide. Clinical development of drugs for multiple myeloma, and the overall clinical trial process, are reviewed. Because optimal therapy for newly diagnosed patients remains controversial, existing treatment guidelines and recommendations are discussed, including data from recent clinical trials. Special considerations should be given to patients considering hematopoietic stem cell transplant since some treatments may decrease the ability to effectively harvest stem cells. Since many patients are refractory to treatment or subsequently relapse, treatment regimens for relapsed/refractory multiple myeloma as well as chemotherapy-based salvage therapy are also discussed. The use of biomarkers in multiple myeloma, such as kappa/lambda serum free light chain (FLC) and gene expression profiling (GEP), are becoming standard for risk prognosis and monitoring of response to therapy. Clinical trial results using the histone deacetylase (HDAC) inhibitor panobinostat and the proteasome inhibitor carfilzomib for treatment of relapsed/refractory disease are presented. Familiarity with risk-stratification tools such as mSMART and treatment guidelines will help advanced practitioners understand the rationale for patient assessment and selection of treatment options. Advanced practitioners can offer patients the opportunity to enroll in ongoing clinical trials, based on their risk status and eligibility for transplant.

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Multiple myeloma (MM) is an incurable but highly treatable clonal malignancy of plasma cells. These malignant plasma cells overproduce monoclonal proteins or immunoglobulins, which together with changes in the bone marrow microenvironment lead to the hallmark clinical characteristics of anemia, renal insufficiency, and osteolytic bone

disease. The majority of MM patients will face multiple relapses over the course of their disease, requiring ongoing continuous or intermittent therapy.

The survival of patients with MM has increased over the past decade as new classes of drugs with novel mechanisms of action have been added to the treatment armamentarium. Seven therapeutic classes of drugs are currently approved by the US Food and Drug Administration (FDA) to treat myeloma. These include (1) alkylating agents (melphalan and cyclophosphamide), (2) chemotherapy (such as doxorubicin, vincristine, and etoposide), (3) corticosteroids (dexamethasone and prednisone), (4) immunomodulatory agents (lenalidomide, pomalidomide, and thalidomide), (5) proteasome inhibitors (bortezomib, carfilzomib and ixazomib), (6) histone deacetylase inhibitors (panobinostat), and (7) monoclonal antibodies (elotuzumab, daratumumab; NCCN, 2016). However, there is no clear consensus as to which drugs should be used and in which order over the course of the disease, and how this may affect survival (Kumar et al., 2008; Kumar et al., 2014; Ozaki et al., 2014).

Through research, treatment options for MM have evolved over time, but knowing which drug to use when can be confusing to the patient and to the advanced practitioner or physician. The purpose of this paper is to (1) review the clinical trial process, (2) provide insight into personalized sequencing of available MM treatments using biomarkers and the patient's prior experience, and (3) discuss how the advanced practitioner can identify and refer patients who are eligible to participate in MM clinical trials.

CLINICAL TRIAL PROCESS

Clinical trials are essential to test the value of treatments for safety and efficacy in a controlled environment (National Institutes of Health, 2015). All of the novel agents used to treat MM have been developed and studied through the clinical trials process, with substantial impact on the survival of MM patients. For this reason, all patients should be considered for clinical trial participation at each phase of treatment. As of December 12, 2015, there were nine FDA-approved agents for the treatment of MM within the 7 therapeutic classes (refer to the Appendix on page 83 for a table listing approved drugs). Each of these drugs has different side-effect profiles and mechanisms of action. All have demonstrated improved survival in clinical trials (Benboubker et al., 2014; Novartis, 2015; Faiman & Richards, 2014; Amgen, 2016; Celgene Corporation, 2013, 2015; Palumbo et al., 2014a; Richardson et al., 2014).

The drug approval process can be lengthy, taking an average of 15 years for the development of a new drug (ClinicalTrials.gov). Each trial is designed with primary and secondary endpoints that can include evaluation of safety, pharmacokinetics, and in many cases biomarker analysis and quality of life. The phases of clinical trials range from preclinical studies to phase III trials (Table 1). Familiarity with the clinical trials process and available trials for the MM patient will improve the ability to integrate these trials into the treatment plan for individual patients over the course of their disease. For example, there are now many trials available for newly diagnosed patients who, once treated, will no longer be eligible for these trials, limiting the ability to clarify preferred sequencing of treatment. Additional considerations for clinical trial participation include comorbidities, previous treatment, unresolved adverse events, and transplant eligibility. Up-to-date information regarding available clinical trials, eligibility and exclusion criteria and study sites can be found in the *Myeloma Matrix* (myeloma.org), sponsored by the International Myeloma Foundation (IMF), or at ClinicalTrials.gov, sponsored by the US National Institutes of Health (NIH).

