Support Care Cancer (2015) 23:1431–1445
DOI 10.1007/s00520-014-2552-1

REVIEW ARTICLE

Treatment-related symptom management in patients with multiple myeloma: a review

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Received: 5 September 2014 / Accepted: 30 November 2014 / Published online: 3 February 2015

Abstract
Purpose Recent therapeutic advancements have significantly improved overall survival of patients with multiple myeloma (MM). As a result, the impact of disease- and treatment-related symptoms must be managed effectively to improve patient quality of life, given prolonged survival after diagnosis. This review discusses current MM treatment options, effective symptom management approaches, and practical strategies for supportive care.
Methods A literature search was performed using MEDLINE/PubMed and scientific congress databases, focusing on clinical trials, review articles, clinical practice guidelines, and other guidance documents on treatment paradigms and supportive care strategies in MM. Additionally, clinical practice worksheets were developed from published sources, and nursing "pearls of wisdom" were gathered from practical experience in the clinic.
Results Current therapeutic regimens for relapsed/refractory MM include proteasome inhibitors (i.e., bortezomib, carfilzomib) and immunomodulatory agents (i.e., thalidomide, lenalidomide, pomalidomide), alone or in combination with chemotherapy or corticosteroids. Toxicities associated with agents and combination regimens used in the treatment of MM include myelosuppression, venous thromboembolism, peripheral neuropathy, infections, fatigue, gastrointestinal disorders, and/or cardiac events. Treatment-specific tools and clinical assessments can be useful for optimizing dosing and schedule adjustments to increase therapy duration, and implementing supportive care strategies (e.g., growth factors, transfusional support, intravenous hydration, bisphosphonates, antiviral therapies) to manage treatment-related symptoms.
Conclusions Improved survival after MM diagnosis has led to increased patient susceptibility to other diseases and comorbidities due to advanced age. In addition to appropriate drug dosing and administration, effective supportive care and health maintenance are crucial for maximizing quality of life and disease control.

Keywords Multiple myeloma · Symptom management · Supportive care · Quality of life · Proteasome inhibitors · Immunomodulatory agents

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Introduction

Multiple myeloma (MM) represents 1 % of all cancer and 10 % of hematologic malignancies in the USA and Europe [1]. MM is a B cell neoplasm of plasma cells that overproduce immunoglobulin heavy- and light-chain M-proteins, accumulate in bone marrow, and frequently invade adjacent bone [2–4]. Primarily a disease of the elderly, MM is also more prevalent in men than women and in blacks than whites [5, 6]. Typical clinical manifestations of MM include bone pain due to lytic lesions or osteoporosis, anemia, renal insufficiency, hypercalcemia, immunodeficiency, and increased susceptibility to infection [2]. Cytogenetic abnormalities are also common in patients with MM and are recognized as important prognostic factors [7].

MM is considered to be a highly treatable but incurable disease, and a majority of patients relapse or become refractory to treatment [8]. Overall survival (OS) has significantly improved with recent therapeutic advancements [9], namely proteasome inhibitors (PIs) and/or immunomodulatory drugs (IMiDs) with corticosteroids in combination with supportive care strategies, including growth factor (i.e., granulocyte colony-stimulating factor [G-CSF]) and transfusional support (i.e., red blood cells, platelets), intravenous (IV) hydration,

bone strengtheners (i.e., bisphosphonates), and antiviral therapy and early antibiotic intervention to combat high infection risk. However, survival improvements have led to increased comorbidities in patients due to the disease itself and treatment-related adverse effects [10]. This review will discuss MM treatment options, disease-related symptom considerations, approaches to effective symptom management, and practical strategies for supportive care based on US research experience at the Dana-Farber Cancer Institute (DFCI) and others.

Treatment options for patients with MM

MM treatment overview

The treatment goal for patients with MM is disease control in an effort to prolong survival and improve quality of life (QOL). Approaches differ based on various factors, including age, comorbidities, and performance status [11]. Current therapeutics approved or in development for MM include PIs, IMiDs, chemotherapy, corticosteroids, deacetylase inhibitors (DACis), and monoclonal antibodies (mAbs). Each class of agents has their own profile of associated adverse events (AEs) (Table 1). Guidelines for selecting a treatment regimen and providing supportive care to patients are provided by the National Comprehensive Cancer Network, International Myeloma Working Group, and International Myeloma Foundation Nurse Leadership Board (IMF-NLB) [12–15].

Patients with active MM can be classified into three major categories: newly diagnosed (NDMM) eligible for stem cell transplant (SCT), NDMM ineligible for SCT, and relapsed and/or refractory (RRMM) [11]. Autologous stem cell transplant (ASCT), in combination with antimyeloma agent induction or maintenance/consolidation therapy, remains a standard of care for eligible patients with NDMM [12, 13]. Patients who undergo ASCT receive high-dose chemotherapy to reduce the amount of MM cells, followed by IV administration of their own blood-forming stem cells [16]. Standard treatment for ASCT-ineligible patients can include reduced-intensity frontline therapy with PIs or IMiDs and corticosteroids, followed by optional maintenance therapy or clinical trials [14]. Current treatment algorithms for RRMM are complex, and treatment decisions are based on patient characteristics and previous drug exposure and outcomes [8].

