Current and Emerging Treatments for Multiple Myeloma

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ABSTRACT

BACKGROUND: The prognosis and treatment of multiple myeloma (MM) has evolved greatly over the past decade. The development and incorporation of new agents such as immunomodulators and proteasome inhibitors into therapy has improved outcomes and is helping patients enjoy longer periods of remission.

OBJECTIVE: To review current treatments for MM, including overview of drug therapy and management of adverse effects of therapy and comorbidities. Additionally, an overview of agents being studied and evaluated for use in MM and myeloma-related conditions, such as metastatic bone disease and venous thromboembolism, will be discussed.

SUMMARY: Great strides have been made regarding the understanding of disease pathology in MM, leading to therapies that may be targeted to each individual, based on their unique biology of disease. Therapy is currently tailored based on patient issues and stage of disease, but may soon be tailored individually based on the cytogenetic profile of a patient.

Recent treatment guidelines have been published by the National Comprehensive Cancer Network which were updated with impressive results from clinical trials involving agents such as immunomodulators and proteasome inhibitors. This guideline also provides information on the management of myeloma and treatment-related morbidities.

As with the treatment of any cancer, clinicians must weigh risk versus benefit when determining the most appropriate therapy. Currently, corticosteroids, lenalidomide, thalidomide, and bortezomib are all used in patients with MM. The use of chemotherapy, including high-dose therapy with stem cell transplant, is an important component of treatment for many patients. The use of high-dose therapy is continually being evaluated, and the issue of risk versus benefit is weighed for individual patients. Depending on the prognosis, it may be of benefit to endure the toxicity of higher doses to achieve a better overall response and achieve longer remission periods.

Although stem cell transplantation is often performed in MM to improve survival and remission rates, some patients are unable to undergo transplant for a variety of reasons, including age (older than 65 years), comorbidities, and/or organ dysfunction.

Newer drug therapies and combinations of therapy are being evaluated to better manage this population and patients who previously received high-dose chemotherapy and a stem-cell transplant. Additionally, the management of relapsed, or refractory, disease continues to be a challenge in treating the myeloma patient. Despite aggressive and improved treatments, most myeloma patients will eventually have resistance to therapy or relapse. Treatment strategies in these patients are also evolving.

CONCLUSION: Major advancements in the diagnosis, staging, and treatment of myeloma offer promise in the future for changing MM from a terminal illness into a chronic, manageable condition.

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Prognosis and Treatment

The prognosis and treatment of an individual with multiple myeloma (MM) depends on many patient-specific factors, including age, overall state of health, and comorbidities. Currently, initiation of therapy is primarily determined by the stage of myeloma. One of the major treatment considerations for an individual with MM is the assessment of the patient's ability to receive high-dose chemotherapy (HDC) followed by hematopoietic stem cell transplant (HSCT). Disease-specific factors (e.g., bone lesions, anemia, and renal dysfunction) also may play a major role in treatment decisions. For example, adjunctive therapy with bisphosphonates is considered based on the presence of bone involvement.[1]

Disease control, described in terms of molecular response, has been achieved with newer therapies in clinical trials. A complete response (CR) is defined as having no detectable monoclonal (M) protein in the serum and urine, normal percentage of plasma cells in bone marrow, no increase in size or number of osteolytic bone lesions, and the disappearance of soft tissue plasmacytomas. The National Comprehensive Cancer Network (NCCN) currently defines partial response (PR) as greater than or equal to a 50% reduction in serum M protein, maintained for a minimum of 6 weeks; greater than or equal to a 50% reduction in the size of soft-tissue plasmacytomas; no increase in the size or number of lytic bone lesions; and for patients with nonsecretory myeloma only, greater than or equal to a 50% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, maintained for a 6-week minimum. Nonsecretory myeloma occurs in about 2% of all MM patients and is characterized by the absence of M protein in both the urine and serum.[2] The NCCN guidelines also refer to *stable disease* as *plateau* and require that stable values be maintained for at least 3 months.[3,4]

The Multiple Myeloma Research Foundation (MMRF) has further broken down potential outcomes into *near complete response* (same criteria for CR, but with a positive immunofixation test), *very good partial response* (greater than 90% decrease in M protein), *minimal or minor response* (less than 50% decrease

in M protein), *stable disease* (myeloma that has not responded to treatment, but has not progressed), and *progressive disease* (greater than 25% increase in M protein, new bony lesions, or a new plasmacytoma).[4]

The evaluation of response continues to be defined by techniques that can be used to measure minimal residual disease.