THE IMPACT OF BIOMARKERS AND GENOMICS ON TREATMENT DECISION-MAKING

Advances in the science of MM cell development and the human genome have led to biomarker discovery in MM. Existing and commonly used biomarkers for MM disease activity, including serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), and kappa/lambda serum free light chain (FLC), are being combined with new methods such as gene expression profiling (GEP) to estimate prognosis (Faiman, 2014; Kurtin et al., 2016). Knowledge of biomarker and genomic results is essential in stratifying pa-

Table 1. Clinical Trial Phases

Stages of clinical trials	Purpose	Participants
Preclinical	• Laboratory (in vitro) or animal studies performed by research institutions, pharmaceutical, or other organizations responsible for drug development	
Phase I	• First-in-human testing • Safe dose (maximum tolerated dose) • Decides how to administer new treatment, e.g., IV or PO • Phamacokinetic and pharmacodynamic testing, which studies the drug's metabolism, absoption, and excretion, along with effects of drug on the body • Assesses new treatment on the patient • Assesses side-effect profile	• 15–30 patients • Patients divided into cohorts (small groups of patients), typically with dose escalation by cohort until the maximum tolerated dose and schedule are determined
Phase Ib	• Studies conducted in patients with a disease for which the drug was intended	
Phase I/II	• Combines both phase I and phase II clinical trials, transitioning both phases into one study • Phase I determines maximum tolerated dose; phase II evaluates efficacy and safety	• Fewer than 100 patients
Phase II based on phase I safety	• Benefit of new treatment • Efficacy • Continued monitoring of treatment side effects	• Up to several hundred patients
Phase III	• After new treatments have shown positive benefit in a small group of patients, the new treatment is then studied in a larger number of patients • Theses studies confirm benefit and efficacy of the new treatment	• Hundreds to thousands, often global • Patients are randomized into treatment arms or groups by a computer to avoid bias • Control group: Receives standard treatment (already approved drug) for that particular disease • Study groups: Treated with new treatment/drug being studied or a placebo
Phase IV	• Begins after phase I–III clinical trials • Further studies FDA-approved treatments to determine if they are effective against other illnesses, or examines different routes of administration, e.g., tablets, capsules, time-released capsules or liquids • Evaluates long-term side effects	

Note. Information from http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm; http://www.cancer.gov/about-cancer/treatment/clinical-trials

tients into risk categories that are associated with favorable, intermediate, or unfavorable outcomes, and this may also guide treatment selection (Landgren & Morgan, 2013; Shah et al., 2014; Van Wier et al., 2013; Rajkumar, 2014).

Genetic aberrations can lead to myeloma cell development and resistant disease. Three main ways to identify genetic aberrations in MM patients include (1) standard karyotype chromosomal analysis, (2) fluorescence in situ hybridization (FISH) analysis for specific tumor cell characterization, and (3) GEP. Thus, according to the International Myeloma Working Group (IMWG), the standard investigative workup for suspected MM should include standard biomarker tests (e.g., SPEP, UPEP, serum FLC) and prognostic indicators such as cytogenetics, FISH, and GEP testing (Kurtin et al., 2016). A comprehensive testing panel is recommended at baseline for appropriate diagnosis and prognostic stratification (Faiman, 2014).

Historically, the clinical diagnosis of symptomatic MM has been made when patients have "CRAB"-related end-organ damage: hypercalcemia, renal insufficiency, anemia, or bone disease detected on skeletal survey or other techniques (Durie et al., 2006). In addition to the above criteria for diagnosis of MM, the IMWG now recommends consideration of treating asymptomatic/smoldering myeloma at high risk of organ damage. Thus, patients should be treated for MM if one of three findings exists: (1) a high degree of plasma cell burden (≥ 60% clonal plasma cells on bone marrow biopsy), (2) more than 1 focal lesion noted on MRI, or (3) serum free kappa/lambda ratio of > 100 mg/L (Durie et al., 2006; Rajkumar et al., 2014). Further risk stratification is performed with FISH and GEP testing to determine high- and standard-risk groups. A patient is considered to be high risk if the individual harbors a deletion of 17p [del(17p)], t(4;14), or t(14;16) without concurrent trisomies (Fonseca et al., 2009; Rajkumar, 2014). A list of standard- and high-risk prognostic biomarkers is provided in Table 2.