Proteasome inhibitors

Proteasome complexes play a major role in intracellular protein degradation and clearance of misfolded and/or unfolded proteins [17]. Because MM cells produce large amounts of immunoglobulin, proteasome function is crucial for their survival [2, 4, 17]. Exposure of MM cells to PIs induces accumulation of misfolded protein aggregates, leading to MM cell protein overload and apoptosis [17].

Bortezomib, a PI approved for the treatment of NDMM and RRMM, is used in frontline/induction therapy for both ASCT-eligible and -ineligible patients, and in maintenance or salvage therapy regimens. It is often administered in combination with corticosteroids (e.g., dexamethasone) or IMiDs (e.g., lenalidomide) [12, 18]. Peripheral neuropathy (PN) is a major toxicity of concern for patients undergoing bortezomib treatment. Bortezomib-induced PN is predominantly sensory and related to risk factors such as cumulative IV dose and

Table 1 Adverse events commonly associated with multiple myeloma therapeutic agents

		PN	Myopathy	VTE	Thrombocytopenia	Neutropenia	Lymphopenia	Anemia	Decreased NK cells	Infection	Pneumonia	Fatigue	Nausea	Diarrhea	Constipation	2° primary malignancy	High blood glucose	Infusion reaction	Osteoporosis	Rash	Edema	Mood disorders
PIs	Bortezomib	X			X					X		X	X	X	X							
	Carfilzomib				X	X	X	X			X	X	X	X							X	
IMIDs	Thalidomide	X		X		X						X	X		X					X	X	
	Lenalidomide			X	X	X		X		X		X	X	X	X	X				X	X	
	Pomalidomide			X	X	X		X				X	X		X					X		
Chemotherapy	Cyclophosphamide				X	X		X		X			X			X						
	Melphalan				X	X		X					X	X		X						
Corticosteroids	Dexamethasone		X	X						X			X				X		X		X	X
	Prednisone		X	X						X			X				X		X		X	X
DACis	Panobinostat				X	X	X	X			X	X		X								
	Vorinostat				X			X				X	X	X								
mAbs	Elotuzumab							X			X	X	X	X			X	X				
	Daratumumab				X				X									X				

NK natural killer, *PN* peripheral neuropathy, *VTE* venous thromboembolism

evidence of preexisting neuropathy [19]. Administration of bortezomib subcutaneously (SC) significantly reduces the occurrence of PN (grade 3/4, 6 vs 16 %; P=.026) and other treatment-related toxicities, but most importantly, efficacy is not compromised compared with IV administration. Moreover, SC bortezomib retreatment of patients with relapsed MM does not result in accumulating toxicity [20–23]. The clinical benefits of SC bortezomib have also been observed through practical and anecdotal experience at various institutions, in conjunction with monitoring PN prior to initiating each new treatment cycle. In addition to PN, other frequently occurring toxicities include transient thrombocytopenia, neutropenia, nausea, diarrhea, neuralgia, anemia, leukopenia, vomiting, fatigue, and herpes zoster infection (HZI), all of which are generally considered to be manageable [24–26].

Carfilzomib is a second-generation PI approved for treating RRMM after ≥2 prior treatments, including bortezomib and IMiDs [27]. Carfilzomib also demonstrated promising activity as an alternative frontline therapy in combination with lenalidomide and dexamethasone for ASCT-eligible or -ineligible elderly patients (3-year progression-free survival [PFS], 79.6 %; 3-year OS, 100 %) [12, 28]. Carfilzomib exhibits higher proteasome selectivity than bortezomib and can irreversibly inhibit proteasomes [29]. Unlike bortezomib, carfilzomib is not associated with PN; rather, frequently occurring toxicities include fatigue, anemia, nausea, transient thrombocytopenia, dyspnea, diarrhea, pyrexia, upper respiratory tract infection, lymphopenia, and neutropenia [27, 30, 31]. Cardiac events (congestive heart failure or cardiac arrest) have led to treatment discontinuation in a small percentage of cases; thus, it is recommended that patients with MM have an electrocardiogram, pulmonary function tests, and echocardiogram prior to carfilzomib treatment.

Immunomodulatory drugs

In MM, thalidomide and its analogues are collectively referred to as IMiDs [32]. Although the mechanism of action is not completely understood, IMiDs are believed to inhibit MM cell proliferation and angiogenesis and produce immunomodulatory effects by affecting cytokines related to tumor growth. For example, lenalidomide and pomalidomide directly downregulate tumor cell function and indirectly influence MM cell-microenvironment interactions. Thalidomide and lenalidomide are known to exhibit antiangiogenesis effects and induce apoptosis [32].

Thalidomide, approved for treating NDMM in combination with dexamethasone [33], has also been used as an alternative primary therapy regardless of ASCT eligibility, in maintenance therapy regimens, and as a salvage therapy in RRMM [12, 34]. Toxicities associated with thalidomide include fatigue, sedation, or somnolence, hypocalcemia, PN, infection, edema, constipation, muscle weakness, leukopenia, neutropenia, skin rash, and venous thromboembolic events (VTEs) [34, 35]. Like bortezomib, PN associated with thalidomide is related to treatment duration and cumulative dose. Thalidomide-related PN and constipation are more frequent in elderly patients; caution and lower doses are recommended for this patient group [34].