Pharmacotherapy for Multiple Myeloma

Immunomodulatory Drugs

Thalidomide is an oral agent shown to be effective across the spectrum of myeloma disease.[5] Thalidomide's mechanism of action in MM is not fully understood. Proposed mechanism(s) include the inhibition of tumor necrosis factor-alpha (TNF-alpha), prevention of free-radical-mediated DNA damage, suppression of angiogenesis, increase in cell-mediated cytotoxic effects, and alteration of the expression of cellular adhesion molecules. Thalidomide may also inhibit the activity of nuclear factor-kappa B (NF-kappaB) and the enzymes cyclooxygenase-1 and cyclooxygenase-2. Thalidomide is contraindicated in pregnancy, and because of concern with teratogenicity, is monitored closely in individuals on therapy.[6] Thalidomide may be obtained only through practitioners and pharmacies registered in the System for Thalidomide Education and Prescribing Safety program.

The dosing of thalidomide depends somewhat on patient tolerance. The drug is typically initiated at a dose of 200 mg per day and increased to 400 mg per day after 2-4 weeks, if tolerated. To minimize long-term toxic effects, the dose should be adjusted to the lowest level that can achieve and maintain a response. Doses greater than 200 mg are generally not indicated when thalidomide is combined with corticosteroids or chemotherapy.[6] Thalidomide should be taken with a glass of water, preferably at bedtime, because drowsiness is a common effect, and at least 1 hour after the evening meal. Dosage adjustment recommendations for patients with renal dysfunction or undergoing hemodialysis are not available, and data are lacking.[7]

Side effects of thalidomide are typically dose dependent and may include somnolence, fatigue, constipation, and rash. Other adverse effects include dizziness, edema, bradycardia, neutropenia, impotence, and hypothyroidism.[8] Peripheral neuropathy may occur with long-term use and may necessitate the discontinuation of therapy or dosage reduction. The incidence of peripheral neuropathy is related to pretreatment neuropathy and duration of use. In 1 study, the incidence of peripheral neuropathy increased from a rate of 38% at 6 months to 73% at 12 months. Thalidomide may be a challenging medication for an elderly patient because of the impact of neuropathy on function.[9,10]

Pulmonary embolism and deep vein thrombosis (DVT) characterize different manifestations of the same clinical entity known as venous thromboembolism (VTE).[11] VTE occurs in 1%-3% of patients receiving single-agent thalidomide; however, when thalidomide is combined with dexamethasone, the risk increases to 10%-15%. The risk rises to 25% when thalidomide is administered with other cytotoxic agents, particularly doxorubicin.[6] The risk of VTE with thalidomide has led to the use of VTE prophylaxis with a variety of agents, including low-molecular-weight heparin, warfarin, and aspirin.[3,12-14]

Lenalidomide, an oral thalidomide analogue synthesized with the aim to increase efficacy and decrease nonhematologic toxicity including teratogenicity, has been evaluated for the treatment of MM. Lenalidomide's activity appears to be more potent and promising than that of thalidomide.[15] The mechanism of action is not fully characterized. Similar to thalidomide, lenalidomide is an antiangiogenic agent and inhibits the adhesion of myeloma cells to bone marrow stromal cells. It also reduces the secretion of growth and survival factors, induces direct apoptosis of myeloma cells, promotes the cytotoxic activity of natural killer and T cells against myeloma cells by stimulating their proliferation and the secretion of interleukin 2 and interferon gamma, and down-regulates the activity of NF-kappa B.[16]