Several prospective trials have evaluated the use of newer drugs in patients with high-risk MM over the last decade (Cavo et al., 2010; Nooka et al., 2014; Richardson et al., 2012; Van Wier et al., 2013). Current evidence suggests that patients with high-risk MM do better with newer drugs, but no drug combinations have overcome the poor prognosis of patients who harbor del(17p) specifically. In a large, prospective cohort analysis of a MM disease registry it was determined that age, stage (per International Staging System), and comorbidities impact overall survival (OS) irrespective of IMWG cytogenetic risk, and that patients who receive three-drug regimens tend to have better survival (Shah et al., 2014). Unfortunately, three-drug therapy in patients with del(17p) does not overcome poor prognosis (Shah et al., 2014). Current clinical trials of patients with high-risk MM are investigating the use of upfront newer agents in three-drug regimens (e.g., carfilzomib, lenalidomide, and dexamethasone) or four-drug combinations (e.g., elotuzumab, bortezomib, lenalidomide, and dexamethasone).

TREATMENT GUIDELINES FOR MM

The optimal treatment for newly diagnosed MM (NDMM) remains controversial. For instance, treatment should only be given to patients with smoldering multiple myeloma in the context of a clinical trial (Rajkumar et al., 2014). Therefore, clinical trial participation is strongly encouraged. Guidelines from the IMWG, Mayo Stratification for Myeloma And Risk-adapted Therapy (mSMART), and National Comprehensive Cancer Network (NCCN) exist and provide a framework for treatment of NDMM patients who do not participate in clinical trials. Other institutions, such as Cleveland Clinic, have developed a response-adapted approach to sequencing since there is no clear agreed-upon standard. All of the current guidelines, including the IMWG consensus guidelines for transplant-ineligible patients, support the use of a lenalidomide- or bortezomib-based regimen at diagnosis, and emphasize the importance of avoiding alkylating agents in patients who are candidates for stem cell transplantation (Mikhael et al., 2013; Narkhede et al., 2014; NCCN, 2016; Palumbo et al., 2014b).

The Mayo Clinic mSMART guidelines are among the most widely recognized for the treatment of MM. The mSMART guidelines incorporate host factors, disease stage, and risk profile in guiding treatment recommendations (Figure 1). The NCCN guidelines also recommend a standard workup for MM, and provide evidence for the use of lenalidomide- or bortezomib-based therapies in the newly diagnosed patient. NCCN guidelines, however, also acknowledge emerging clinical trial evidence and the use of commercially available agents that are not yet FDA approved for NDMM (e.g., carfilzomib, pomalidomide) in specific situations (NCCN, 2016).

The Cleveland Clinic uses a response-adapted and sequenced approach to therapy to minimize exposure to multiple drugs at diagnosis for non-high-risk individuals (Baz et al., 2013; Narkhede et al., 2014); see Figure 2. Patients who are ineligible for or decline participation in a clinical trial receive either two drugs (lenalidomide- or bortezomib-based therapy) or three drugs (often bortezomib, lenalidomide, and dexamethasone) to achieve a deeper response. The carepath was developed and implemented as a pilot to provide the patient with an opportunity to respond to a two-drug induction (either lenalidomide- or bortezomib-based therapy) and add additional agents only if the patient does not respond to first-line therapy (Narkhede et al., 2014).

Table 2. Standard and High-Risk Genetic Biomarkers[a]

Name	Origin	Use	Notes
Serum protein electrophoresis with immunofixation (SPEP + IFE)	Serum	To diagnose and monitor MM	The presence of a monoclonal protein is not definitive for diagnosis
Urine protein electrophoresis with immunofixation (UPEP + IFE)	Urine	To diagnose and monitor MM	The presence of a monoclonal protein is not definitive for diagnosis
Kappa/lambda free light chain	Serum	To diagnose and monitor MM	The presence of a monoclonal protein is not definitive for diagnosis
Beta-2 microglobulin	Serum	Prognosis	β_2M is a nonspecific biomarker; higher levels mean the individual is at risk for poorer prognosis
Lactate dehydrogenase (LDH)	Serum	Prognosis	Elevated LDH is associated with poorer survival in MM
del(13)	Bone marrow aspirate	Prognosis	The presence of del(13) on cytogenetics is a poor prognostic factor
del(17p) t(14;16) t(14;20)	Bone marrow/ FISH	Prognosis	High-risk disease with associated poor survival outcomes/25% of patients
t(4;14)	Bone marrow/ FISH	Prognosis	Intermediate risk
t(11;14) t(6;14)	Bone marrow/ FISH	Prognosis	Standard risk/75% of patients
del(1)	Bone marrow/ FISH	Prognosis	del(1) confers a poor prognosis in post-transplant patients
Gene expression profiling/ MyPRS	Bone marrow	Prognosis	High-risk GEP is associated with shorter durations of complete remissions, event-free survival, and overall survival