Lenalidomide is approved in combination with dexamethasone for treating patients with MM who have received ≥1 prior therapy, and is often used in frontline/induction therapy for both ASCT-eligible and -ineligible patients and in maintenance or salvage therapy regimens [12, 36]. Lenalidomide appears to be as efficacious as thalidomide in MM but less toxic [37]. Common lenalidomide-related toxicities include fatigue neutropenia, constipation, diarrhea, muscle cramp, anemia, pyrexia, edema, nausea, back pain, infections, skin rash, and thrombocytopenia [25, 38]. A low rate of increased risk of secondary primary malignancy has also been observed in studies of lenalidomide-based regimens compared with placebo (4–8 vs 1–3 %, with upper-range percentages generally in elderly patients) [38]. Rash can occur with lenalidomide, which typically can be managed by antihistamine therapies (e.g., cetirizine, loratadine), steroids, and/or appropriate dose modification [39]. Severe lenalidomide-induced rashes (e.g., Stevens-Johnson syndrome) have been observed during practical experience, and patients should be routinely monitored for skin-related AEs during treatment.

Pomalidomide, the newest IMiD, was recently approved for treating RRMM after ≥2 prior treatments, including lenalidomide and bortezomib, and has also been used in salvage therapy in combination with dexamethasone [12, 40]. Pomalidomide demonstrated more powerful inhibitory effects on target cytokines compared with other IMiDs in preclinical studies, and is efficacious in heavily treated and lenalidomide- and/or bortezomib-resistant patients [41]. Pomalidomide-associated toxicities include fatigue and asthenia, neutropenia, febrile neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, infection, back pain, and thrombocytopenia [39, 42]. Similar to lenalidomide, manageable rash can occur with pomalidomide treatment [39].

Chemotherapy and corticosteroids

Agents historically used to treat MM are now commonly used in combination with PIs and IMiDs [12]. Alkylating agents, a class of cytotoxic chemotherapeutics, have been used to treat MM for ≥40 years [9]. Cyclophosphamide is currently used in combination with PIs or IMiDs in salvage therapy regimens for RRMM, and melphalan is often used in primary induction therapy for ASCT-ineligible patients [12, 25]. Frequently occurring toxicities with alkylating agents include nausea,

vomiting, diarrhea, alopecia, pruritus, myelosuppression, rash, mouth sores, and hypersensitivity reactions [43].

Corticosteroids were widely used for MM treatment prior to the introduction of PIs and IMiDs, and are currently used in combination with bortezomib, carfilzomib, lenalidomide, pomalidomide, and/or thalidomide [9, 12]. In addition to their anti-inflammatory properties, which reduce swelling around tumors and associated pain, corticosteroids can induce apoptosis in MM cells [44]. Dexamethasone is often combined with PIs and/or IMiDs for primary therapy, regardless of patient ASCT eligibility, and for salvage therapy in RRMM [12]. For example, combined cyclophosphamide, bortezomib, and dexamethasone (CyBorD) demonstrated high overall response rates (89 %) and 5-year OS (70 %) in NDMM, including in high-risk patients [45]. Prednisone is used in induction therapy for ASCT-ineligible patients [12]. Long-term use of high-dose steroids is not recommended due to an association with increased infection risk, osteoporosis, VTEs, myopathy, and elevated blood glucose [12, 46, 47]. Steroids also commonly cause fluid retention, elevated blood pressure, behavioral and mood changes, and increased appetite and weight gain [48].

Deacetylase inhibitors

As most patients will relapse and become refractory to currently available treatments, several novel therapeutic agents are in development for MM treatment, including DACis, which inhibit aggresome formation. Aggresomes are protein aggregates that develop when production of misfolded proteins exceeds the capacity of proteasome complexes, and have recently been recognized as a secondary pathway for lysosome-mediated protein degradation [17]. DACi agents target key components involved in aggresome function, which can lead to accumulation of the proteins overproduced in MM cells, and enhance MM cytotoxicity induced by PIs [17].

Panobinostat, a potent, oral pan-DACi, has demonstrated clinical efficacy in combination with bortezomib and dexamethasone in MM [49–51]. In a phase 3 study (PANORAMA 1), patients with RRMM received panobinostat (20 mg) or placebo three times per week plus IV bortezomib (1.3 mg/m^2; days 1, 4, 8, and 11) during weeks 1 and 2, with oral dexamethasone (20 mg) on the days of and after bortezomib, during eight 3-week cycles. Patients benefitting from these first eight 3-week cycles proceeded to a maintenance phase, with the same panobinostat dosing and less-frequent bortezomib/dexamethasone dosing. Patients receiving panobinostat/bortezomib/dexamethasone in this study had improved overall response (61 vs 55 %), with a near doubling of the complete response (CR)/near CR (27.6 vs 15.7 %), and longer PFS (12.0 vs 8.1 months; $P<.0001$) compared with placebo/bortezomib/dexamethasone [49]. Panobinostat-associated toxicities include transient thrombocytopenia, lymphopenia, leukopenia, neutropenia, diarrhea, anemia, fatigue and asthenia, and nausea and vomiting [49–51], which are manageable. Additional DACis, including vorinostat [17, 52–54] and rocilinostat (ACY-1215) [55–57], are being evaluated in clinical trials.