Currently, lenalidomide is approved by the Food and Drug Administration (FDA) for the treatment of MM in combination with dexamethasone in patients who have failed at least 1 prior therapy. Clinical trials using combination lenalidomide with lower-dose dexamethasone showed an increase in overall survival (96.5% vs. high-dose dexamethasone's 86%) at 1 year. There was, however, a 9% rate of DVT seen in patients receiving low-dose dexamethasone plus lenalidomide; therefore, there is a need for thorough thromboprophylaxis evaluation.[3] Similarly, in a randomized phase 3 trial involving 354 patients with relapsed or refractory MM, lenalidomide demonstrated superior activity when combined with dexamethasone, compared with dexamethasone as a single agent (overall response rate 59.4% vs. 21.1%; $P < 0.001$).[17,18]

Lenalidomide should be taken with water. The approved oral adult dosage is 25 mg daily on days 1-21 along with dexamethasone 40 mg orally on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 therapy cycles. Starting with cycle 5, lenalidomide dose remains at 25 mg daily, but the dexamethasone dose is decreased to 40 mg daily on days 1-4 of each 28-day cycle. Lenalidomide is extensively eliminated unchanged by the kidneys. Clinical trials excluded patients with renal dysfunction, and mandated that researchers withhold lenalidomide in patients who developed renal dysfunction. The risk of adverse events is expected to be greater in patients with renal dysfunction. Renal dose adjustment recommendations have recently been proposed in patients with a creatinine clearance rate of less than 50 mL per min.[19] These recommendations have not been studied in patients with MM; thus, the impact on efficacy and toxicity is unknown.

Compared with thalidomide, lenalidomide has a better safety profile and does not cause significant somnolence, constipation, or peripheral neuropathy, although myelosuppression is an issue.[15,20] The most common adverse effects in two phase 2 trials were grade 3 or higher thrombocytopenia (platelet count less

than 50,000 per mL^3), and neutropenia (neutrophil count less than 1,000 per mL^3). Dose interruption or modification is recommended for patients with a platelet count less than 30,000 per mL^3 and/or neutrophil count less than 1,000 per mL^3. VTE has been reported in 5%-18% of patients prescribed lenalidomide. Incidence of thromboembolism is higher in patients receiving combination therapy with high-dose dexamethasone, concomitant erythropoietin therapy, and prior thalidomide exposure.[6,21] Other common adverse effects associated with lenalidomide include constipation, fatigue, insomnia, muscle cramps, diarrhea, anemia, asthenia, and nausea.

Similar to thalidomide, all prescribers, patients, and pharmacists must comply with the conditions of the RevAssist program when prescribing, dispensing, or receiving lenalidomide, due to the potential risk for teratogenicity.

Proteasome Inhibitors

Bortezomib is a first-in-class proteasome inhibitor. Bortezomib targets the 26S proteasome, a multicatalytic proteinase complex involved in intracellular protein degradation.[16] Bortezomib inhibits transcription factor NF-kappaB activation by protecting its inhibitor I kappa B (IkappaB) from degradation by the 26S proteasome. Degradation of IkappaB by proteasome activates NF-kappaB, which up-regulates transcription of proteins that promote cell survival and growth, decreases apoptosis susceptibility, influences the expression of adhesion molecules, and induces drug resistance in myeloma cells.[16] Bortezomib not only targets the myeloma cell, but also acts in the bone marrow microenvironment by inhibiting the binding of myeloma cells to bone marrow stromal cells and bone marrow-triggered angiogenesis.

The recommended starting dose for bortezomib is 1.3 mg per m^2 administered as a 3- to 5-second bolus intravenous injection on days 1, 4, 8, and 11 of an every-21-day cycle.[6] Dose interruption and modification are recommended for patients experiencing grade 3 nonhematological or grade 4 hematological toxicities. Explicit dose modifications, beginning with grade 1 or 2 toxicity, are recommended for patients experiencing peripheral or motor neuropathy or neuropathic pain. Dose reductions to 1 mg per m^2, or even 0.7 mg per m^2, may be necessary because of toxicity. Bortezomib undergoes hepatic metabolism primarily via cytochrome P450 enzymes 3A4, 2C19, and 1A2. No formal drug interaction studies have been conducted with bortezomib. Bortezomib has been studied in patients with varying degrees of renal impairment, including patients requiring dialysis. The pharmacokinetics of bortezomib does not appear to be influenced by the degree of renal impairment. Dialysis may reduce bortezomib concentrations; so it should be administered following dialysis.[22,23]