Note. MM = multiple myeloma; SPEP = serum protein electrophoresis; IFE = immunofixation; UPEP = urine protein electrophoresis; β_2M = beta2-microglobulin; LDH = lactate dehydrogenase; FISH = fluorescence in situ hybridization; GEP = gene expression phenotype; MyPRS = Myeloma Prognostic Risk Signature assay. Information from Faiman & Tariman (2015), Faiman (2014).
[a]The list is not inclusive of all biomarkers in multiple myeloma.

TREATMENT OPTIONS FOR NEWLY DIAGNOSED MM USING APPROVED AGENTS

Despite the improved ability to risk stratify patients with MM, there is no consensus on the best treatment for newly diagnosed patients. Current guidelines suggest every patient with MM be evaluated for hematopoietic stem cell transplantation (HSCT) at the time of diagnosis (NCCN, 2015). Patients who are eligible for HSCT should not be treated with melphalan-containing regimens as this reduces the ability to effectively collect stem cells.

Bortezomib and lenalidomide are two of the most widely studied FDA-approved therapies to treat NDMM and relapsed and/or refractory MM (RRMM). The drugs have been studied alone and in combination with other agents in multiple phase II and III clinical trials in a variety of settings from smoldering MM (SMM), NDMM, RRMM, and in post-transplant maintenance settings (Mateos, Leleu, Palumbo, & Miguel, 2014; Rajkumar et al., 2010; San Miguel et al., 2008; Wang et al., 2008). How does the practitioner decide which drug to use and when? Following is a discussion of available data on the use of these two drugs and other guidelines.

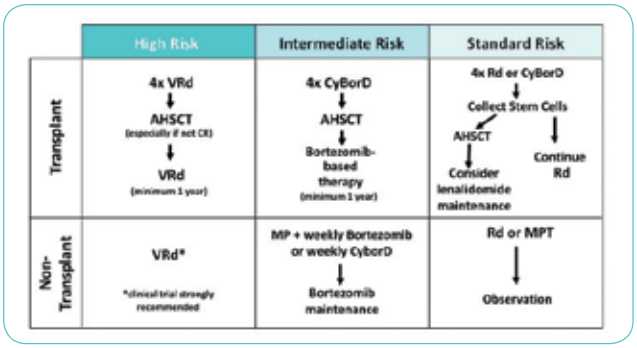

Figure 1. Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013: Newly Diagnosed MM. AHSCT = autologous stem cell transplant; CyBorD = cyclophosphamide, bortezomib, dexamethasone; Rd = bortezomib, low-dose dexamethasone; MP = melphalan, prednisone; MPT = melphalan, prednisone, thalidomide; VRd = bortezomib, lenalidomide, low-dose dexamethasone. [a]Clinical trial strongly recommended. Information from Mikhael et al. (2013), Dispenzieri et al. (2007), Kumar et al. (2009).

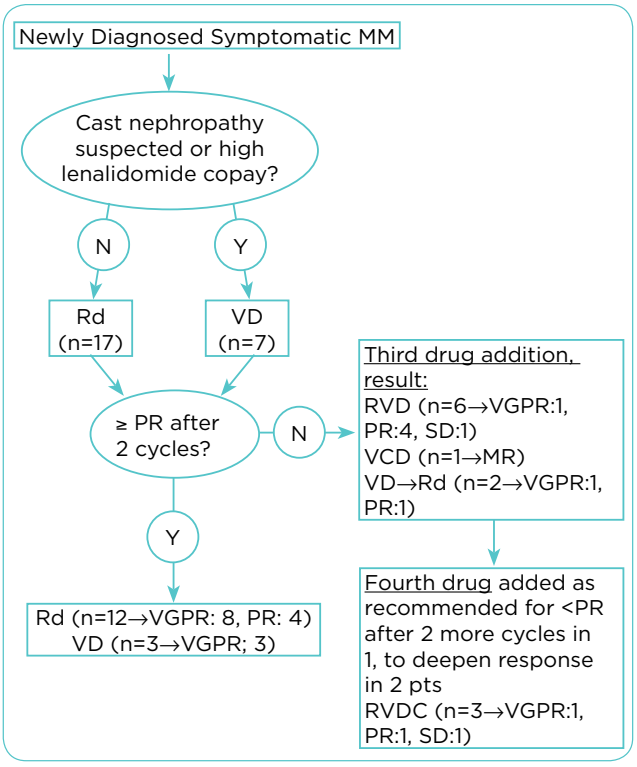

Figure 2. Example of Cleveland Clinic approach to response-adapted therapy in patients with newly diagnosed multiple myeloma. Adapted from Narkhede et al. (2014).