Monoclonal antibodies

mAbs targeting tumor cell-associated surface proteins are also being developed for MM treatment. Elotuzumab, a humanized immunoglobulin-G1 mAb directed against tumor-expressing surface glycoprotein CS-1, showed efficacy in a phase 2 trial in combination with lenalidomide and low-dose dexamethasone in patients with RRMM [58]. Elotuzumab activity in MM continues to be evaluated in ongoing phase 3 trials, including in patients with RRMM (NCT01239797) and NDMM (NCT01335399; NCT01891643). Most elotuzumab-associated toxicities are manageable and include fatigue, anemia, and infusion-related reactions (most commonly nausea, headache, and dyspnea) [58, 59].

Daratumumab is a humanized mAb with broad-spectrum tumor-killing activity directed against MM cells expressing CD38 [60]. In a phase 1/2 study, daratumumab demonstrated single-agent efficacy in patients with RRMM [61]. Preclinical studies demonstrating an ability of lenalidomide to activate T cell-mediated cytotoxicity [62] have supported the development of ongoing phase 1/2 and 3 studies evaluating daratumumab in combination with lenalidomide in patients with RRMM (NCT01615029; NCT02076009). Infusion-related reactions and decreased natural killer cells in the peripheral blood are commonly associated with daratumumab treatment [60, 61]. SAR650984, another humanized anti-CD38 mAb in early-stage development for MM, demonstrated encouraging single-agent activity in heavily-pretreated patients with RRMM in an ongoing phase 1 study [63].

Treatment-related symptoms in patients with MM

Prolonged survival after MM diagnosis directly impacts patient QOL via disease- and treatment-related symptoms. As described, in addition to common MM signs and symptoms (i.e., assessed by CRAB criteria: hyper**c**alcemia, **r**enal insufficiency, **a**nemia, and **b**one pain), MM treatment-related AEs include PN, VTE, infections, fatigue, gastrointestinal (GI) issues, and cardiac events. Treatment-related AEs can be mild to severe (Table 2), and depend on the agent or combination of agents. Awareness and effective management of treatment-related adverse effects are needed to maximize patient outcomes.

PN, defined as any damage, inflammation, or degeneration of the peripheral nerves, is typically the most problematic

Table 2 Treatment-related patient complications in multiple myeloma

AE [Reference]	Possible patient complications	
	Mild to moderate	Severe
Peripheral neuropathy [10, 26, 64]	• Numbness/tingling in hands and feet • Mild burning pain • Sensitivity to touch and heat • Muscle weakness • Skin, hair, or nail changes • Lack of coordination	• Sharp, jabbing or electric-like pain • Changes in blood pressure • Heat intolerance • Extreme sensitivity to touch • Bowel, bladder, or digestive problems • Paralysis
Vein thromboembolic events [66]	• Redness of the skin • Angina and/or pain in extremities • Shortness of breath • Rapid heart beat • Deep vein thrombosis	• Pulmonary embolism • Death
Neutropenia [25, 87]	• Frequent infections • Fever • Subtle inflammation	• Severe infection
Thrombocytopenia [88, 89]	• Prolonged bleeding time • Impaired or delayed clot retraction	• Serious hemorrhage • Development of solid tumors or hematologic malignancies
Infection (bacterial or viral) [25, 72]	• Fever (non-MM related) • GI disorders • Respiratory symptoms	• Sepsis • Death
Fatigue [74]	• Sleep-wake disturbances • Insomnia • Decreased daytime activity	• Development of mood disorders • Depressive symptoms • Physiological deconditioning • Diminished activity tolerance
GI disorders [10]	• Acute nausea and vomiting • Loss of appetite • Constipation • Diarrhea	• Chronic nausea and vomiting • Anorexia • Severe constipation • Stress-related hyperacidity and peptic ulceration
Cardiac events [79, 90]	• Angina • QTc prolongation • Slow heart rate	• Arrhythmia • Heart failure • Death

AE adverse event, *GI* gastrointestinal, *MM* multiple myeloma, *QTc* corrected QT

treatment-related complication in MM [10, 26, 64]. PN is most associated with bortezomib and thalidomide treatment (up to ≈75 % of treated patients with MM), but is also a symptom of the disease itself (up to 20 % of patients with MM prior to treatment) [10, 26, 64, 65]. General PN symptoms manifest in MM as paresthesia, numbness, burning sensations, and weakness [26, 64]; treatment-induced PN symptoms in MM are usually symmetric, distal (beginning in hands and feet), progressive, and mild, but can also be disabling or life threatening [64, 65]. With the exception of bortezomib-related PN, which can be reduced by SC administration, there is no gold standard for preventing or treating PN [64].

VTEs include deep vein thrombosis and potentially lethal pulmonary embolism, which occur in up to ≈9 % of patients with MM [10, 66]. The risk of VTEs is increased in patients with MM treated with thalidomide or lenalidomide combined with high-dose steroids and cytotoxic agents [10, 66]. For example, in clinical trials in which VTEs was not proactively managed, IMiDs (i.e., lenalidomide and thalidomide) in combination with dexamethasone resulted in VTEs in a significant proportion (>25 %) of patients [47, 66–69]. Treatment-induced VTE risk is generally higher in patients with NDMM than RRMM [66], and in contrast with IMiDs, bortezomib treatment does not increase VTE risk in patients with MM [10, 66]. Management of treatment-related VTEs in MM typically includes patient risk assessment followed by thromboprophylactic approaches, which can be mechanical (e.g., sequential compression devices, antiembolism stockings, exercise), pharmacological (e.g., low-molecular-weight heparin, warfarin, aspirin), or regimen based (e.g., changes to IMiD or steroid dosing and scheduling) [10, 66, 70]. For example, the high incidence of symptomatic VTEs with lenalidomide or thalidomide decreased to 15 to 18 % with the introduction of daily aspirin [66, 67]. Risks for VTEs include patient factors (e.g., previous VTE, obesity, comorbidities), myeloma-related factors (e.g., hyperviscosity, disease burden), and treatment-related factors (e.g., concurrent use of high-dose steroids with thalidomide or lenalidomide) [10].