The most common adverse events associated with bortezomib are gastrointestinal disorders, thrombocytopenia, and peripheral neuropathy. Patients may require antiemetic and antidiarrheal medications or fluid replacement because of the high incidence of nausea and diarrhea.[24] Grade 3 or 4 thrombocytopenia occurs in more than 30% of patients and has been found to be transient and cyclical. Platelet counts decrease and recover predictably during each treatment cycle with no evidence of cumulative toxicity.[25] Initial platelet count prior to bortezomib therapy is an important predictor of severe thrombocytopenia. Patients with a baseline platelet count of less than 70,000 per mL^3 have been shown to be at higher risk for grade 3 or 4 thrombocytopenia.[25] Peripheral neuropathy occurs in 37% of patients undergoing bortezomib therapy. Grade 3 or 4 peripheral neuropathy occurs in 11% of patients. The incidence of peripheral neuropathy does not appear to be influenced by baseline neuropathy or previous therapy with neurotoxic agents. Other grade 3 or 4 toxicities include fatigue (16%), neutropenia (14%), and anemia (12%). Other common adverse effects include pyrexia, edema, cough, and headache.[6]

The role of bortezomib in the treatment of MM has evolved since the drug was introduced to the market. Bortezomib-based combinations in newly diagnosed patients have resulted in high overall and CR rates. Additionally, there does not seem to be a negative impact on stem cell harvest or engraftment in patients who receive bortezomib as part of their induction regime.[26]

A new proteasome inhibitor (NPI-0052) is currently being evaluated in a phase 1 trial of patients with relapsed or refractory MM. As with bortezomib, NPI-0052 triggers apoptosis in MM cells but is distinct from bortezomib in its chemical structure, effects on proteasome activities, and mechanism of action. In vitro, apoptosis triggered by either bortezomib or NPI-0052 is associated with sequential occurrence of proteasome inhibition, but with different kinetics. The cellular response to NPI-0052 occurs much earlier than that of bortezomib. Orally administered NPI-0052 is cytotoxic to myeloma cells, with reduced toxicity against normal cells, compared with bortezomib, according to a recent preclinical study.[27] Because of the different kinetics and cellular responses, it is possible that both bortezomib and NPI-0052 could be used in combination.[28] In vitro data have demonstrated synergistic apoptotic activity between bortezomib and NPI-0052 in MM cell lines.[29,30]

Treatment Strategies for Myeloma

Hematopoietic Stem Cell Transplant

Traditionally, the aim of induction therapy in MM has been to achieve a CR or PR in preparation of HDC and HSCT.[31] However, the role of stem cell transplantation in myeloma is beyond the scope of this article.

Unfortunately, some individuals may not be eligible for HSCT. Historically, transplantation was not considered an option for adults older than 65 years. As myeloma is a disease seen predominantly in older adults, factors such as comorbidities, organ dysfunction, resources, and/or preference must be evaluated when considering HDC followed by HSCT. Currently, advances

TABLE NCCN Multiple Myeloma Practice Guidelines Induction Therapy Recommendations[a]

Induction Therapy for Transplant Eligible Patients	Frontline Therapy for Individuals Not Eligible for Transplant	Salvage Therapy
Vincristine/doxorubicin/dexamethasone (VAD)	Melphalan/prednisone (MP)	Repeat primary induction therapy (if relapse at >6 months)
Dexamethasone	Melphalan/prednisone/thalidomide (MPT) (category 1)[b]	Bortezomib (category 1)[b]
thalidomide/dexamethasone	Melphalan/prednisone/bortezomib (MPB) (category 2B)[b]	Bortezomib/dexamethasone
Liposomal doxorubicin/vincristine/dexamethasone (DVD)	VAD	Bortezomib/liposomal doxorubicin (category 1)[b]
Lenalidomide/dexamethasone (category 2B)[b]	Dexamethasone	Lenalidomide
Bortezomib/dexamethasone (category 2B)[b]	Thalidomide/dexamethasone	Cyclophosphamide-VAD
Bortezomib/doxorubicin/dexamethasone (category 2B)[b]	DVD (category 2B)[b]	High-dose cyclophosphamide
Bortezomib/thalidomide/dexamethasone (category 2B)[b]		Thalidomide
		Thalidomide/dexamethasone
		Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE)