Bortezomib-Based Regimens

The combination of injectable bortezomib and oral dexamethasone in NDMM has been shown to effectively treat MM. Bortezomib has led to improved OS in randomized trials. Most notably, patients who are ineligible to undergo transplant and who received the combination bortezomib, melphalan, and prednisone (VMP) in the VISTA trial had a longer remission and better survival compared to patients who received bortezomib and dexamethasone. In addition, patients had a better outcome when higher, cumulative doses of bortezomib were given. Patients who received bortezomib doses greater than 39 mg/m^2 had an improved survival compared to those who received less, suggesting that longer duration of therapy is preferred (Mateos et al., 2013).

Long-term follow up of two recent bortezomib-based studies with sequential doses were reported. The first evaluated sequential doses of bortezomib, thalidomide, and dexamethasone (VTd) compared to Td (Cavo et al., 2012). At 5-year follow-up, patients who received VTD had no survival advantage when compared to Td, likely because most patients were given bortezomib at relapse (Cavo, 2014).

Another study of 386 patients with NDMM evaluated different treatment induction approaches prior to stem cell transplant (Rosiñol et al., 2014). Patients were randomized to receive three different induction regimens: (1) six 4-week cycles of Td (thalidomide 200 mg daily; dexamethasone 40 mg on days 1–4 and 9–12); (2) six 4-week cycles of VTD (Td plus IV bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11); or (3) bortezomib (4 cycles of alternating vincristine, carmustine, melphalan, cyclophosphamide, and prednisone [VBMCP] and prednisone/vincristine, BCNU, adriamycin, dexamethasone [VBAD] chemotherapy followed by two cycles of IV bortezomib at the usual dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 every 3 weeks). Patients who received the VTD regimen had a significantly longer progression-free survival (PFS) when compared with Td and VBMCP/VBAD/B (56.1 months vs. 29.2 and 39.9 months, respectively; p = .005). A deeper response (complete response) at the end of induction correlated with a longer PFS than patients achieving a lower response (median 62 months vs. 28 months, respectively; p = .00001).

Panobinostat was approved on February 23, 2015, to be given in combination with bortezomib and dexamethasone, based on promising phase III results. One hundred ninety-three patients with RRMM were randomized to receive panobinostat, bortezomib, and dexamethasone (PVd) or bortezomib and dexamethasone (Vd) alone. Patients who received PVd had a longer PFS of 10.6 months compared with 5.8 months in patients who received Vd. Fatal and serious cardiac and gastrointestinal toxicities such as diarrhea were observed in the trial among patients who received PVd. Thus, it is important to proceed with caution when using panobinostat in patients with known cardiac issues and to assess for prolongation of the QTc interval. Antidiarrheal medication such as loperamide can be recommended at the first sign of abdominal cramping, loose stools, or onset of diarrhea (Novartis, 2015).

Lenalidomide-Based Regimens

Lenalidomide and dexamethasone have also been shown to be effective in newly diagnosed and relapsed MM (Benboubker et al., 2014; Weber et al., 2007). As with bortezomib, the duration of therapy is important. A phase III trial evaluated 1623 NDMM patients who were randomized to either (1) lenalidomide plus dexamethasone (Rd) in 28-day cycles until disease progression (n = 535), (2) Ld for 72 weeks (18 cycles; n = 541; Ld18), or melphalan, prednisone, and thalidomide (MPT) for 72 weeks (n = 547). Median PFS was 25.5 months in the continuous Ld arm, 20.7 months in the Ld18 arm, and 21.2 months in the MPT arm. The 4-year OS rate in the Ld continuous group was 59% compared to 51% among patients who received MPT (Benboubker et al., 2014).

Patients with RRMM can also receive lenalidomide in combination with dexamethasone. In a phase III trial, patients were randomized to receive either lenalidomide 25 mg PO daily for 21 days with high-dose dexamethasone (40 mg/day on days 1–4, 9–12, and 17–20 of a 28-day cycle) or low-dose dexamethasone (40 mg/day on days 1, 8, 15, and 22 of a 28-day cycle). The trial was halted early because of the increased 1-year survival rate observed in the low-dose dexamethasone arm (96%) compared to the high-dose arm (87%), and patients receiving high-dose dexamethasone had increased risk of infections and venous thromboembolism (Rajkumar et al., 2010). This study demonstrated that high doses of pulsed dexamethasone leads to toxicity; therefore, lower doses of dexamethasone are recommended.