Thrombocytopenia and neutropenia are common hematologic events generally related to antimyeloma treatments rather than the disease itself, and are associated with nearly all PI, IMiD, and emerging-agent regimens to various extents [24, 25, 30, 38, 42, 71]. Thrombocytopenia is more frequent with bortezomib- and lenalidomide-based treatments, but rare for thalidomide regimens [25, 51]. Thrombocytopenia is cyclical, often reversible, and generally managed by platelet transfusions and/or dose modifications. Neutropenia is a particularly common AE for lenalidomide and alkylating agents but less frequent for bortezomib, and febrile neutropenia occurrence is generally low (<4 %) [25, 42, 71]. Treatment-related neutropenia is usually managed by dose and schedule adjustments; however, additional treatment with G-CSF is often considered for high-risk patients or those experiencing severe treatment-induced neutropenia [25, 71].

Risk of infection and its associated complications (e.g., cellulitis, upper respiratory infection, pneumonias) are increased in MM and the leading cause of death for patients with this disease [10, 25, 72]. MM regimens can be associated with increased infection risk, with infections occurring in up to ≈22 % of treated patients, most likely due to treatment-associated immunosuppressive adverse effects (e.g., neutropenia) [25, 72]. HZIs commonly occur in patients treated with PIs (i.e., bortezomib and carfilzomib) or after ASCT, treatments that can affect cell-mediated immunity and/or result in virus reactivation [25, 30, 72]. A low threshold should be set for implementing infection management and prevention strategies, including short-term antibiotic regimens, vaccines, and IV prophylactic immunoglobulin replacement [10]. For patients receiving a PI after ASCT or with chronic HZIs, preventative treatment with antiviral agents (e.g., acyclovir) is recommended [10]. Monitoring for infection is also important during treatment with steroids, especially dexamethasone, as the general anti-inflammatory properties of these agents can mask signs that an infection is present [44]. Patient education on general measures to prevent infection is also strongly recommended [72].

Fatigue is considered to be the most serious complication of MM and a major factor in decreased functioning and QOL. Fatigue occurs in many patients with the disease (≈80 %) and worsens with time after diagnosis [10, 73]. Most patients with MM receiving intensive treatment experience fatigue, which often presents as a result of multiple treatable physical and psychological factors [10, 74]. Management of the contributing factors can improve fatigue, and strategies may include blood transfusions, treatment for depression, sleep disturbance assessments, and comprehensive exercise programs [10, 74]. Functioning and QOL appear to improve when patients participate in exercise programs that incorporate low to moderate intensity aerobic exercise, education classes (e.g., group fitness, sessions on benefits of exercise, and proper nutrition), and support from peers and program specialists [75, 76].

GI disorders, including constipation, diarrhea, nausea, and vomiting, are common MM treatment-related AEs that are rarely associated with the disease itself [25, 77]. The type and degree of GI symptoms vary depending on treatment, but can reduce QOL, interfere with optimal therapy, and are most associated with lenalidomide, bortezomib, and panobinostat [25, 49, 77]. Approximately, 60 % of patients receiving MM treatment experience GI-related events, which are typically grade 1 to 3 [77]. Management strategies for GI toxicities include changes in diet and fluid uptake, pharmacological agents, and dose modifications of antimyeloma agents in severe cases [77].

Management of treatment-related cardiac events should include avoiding concomitant medications known to induce corrected QT (QTc) prolongation (e.g., cytochrome P450 inhibitors), risk assessment and monitoring of patients with preexistent cardiopathy, or MM treatment dose modifications when necessary [25, 78]. QTc prolongation increases the risk of cardiac arrhythmias (i.e., torsades de pointes) that can degenerate to ventricular fibrillation and sudden death [79]. When drug-induced cardiac events such as QTc prolongation occur during MM treatment, they are usually reported in patients with a history of cardiovascular comorbidities (e.g., congestive heart disease or rhythm disturbances); however, cardiac events related to MM treatment have also been observed in patients without baseline cardiac risk factors [25, 78].

Clinical management of treatment-related symptoms

Dose and scheduling modifications, including adjustments or interruptions, are common and effective strategies to allow recovery from MM treatment-induced symptoms (Table 3) [12, 25, 71]. While reports of treatment-associated AEs are accessible through primary publications and package inserts for antimyeloma agents, understanding the severity of individual AEs is important for effective symptom management. For example, the National Cancer Institute Common Terminology Criteria for Adverse Events for specific toxicities associated with MM treatments are often incorporated into dose reduction and interruption strategies and recommendations [39, 71, 80]. Patient education to heighten awareness and encourage prompt reporting of potential MM treatment-related symptoms is also essential for addressing and reducing the severity of AEs and improving QOL [81, 82].