[a] *NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 1.2008) ©2007 National Comprehensive Cancer Network, Inc.*

[b] *Category 1 denotes uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate. Category 2A is assigned when there is uniform NCCN consensus that the recommendation is appropriate based on lower-level evidence, including clinical experience. Category 2B denotes nonuniform NCCN consensus, based on lower-level evidence, including clinical experience, that the recommendation is appropriate.*[2]

Note: The FDA recently approved bortezomib for frontline therapy for individuals not eligible for transplant.[32]

in supportive care have made HDC with HSCT an option for older adults who are in relatively good health.

Induction Therapy

Induction therapy for individuals who are candidates for HDC with HSCT has evolved in the past decade. Agents that have demonstrated activity in patients after disease progression following HSCT (recurrent or relapsed disease) have now been moved to frontline therapy as induction. Alkylating agents, such as melphalan, once considered standard initial myeloma treatment, are now avoided in this population as their use has been shown to compromise stem cell reserves prior to bone marrow harvest. Induction strategies for individuals with myeloma are outlined in the Table above.[3,32] Strategies for initial induction therapy continue to be evaluated and redefined, with a goal to determine the most effective therapy and assure quality of life. Additionally, it is important to determine the role of specific agents and/or combinations in select patient subsets. It is becoming increasingly clearer that disease-related aspects (e.g., genetic profiles and cytogenetic abnormalities) define patients who have more aggressive myeloma. Newer agents may demonstrate increased activity in a subset of these patients with aggressive disease.

After induction therapy, patients are evaluated to determine response to treatment. If there is good disease response, the role of HDC with HSCT is considered in patients who are considered good candidates. At this point, HSCT candidates undergo a stem cell harvest. If possible, a sufficient quantity (or number) of stem cells should be collected to support two HSCT; these could be used for a tandem transplant or if a single HSCT is done, a second transplant may be considered in the case of relapsed disease.[6,31]

Frontline Therapy in Patients Not Eligible for Hematopoietic Stem Cell Transplant

Historically, combination chemotherapy with melphalan and prednisone (MP) has been the standard treatment option for these patients. Single-agent dexamethasone has also been used in select patients. Individuals with MM who are not considered transplant candidates can receive treatment with a variety of agents, including chemotherapy, corticosteroids, immunomodulating agents, bortezomib, or a combination thereof. Clinical trials continue to evaluate available treatment combinations and to compare with what was once the standard approach of melphalan and prednisone.[33] Treatment regimens used in patients who are not considered transplant candidates are listed in the Table.[3]

The combination of thalidomide, melphalan, and prednisone (MPT) has been associated with significant increases in response rates. Palumbo et al. reported the results of a trial that randomized 255 patients with newly diagnosed MM to receive either MP or MPT. Of those who completed the cycle series, 15.5% of the MPT arm achieved CR versus 2.4% for the MP arm. Results also showed that a combined point of CR and PR was achieved in 76% of the MPT arm and 47.6% for MP arm. Additionally, 2-year, event-free survival rates were 54% for the MPT group and

27% for the MP group. The MPT group experienced greater than or equal to 1 adverse event at a rate of 48% versus 25% for MP ($P=0.0002$). Because of the higher incidence of thromboembolism in the MPT arm, (12% vs. 2% for MP, $P=0.001$), thorough evaluation of thromboprophylaxis should be considered.[10]

The promising results from recent trials have provided new options for treatment in individuals with MM who are not considered transplant candidates. Some of these regimens use oral therapy and require assessment of the patient and/or caregivers for appropriateness of this approach to treatment (e.g., ability to understand the regimen and adherence). Clinicians (with patient discussion) should choose a regimen after considering toxicity, cost, convenience, and patient preference.