Most recently, lenalidomide and dexamethasone (Rd) were approved in combination with two newly approved agents. Elotuzumab, a newly approved immunostimluatory antibody, is indicated for the treatment of patients with MM who have received two prior therapies (Bristol-Myers Squibb, 2015). Ixazomib, a new oral proteasome inhibitor, is approved in combination with Rd for patients who have received at least 1 prior therapy. Additional details about these newly approved agents are provided elsewhere in this supplement (Faiman et al., 2015; Gleason et al., 2015).

TREATMENT STRATEGIES FOR RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA

Pomalidomide-Based Therapies

Pomalidomide (Pomalyst), an oral agent, was approved by the FDA for use in the treatment of MM in February 2013. Pomalidomide was approved for patients who have received at least two prior therapies, including lenalidomide and bortezomib and whose disease did not respond to treatment and progressed on or within 60 days of the last treatment (Celgene Corporation, 2013).

Pomalidomide is an immunomodulatory drug from the same class as thalidomide and lenalidomide. In a phase II study, patients with RRMM were randomized to receive pomalidomide alone or with low-dose dexamethasone. Low-dose dexamethasone could be added to patients who progressed on single-agent pomalidomide at the discretion of the treating physician. All patients received prophylaxis for deep vein thrombosis. Pomalidomide-dexamethasone resulted in an overall response rate (ORR) of 33% and median PFS of 4.2 months in patients who had received prior lenalidomide and bortezomib. Neutropenia was the most notable adverse event in the study, with 13% of patients experiencing grade 4 neutropenia (Richardson et al., 2014).

Preliminary results of a randomized trial comparing pomalidomide, cyclophosphamide, and dexamethasone (PCD) with pomalidomide and dexa-

Table 3. Practical Approach to the Treatment of Patients With Newly Diagnosed or Relapsed Multiple Myeloma

How fit is the patient?

Comorbid conditions and overall fitness are important considerations in treatment selection. Comorbidities may be present at diagnosis and resolve, or emerge over time. Some patients present with serious comorbidities that subsequently improve with effective treatment of the MM. In other cases, the presence of a comorbid condition guides treatment selection. For example, a patient with severe cardiopulmonary disease may not tolerate carfilzomib, and a patient with a strong history of thrombosis may not be a good candidate for immunomodulatory therapy. Health maintenance and supportive care practices should be maintained to maximize function.

Is the patient eligible for a stem cell transplant?

If the patient is eligible for a stem cell transplant, evaluation by a transplant center soon after diagnosis is recommended. Some patients may want to delay the procedure to a later date (e.g., waiting until retirement to undergo ASCT). There are a number of considerations in determining transplant eligibility, including frailty, lack of social or financial resources, and multiple comorbid conditions.

Length of therapy

Two clinical trials in nontransplant patients have demonstrated that the longer patients remain on therapy, the better the response (Benboubker et al., 2014; Mateos et al., 2013). Maintenance lenalidomide or bortezomib therapy has been shown to improve outcomes post-transplant, and treatment may continue until unacceptable toxicity or progressive disease to suppress the malignant MM clone.

What treatment has the patient received? How did it work? And how did the patient tolerate it?

For each patient, evaluating the sequence of treatments, efficacy, tolerability, duration of response, and reason for any changes in treatment is essential to identify the best options for continued therapy. For example, if a patient has discontinued bortezomib due to increasing neuropathy and has progressive disease 6 to 9 months after stopping the treatment, they may benefit from reintroducing bortezomib (Takeda, 2014).

The practitioner should consider which drugs (if any) were given to treat the disease, response, and tolerabilityto the drugs. Just because lenalidomide was no longer effective in treating MM does not mean that the patient will not respond if bortezomib or other agents are added. Similarly, if the patient has progressed on a lenalidomide-based regimen, they may still achieve benefit from other immunomodulatory agents, such as pomalidomide.

Have you used all of the standard drugs to treat MM?