Additionally, the way in which antimyeloma drugs are administered can affect the frequency and/or severity of associated AEs. For example, SC administration of bortezomib demonstrated similar efficacy and improved safety over IV dosing [20]. SC administration can also contribute to improved QOL, as less time in the clinic is required. Based on practical experience from the DFCI and others [83], SC

Table 3 Considerations for multiple myeloma treatment administration

Agent [Reference]	Considerations	Routine assessments	Drug cautions	Dosing	Recommended adjustments
Agents approved for the treatment of MM					
Bortezomib [18, 39, 80, 83]	• Patients may experience - Myelosuppression - PN - Nausea and/or vomiting - Diarrhea or constipation - Neuralgia - Fatigue - Infection - Hypotension • Antibiotics and/or HSV prophylaxis recommended • SC or weekly IV administration appears less toxic but effective	• PN monitoring • CBCs	• CYP3A4 substrates, which can affect drug exposure	• 1.3 mg/m^2 IV or SC on days 1, 4, 8, 11 • Repeat cycle every 21 days for 4 cycles • Usually dosed with dexamethasone • Inject SC doses slowly (to avoid skin reactions) and at a 90° angle with a needle of the proper gauge • Use gauze pad instead of alcohol swab to avoid smearing drug that comes out of injection site	• PN management - Moderate: 1.0 mg/m^2 - Severe: 0.7 mg/m^2 - Life threatening: discontinue • TCP management - Withhold upon low platelet or ANC - Reduce dose level if withheld for ≥ 3 days • Renal insufficiency requires dialysis, but not dose reduction
Carfilzomib [27, 39]	• Patients may experience - Fatigue - Myelosuppression - Nausea - Shortness of breath - Diarrhea - Fever - Upper respiratory tract infection - Headache - Cough - Edema • Antibiotics and/or HSV prophylaxis recommended • Patients at risk for impaired cardiac function or TLS should be monitored • Gout and VTE prevention recommended for patients at risk	• CBCs • VTE risk • Liver enzyme monitoring	• No strong drug interactions expected	• 28-day cycles • Cycle 1: 20 (cycle 1) or 27 (cycle 2) mg/m^2 IV on days 1, 2, 8, 9, 15, 16 every 28 days • Usually dosed with lenalidomide and/or dexamethasone	• Start carfilzomib at 20 mg/m^3 and escalate as tolerated • Nausea and vomiting management - Premedication with 5-HT3 receptor agonist • PN and TCP management - Withhold for grade 3/4 event, then continue or reduce dose depending on time to recovery - Reduced dose can be reescalated with caution • Renal impairment management - Dose given after dialysis on dialysis days - Oral hydration should be encouraged
Thalidomide [33, 39, 71, 80]	• Patients may experience - Fatigue and/or somnolence - Hypocalcemia - PN - Infection - Edema - Constipation - Muscle weakness - Myelosuppression - Skin rash	• ANC counts • VTE risk	• Opioids • Antihistamines • Antipsychotics • Antianxiety agents • Other CNS depressants (e.g., alcohol)	• 28-day cycles • 200 mg orally once daily • Dosed with dexamethasone at 40 mg on days 1–4, 9–12, and 17–20	• Achieve target dose gradually (e.g., escalate 50–100 mg each week) to improve tolerability • VTE management - Administer aspirin 81–325 mg daily - Stratify for VTE risk to determine if

Table 3 (continued)

Agent [Reference]	Considerations	Routine assessments	Drug cautions	Dosing	Recommended adjustments
Thalidomide [33, 39, 71, 80]	- Anorexia - Nausea - Confusion or anxiety - Tremor - VTE or PE - Drug hypersensitivity • Teratogenic; women should avoid pregnancy • Sedating; evening dosing and avoidance of other drowsiness-inducing medications recommended • Patients should be alerted to VTE risk • Caution should be used with the elderly				anticoagulant therapies should be used • PN management - Grade 2/3: reduce dose or suspend; resume at low dose; grade 4: discontinue
Lenalidomide [36, 39, 71, 80]	• Patients may experience - Fatigue - Myelosuppression - Constipation - Diarrhea - Muscle cramp - Fever - Peripheral edema - Nausea - Back pain - Skin rash - DVT or PE - TLS - Secondary malignancies - Drug hypersensitivity • Teratogenic; women should avoid pregnancy • Patients should be alerted to VTE risk	• CBCs • VTE risk • Dermatologic • TLS monitoring	• Digoxin, which can affect drug exposure • Erythropoietin-stimulating or estrogen-containing therapies may increase VTE risk	• 28-day cycles • 25 mg orally on days 1–21 • Dosed with dexamethasone at 40 mg on days 1–4, 9–12, and 17–20 for the first 4 cycles, then days 1–4 for subsequent cycles	• VTE management - Administer aspirin 81–325 mg daily - Stratify for VTE risk to determine if anticoagulant therapies should be used • Rash management - Antihistamines (e.g., cetirizine, loratadine) • Diarrhea management - Loperamide, diphenoxylate-atropine, diet • Myelosuppression management - Withhold upon low platelet or ANC count - On recovery, resume at lower dose • Adjust dose as necessary for renal function
Pomalidomide [39, 40, 80]	• Patients may experience - Fatigue and/or asthenia - Myelosuppression - Constipation - Nausea - Diarrhea - Shortness of breath - Upper respiratory tract infections - Back pain - Skin rash • Teratogenic; women should avoid pregnancy	• CBCs	• CYP1A2 inhibitors can increase exposure	• 28-day cycles • 4 mg on days 1–21 • Often dosed with dexamethasone	• Rash management • Antihistamines (e.g., cetirizine, loratadine) • Myelosuppression management - Withhold upon low platelet or ANC count - On recovery, resume at lower dose