Management of Relapsed Myeloma

At some point it is inevitable that, despite treatment, most individuals will have primary or secondary resistance to therapy. Almost all individuals who have responded to therapy following HDC and HSCT relapse within 10 years of treatment initiation.[21] When relapse occurs, salvage therapy is often necessary. The treatment strategies for salvage therapy are dependent upon many factors, including the initial therapy a patient received (see Table). Additional treatment options include HSCT.[31]

Disease and Treatment Complications in Myeloma

Disease-related complications include myeloma bone disease, hypercalcemia, renal insufficiency, infection, anemia, pain, and hyperviscosity syndrome.[34] Treatment-related complications vary with the drug therapy and treatment strategies used for disease management. The treatment team should evaluate the impact of these disease- and treatment-related issues for every patient, as the severity of the toxicity may depend on the individual's age, comorbidities, or concurrent drug therapy. Of note, this evaluation should occur throughout the course of the disease.

Bone Disease

Up to 75% of MM patients present with signs of bone disease at diagnosis.[35] Skeletal involvement often leads to pain, pathological fractures, and hypercalcemia.[3] Recently published guidelines from NCCN recommend that all patients with documented bone disease, including osteopenia, receive bisphosphonate therapy.[3] The International Myeloma Working Group recommends that bisphosphonates should no longer be used indefinitely or in an open-ended manner. The duration of bisphosphonate therapy should be modified based on the evidence of ongoing active bone disease. Two years of therapy are considered routine. In patients who have achieved complete or good partial response with other therapies in the posttransplant setting and/or in the nontransplant setting, the International Myeloma Working Group also recommends bisphosphonate use for 1 year if there is no evidence of active bone disease. Conversely, longer therapy is justified if there is evidence of continued active bone disease in patients with lesser degrees of response.[28]

Therapeutic options for myeloma bone disease may include bisphosphonates, pain control, surgical intervention to prevent or treat fractures, and vertebroplasty or kyphoplasty for selected vertebral lesions to reduce pain and maintain height. Patients should be encouraged to maintain activity to prevent osteopenia and VTE.[6] Preliminary studies of bortezomib indicate that this agent may increase osteoblastic activity, thus increasing bone formation, and therefore may play a role in treating myeloma bone disease.[36]

Bisphosphonates

Bisphosphonates have a long history in the management of myeloma bone disease. These agents inhibit the dissolution of the hydroxyapatite crystals and down-regulate osteoclast function. Studies conducted in the early 1990s demonstrated the impact of intravenous pamidronate in patients with bone disease with myeloma. Pamidronate 90 mg infused over 2-4 hours, once monthly, was the initial agent used in this treatment setting. An early trial involving patients with stage III MM, and at least 1 osteolytic lesion, demonstrated a reduced likelihood of skeletal events by nearly 50%, compared with placebo.[37]

Side effects of pamidronate therapy include fatigue, gastrointestinal effects, anemia, and skeletal pain (though that may be related to the underlying disease). These side effects are not common, but can be problematic in some patients.[38]

Certain bisphosphonates (the more potent nitrogen-containing compounds) also appear to have antitumor activity and have been shown to reduce production of the growth factor interleukin 6 (IL-6), which plays a role in the growth and survival of myeloma cells. Pamidronate also stimulates an immune response against MM that is mediated by T cells. Pamidronate and zoledronic acid have been shown to induce apoptosis (programmed cell death) in the laboratory.[38] A number of trials have demonstrated the equivalency of pamidronate and zolendronic acid for bone protection in myeloma. Avascular osteonecrosis of the jaw has been described as a complication of bisphosphonate use. The American Academy of Oral Medicine published a position paper in 2005 that provides some guidance for patient counseling and management.[39] The Mayo Clinic Myeloma Group has also published a consensus guideline for the use of bisphosphonates in myeloma, which offers guidelines for treatment based on a clinical scenario.[40]

Infection

Infection is a common complication in MM patients. Patients should be vaccinated against *Streptococcus pneumonia, Hemophilus influenzae,* and influenza.[3,6] Although the efficacy of vaccinations in MM patients is highly variable, there is no medical contraindication to vaccinate. Up to 20% of MM patients may develop varicella-zoster virus infections, and prophylaxis should be

considered.[28] Varicella prophylaxis is currently recommended for use with single-agent bortezomib.[3] When corticosteroids are used, prophylactic broad-spectrum antibiotic therapy may be considered. A randomized Eastern Cooperative Oncology Group (ECOG) phase 3 trial is under way, comparing fluoroquinolones versus trimethoprim-sulfamethoxazole versus observation in newly diagnosed patients during the first 2 months of therapy; although at this point, there is no recommendation for antibiotic prophylaxis. Intravenous immunoglobulin therapy should be considered in the setting of recurrent life-threatening infection.[28]

Anemia

Anemia often worsens during resistant or progressive disease, but may improve when the disease is controlled. Patients with anemia from reversible causes such as deficiencies in iron, folate, or B_{12} should receive treatment.[6,41] The impact of anemia on quality of life has been well established.