In RRMM patients, consider if all of the available immunomodulatory drugs, proteasome inhibitors, HDAC inhibitors, and chemotherapeutics have been used to treat the disease. Clinical trials should be considered at each point of transition.

methasone (Pd) in RRMM showed a superior ORR (65% versus 39%, respectively) and an improved PFS compared to Pd (Baz et al., 2014). Lacy et al. (2014) reported the results of 50 patients who received between 1 and 4 prior regimens and were refractory to lenalidomide. Patients were randomized to receive pomalidomide 4 mg PO on days 1 to 21 every 28 days, bortezomib 1.3 mg/m^2 on days 1, 8, and 15, and dexamethasone 40 mg PO on days 1, 8, 15, and 22 (PVD) (Lacy et al., 2014). A high ORR (85%) was seen in patients who received the three-drug regimen.

Chemotherapy-Based Salvage Therapy in RRMM

Chemotherapy-based salvage therapy in patients with aggressive disease not responding to therapy with newer drugs has been studied. Two multiagent regimens consisting of bortezomib, high-dose dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide (VTD-PACE) and dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) have been studied (Barlogie et al., 2007; Park et al., 2014). The VTD-PACE regimen is considered a reasonable salvage regimen for patients with RRMM but requires aggressive supportive care in terms of blood and platelet transfusions, antibiotics, and growth factor support (NCCN, 2015). The DCEP regimen was retrospectively evaluated in one study, with an ORR of 45.1%. The most severe and life-threatening adverse event was grade ≥ 3 neutropenia observed in 91.5% of patients, which warrants the use of granulocyte colony-stimulating factor and neutropenic precautions. Treatment-

Table 4. Supportive Care in Multiple Myeloma

Supportive care should be started at the time of diagnosis for all patients with MM and continued throughout the course of the disease as appropriate.

Bone disease

Bone damage is common in MM. All patients with NDMM should be started on bisphosphonate therapy for at least 1 year to decrease risk of skeletal fractures (Miceli, Colson, Faiman, Miller, & Tariman, 2011; Palumbo et al., 2014a,b). Monitoring for osteonecrosis of the jaw is also suggested (Faiman, Pillai, & Benghiac, 2013).

Kidney disease

Kidney disease is often multifactorial but must be assessed in MM at diagnosis and throughout the disease. Routine disease monitoring and avoidance of drugs that can contribute to renal disease such as nonsteroidal agents, contrast dyes, and aminoglycoside antibiotics are essential (Faiman, Mangan, Spong, & Tariman, 2011).

Peripheral neuropathy

Peripheral neuropathy, characterized by numbness and tingling or changes in sensation, can be present at diagnosis or occur over time. Patients most at risk are those who receive bortezomib or thalidomide (Richardson et al., 2012; Tariman, Love, McCullagh, & Sandifer, 2008). The advanced practitioner (AP) must assess for signs/symptoms of neuropathy at each visit and modify the drug dose as indicated. In some cases, drugs must be discontinued. Surveillance for secondary causes of neuropathy (e.g., vitamin B deficiency, uncontrolled diabetes) should be considered.

Infections

Infections are a major cause of death in MM. All patients treated with a proteasome inhibitor should receive prophylaxis for herpes zoster virus (e.g., acyclovir, valacyclovir). Pneumococcal and seasonal inactivated influenza vaccinations are recommended to prevent these diseases. Live virus vaccines should be avoided. Granulocyte colony-stimulating factors and prophylactic antibiotics may be considered in heavily treated patients to limit neutropenia. Guidelines for immunizations can be found at http://www.cdc.gov/vaccines/schedules/.

Venous thromboembolic events (VTEs)

All patients with MM are at an increased risk of VTEs. The AP should educate patients on ways to minimize VTEs (avoid stasis, immobility, dehydration). All patients on immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide) should be risk-stratified and receive aspirin (< 2 risk factors) or full anticoagulation (>2 risk factors).

Gastrointestinal side effects

Nausea is common with agents such as proteasome inhibitors and cyclophosphamide but is generally mild. Diarrhea, in some cases moderate to severe and progressive, has been reported with long-term lenalidomide use or in patients who are taking panobinostat (Faiman et al., 2013; Simpson, Rajkumar, Lacy, Hayman, & Roy, 2008). Therefore, gastrointestinal side effects of therapy should be addressed at each visit (Faiman et al., 2013; Smith, Bertolotti, Curran, & Jenkins, 2008).

related mortality was reported in eight patients (14.8%), and seven of eight deaths were related to febrile neutropenia (Park et al., 2014).