Table 3 (continued)

Agent [Reference]	Considerations	Routine assessments	Drug cautions	Dosing	Recommended adjustments
Cyclophosphamide [39, 91]	• Patients should be alerted to VTE risk • Patients may experience - Nausea and/or vomiting - Alopecia	• CBCs	• Phenobarbital can increase exposure	• Orally: 50 mg daily	• Low doses are generally well tolerated • Myelosuppression management - Withhold upon hematologic event - On recovery, resume at lower dose • Educate patients on infection risk and preventative measures
Cyclophosphamide [39, 91]	- Myelosuppression - Infection - Hemorrhagic cystitis or urinary bladder fibrosis - Secondary malignancies - Interstitial pneumonitis - Drug hypersensitivity			• IV: 10–15 mg/kg IV every 7–10 days or 3–5 mg/kg twice weekly • Often dosed with dexamethasone and lenalidomide and/or proteasome inhibitors	
Agents frequently used in combination with approved agents					
Melphalan [39, 92]	• Patients may experience - Myelosuppression - Nausea and/or vomiting - Diarrhea - Oral ulceration - Dermatologic events - Secondary malignancies - Drug hypersensitivity	• CBCs	• Cyclosporine, which can increase renal failure risk • Live vaccines	• 16 mg/m^2 IV every 2 weeks for 4 doses, then every 4 weeks • Should be administered in carefully adjusted dosage • Usually dosed with prednisone	• Dose reduction should be considered in patients with renal/ creatinine clearance insufficiency and myelosuppression • Administer antacids to reduce indigestion
Dexamethasone [39, 93]	• Patients may experience - Hypertension - VTE - Endocrine disorders - Edema - GI events - Musculoskeletal issues - Neurological/psychiatric issues - Elevated intraocular pressure - Increased appetite and/or weight gain - Drug hypersensitivity • Avoid use with systemic fungal infections	• Cushing syndrome and diabetes tests • Mood disorders	• Amphotericin B and K^+ -depleting agents due to cardiac risks	• 0.75–9 mg orally daily • Dose should be adjusted for individual patient and disease • Usually dosed in combination with other antimyeloma agents	• Screen patients for mood disorders and diabetes before dosing • Do not stop dosing abruptly • Dose reductions recommended when QOL is negatively impacted
Prednisone [39, 48]	• Patients may experience - Hypotension - Endocrine disorders - Edema - Arthralgia - GI events - Increased appetite and/or weight gain - Musculoskeletal issues	• Cushing syndrome and diabetes tests • Mood disorders	• Amphotericin B, antibiotics • Anticholinest erases and antidiabetics	• 5–60 mg orally daily • Doses should be individuated • Should be taken with food or milk to reduce gastric irritation • Usually dosed in combination with other antimyeloma agents	• Higher doses may initially be required • Screen patients for mood disorders and diabetes before dosing • Do not stop dosing abruptly • Dose reductions recommended

Table 3 (continued)

Agent [Reference]	Considerations	Routine assessments	Drug cautions	Dosing	Recommended adjustments
	- Neurological/psychiatric issues - Ophthalmic issues - Drug hypersensitivity • Avoid use with systemic fungal infections • Teratogenic; women should avoid pregnancy				when QOL is negatively impacted
Agents in development for the treatment of MM					
Panobinostat [51, 94]	• Patients may experience - Myelosuppression - Diarrhea - Fatigue and/or asthenia - Nausea or vomiting - Decreased appetite	• CBCs	• No strong drug interactions expected	• 20 mg orally 3 times per week on a 2-week-on/1-week-off schedule • Dosed with dexamethasone and/or bortezomib	• A treatment rest week may improve tolerability • TCP management - Reduce/interrupt dose ± platelet transfusion - Platelets often recover within 1 week
Vorinostat [95, 96]	• Patients may experience - Myelosuppression - Diarrhea - Fatigue and/or asthenia - Cough - VTE - Hyperglycemia and/or other lab abnormalities	• CBCs	• Coumarin-derivative anticoagulants • Other DACis	• 21-day cycles • 400 mg orally on days 1–21 • Dosed in combination with other antimyeloma agents	• Reduce initial dose for patients with severe hepatic impairment • Supportive care is recommended in addition to dose reduction/ interruption for AE management
Elotuzumab [58, 59]	• Patients may experience - Fatigue - Myelosuppression - Nausea and/or vomiting - Hyperglycemia - Diarrhea - Pneumonia - Infusion-related reactions	• CBCs • Diabetes monitoring	• Data not available	• 28-day cycles • 10–20 mg/kg IV once weekly • Dosed in combination with other antimyeloma agents	• Dose reductions/interruptions of combination agents may improve tolerability of elotuzumab-based regimens
Daratumumab [61, 97]	• Patients may experience - Myelosuppression - Bronchospasm and/or lab abnormalities - Infusion-related reactions	• CBCs	• Data not available	• 4–24 mg/kg IV once weekly • Dose alone or in combination with lenalidomide	• Dose reductions/interruptions of combination agents may improve tolerability-associated AEs