Future Treatment Approaches for Myeloma

Future MM therapy is sure to include agents with new and unique mechanisms of action and new target sites of activity. Two- and 3-drug combination regimens of existing agents are currently under investigation for broad clinical use. New agents under investigation are being studied as single agents and in combination with proven therapies in an attempt to improve efficacy outcomes and minimize toxicity. In addition to IMiDs and proteasome inhibitors, there are HDAC inhibitors, heat shock protein 90 (HSP-90) inhibitors, farnesyltransferase inhibitors, mammalian target of rapamycin inhibitors, insulin growth factor 1 receptor inhibitors, vascular endothelial growth factor inhibitors, TNF-related apoptosis-inducing ligand, and numerous monoclonal antibodies (Mabs) currently being studied.[42]

HSP-90 is overexpressed in MM cells and functions as a chaperone to shuttle proteins in the proper conformation to mediate growth, survival, and drug resistance signaling on the one hand; as well as to shuttle and unfold ubiquitin-labeled proteins prior to their degradation either via proteasomes or aggresomes.[30] HSP inhibitors have shown promising results when combined with the proteasome inhibitor bortezomib in a phase I trial.[28,43] According to a review of upcoming agents by Burris, a phase 3 clinical trial of KOS-953 HSP-90 inhibitor (tanespimycin) in combination with bortezomib is under way in patients with relapsed MM. Another HSP-90 agent is water-soluble IPI-504, which in early studies has had little toxicity and provided disease stabilization in refractory MM patients.[42]

Histone deacetylation is an important factor in the control of transcription. HDAC inhibitors lead to the reactivation of silenced genes and the induction of apoptosis. HDAC inhibitors are currently being evaluated for use in MM clinical trials. These include vorinostat, which has recently been approved for cutaneous T-cell lymphoma, romidepsin (depsipeptide), and LBH 589. Romidepsin is currently an intravenous formulation, whereas vorinostat and LBH 589 are both administered orally.[42]

Arsenic trioxide, currently approved for use in acute promyelocytic leukemia, is being evaluated in trials in combination with ascorbic acid and dexamethasone for the treatment of MM. According to the same review article by Burris, the response rates have ranged from 20% to 48% in different trials of relapsed myeloma patients. Toxicities of neutropenia and thrombocytopenia were reported.[42]

Several Mabs are in phase 1 clinical trials that target the myeloma cell directly and/or the bone marrow microenvironment. These include Mabs to IGF receptor, IL-6, cluster of differentiation (CD)56, CD40, CD138, anti-CS1, CD70, and CD74.[28]

Perifosine is a synthetic novel alkylphospholipid, a member of a class of antitumor agents that interact with the cell membrane and modulate intracellular growth signal transduction pathways. Perifosine induces significant cytotoxicity in myeloma cells. Specifically, it inhibits Akt/protein kinase B activity. Akt signaling is important for myeloma cell survival and antiapoptosis. Perifosine is also being studied in combination with bortezomib because of synergistic effects observed in vitro.[28]

Conclusion

Although MM is still considered incurable, major advances in the treatment of the disease have been achieved, and many more are to come. Randomized trials promise to define further roles of new and existing pharmacologic agents, alternate methods of transplantation, and maintenance therapy. Pharmacogenomic analysis promises a new era of therapy tailored to the individual patient.[6] Studies and novel treatments aimed at improving response rates, overall survival, and improved quality of life for the myeloma patient are ongoing and promising.

DISCLOSURES

Dr. Schwartz is a member of the Speakers' Bureaus for Cytogen Corporation and Merck & Co., Inc. Dr. Vozniak is a member of the Speakers' Bureau for Enzon Pharmaceuticals, Inc.

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