Carfilzomib-Based Therapies

Carfilzomib is a next-generation proteasome inhibitor that is FDA approved for treatment of relapsed MM. In a pivotal study, single-agent carfilzomib was administered IV over 2 to 10 minutes at doses of up to 27 mg/m^2 (standard carfilzomib, i.e., FDA-approved dose); this was proven to be effective for patients with RRMM (Badros et al., 2013; Jagannath et al., 2012; Siegel et al., 2012; Vij et al., 2012a, 2012b). Carfilzomib was recently approved in January 2016 to be administered as a single agent at a dose of 56 mg/m^2 IV over 30 minutes for the treatment of patients with relapsed or refractory MM who have received one or more lines of therapy

Several trials are investigating the use of carfilzomib in newly diagnosed MM and earlier in the disease trajectory. Multiple studies are investigating its earlier use in treatment (Mark et al., 2014), in combination with cyclophosphamide and dexamethasone in patients with an average age of 74 years and in doses as high as 56 mg/m^2 (Lendvai et al., 2012; Palumbo, et al., 2014c; Squifflet et al., 2011).

Current studies have reported promising results when combining carfilzomib with the immunomodulatory drugs (IMiDs) lenalidomide or pomalidomide. In an early phase Ib dose-escalation study, the combination of carfilzomib with lenalidomide and dexamethasone for patients with

relapsed or progressive MM resulted in an ORR of 62.5%, with a duration of response of 11.8 months and overall PFS of 10.2 months (Niesvizky et al., 2013). Another trial in patients with relapsed MM who were treated with the combination of carfilzomib and pomalidomide produced an ORR of 50% (Stadtmauer et al., 2013). The combination was also well tolerated, with limited grade 3/4 toxicities. Additional studies combining the histone deacetylase (HDAC) inhibitor panobinostat with carfilzomib are also in progress. Preliminary results demonstrate promising response rates with a tolerable safety profile and no unexpected toxicities, thus meriting investigation of higher doses (Berdeja et al., 2012; Kaufman et al., 2013; Shah et al., 2012).

The ASPIRE trial was comprised of 792 patients with relapsed myeloma. Patients were randomized to receive carfilzomib, lenalidomide, and dexamethasone (KRd) or lenalidomide and dexamethasone (Rd; Stewart et al., 2014). There was a higher ORR with KRd versus Rd (87.1% vs. 66.7%), a 31% decrease in the risk of disease progression or death, and a significantly greater PFS (increase of 8.7 months) in patients who received KRd (hazard ratio for progression or death, 0.69; $p < .0001$). The most common side effect in both groups was myelosuppression. The study supports the use of a three-drug regimen (proteasome inhibitor, IMiD, and corticosteroid) to treat RRMM (Stewart et al., 2014).

ADDITIONAL CONSIDERATIONS FOR THE ADVANCED PRACTITIONER AND GENERAL APPROACH

Advanced practitioners in oncology, such as nurse practitioners, certified nurse specialists, and physician's assistants, are integral to the diagnosis and management of MM patients. Familiarity with risk-stratification tools, such as mSMART and NCCN and institutional guidelines, together with clinical trial results and post-marketing experiences with these agents and combinations of agents, will improve patient outcomes. For newly diagnosed patients, it is important to determine if the individual is a candidate for stem cell transplantation. An appropriate and well-designed clinical trial should be offered based on the patient's risk status or transplant eligibility. Close attention to disease monitoring and provision of supportive care with concurrent medications should be considered (Richards & Brigle, 2015).

CONCLUSION

Multiple myeloma is a chronic disease, yet many treatment options exist for patients. Because of the heterogeneity of this disease, there is no single gold standard therapy at diagnosis or relapse, and treatment of MM is not a "one size fits all" approach. While there is no clear correct pathway of treatment for all patients with MM, ongoing clinical trials will undoubtedly elucidate better treatment options for this incurable malignancy.

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Disclosure

Dr. Beth Faiman has acted as a consultant, a lecturer, and served on speakers bureaus for Celgene Corporation, Takeda Oncology, and Amgen. Ms. Charise Gleason has acted as a consultant for Celgene Corporation and Takeda Oncology. Ms. Kathleen Colson has acted as a consultant for Celgene Corporation, Takeda Oncology, and Amgen. Ms. Ann McNeill has acted as a consultant for Celgene Corporation and Takeda Oncology and has acted as a lecturer and served on speakers bureaus for Celgene Corporation, Takeda Oncology, Amgen, and Novartis International AG. Ms. Donna D. Catamero has acted as a consultant for Celgene Coporation and Takeda Oncology, and acted as a lecturer and served on speakers bureaus for Celgene Corporation, Takeda Oncology, Amgen, Novartis International AG, and Janssen Pharmaceutica. Members of the International Myeloma Foundation Nurse Leadership Board served as reviewers for this work. The authors are solely responsible for the content.

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