AE adverse event, *ANC* absolute neutrophil count, *CBC* complete blood count, *CNS* central nervous system, *CYP* cytochrome P, *DACi* deactylase inhibitor, *DVT* deep vein thrombosis, *5-HT3* 5-hydroxytryptamine, *GI* gastrointestinal, *HSV* herpes simplex virus, *IV* intravenous, *PE* pulmonary embolism, *PN* peripheral neuropathy, *QOL* quality of life, *SC* subcutaneous, *TCP* thrombocytopenia, *TLS* tumor lysis syndrome, *VTE* venous thromboembolism

Table 4 Adverse event checklist for monitoring patients with multiple myeloma

PATIENT INFORMATION		ASSESSMENT DETAILS	
Name of patient		Name of assessor	
Date of birth	_ _ /_ _ /_ _ _ _	Date of assessment	_ _ /_ _ /_ _ _ _

PATIENT HISTORY					
Diagnosis					
Date of initial diagnosis	_ _ /_ _ /_ _ _ _		Date of most recent assessment	_ _ /_ _ /_ _ _ _	
Prior treatment					
Regimen #	Medications	Start date	End date	Outcome	Treatment complications
Current treatment					
Regimen #	Medications	Start date	Notes from previous assessment		

TREATMENT-RELATED ADVERSE EVENT CHECKLIST					
Please indicate "Yes" or "No" for each of the following criteria. If "Yes," consider recommended actions.					
AE Category	Patient Assessment	Y	N	Recommended Action	Notes
Peripheral neuropathy (PN)	• Numbness, tingling, or pain?			• For bortezomib or thalidomide, reduce dose for severe PN • Prescribe medications for moderate/severe PN (eg, capsaicin, antiseizure medications)	
	• Dizziness or difficulty walking?				
Vein thromboembolic event (VTE)	• Leg swelling?			• Assess VTE risk • For immunomodulatory drugs, VTE prophylaxis recommended (eg, aspirin, low-molecular-weight heparin, warfarin)	
	• History of blood clots, stroke, kidney disease?				
	• Taking pomalidomide, lenalidomide, or thalidomide?				
Neutropenia	• Absolute neutrophil count < 1500 μL?			• Routine complete blood count assessment • Treatment dose interruption or reduction • Provide granulocyte colony-stimulating factor to patients with high risk or treatment intolerance	
Thrombocytopenia	• Excessive bruising or prolonged bleeding?			• Routine complete blood count assessment • Treatment dose interruption (eg, 1 week for bortezomib/panobinostat regimens) or reduction • Platelet transfusion	
	• Blood in urine or stool?				
	• Platelet count < 1.5×10^5/μL?				
Infection	• Fever, chills, or pain during urination?			• Illness assessment (eg, urinalysis, blood cultures or counts, X-ray) • For proteasome inhibitors, give acyclovir or valacyclovir • Pneumonia vaccine every 5 years • Influenza vaccine every year	
	• Recent vaccinations?				
	• Taking bortezomib or carfilzomib?				
Fatigue	• Tiredness, lethargy, somnolence?			• Assess for sleep disturbance • Enroll in comprehensive exercise program	
Gastrointestinal disorder	• Diarrhea?			• Diarrhea: provide medications (eg, loperamide, cholestyramine, bismuth subsalicylate) and/or assess stool for *Clostridium difficile* if infection is suspected • Constipation: provide laxatives (avoid enemas and suppositories in patients with neutropenia) • Nausea and vomiting: assess medications list, provide antacids or proton pump inhibitors for gastric acid, and/or provide preventative medications (eg, ondansetron, dolasetron)	
	• Constipation?				
	• Nausea?				
	• Vomiting?				
Cardiac event	• Shortness of breath?			• Assess for QT prolongation or heart failure (eg, 12-lead electrocardiogram)	
	• History of QT prolongation?				

administration of bortezomib also requires its own set of specific considerations: reconstitution specifications compared to IV dosing (e.g., concentration care when calculating reconstitution volume [typically 2.5 mg/mL for SC vs 1 mg/mL for IV]), selection of an appropriate injection site (i.e., abdomen and thigh are preferred at DFCI), skin-fold and needle-priming techniques (i.e., air sandwich), and needle size (i.e., 25-gauge, 5/8-in needle to ensure that drug is deposited in SC tissue). During SC administration, bortezomib should be injected at a 90° angle (or 45° for very thin patients), slowly and steadily at a rate of ≈1 mL/10 s to allow absorption of medication into surrounding tissue and to avoid fluid backtracking. These measures can reduce injection-site reactions (e.g., skin irritation on contact with the drug).

Continuum of care

Supportive care strategies are key throughout the continuum of patient care to reduce disease- and treatment-related complications and enhance patient QOL [84]. Nurses have vital roles in educating, advocating for, and supporting patients to improve MM treatment tolerability and maximize efficacy [85]. The IMF-NLB has identified the patient needs requiring the most support as renal health, bone health, health maintenance, mobility and safety, and sexual dysfunction [85].

Regardless of the MM therapy used, treatment-related toxicities and patient- and disease-specific comorbidities should be assessed regularly to ensure proper treatment and prompt intervention when needed [85]. MM treatment-specific tools, clinical assessments, and recommended actions (i.e., nursing "pearls of wisdom") are helpful for evaluating patient status and optimizing drug dosing and administration (Table 4 [adapted from references in Table 3]). Examples of preventative and therapeutic interventions for patients with MM undergoing antimyeloma treatment include bisphosphonate therapy to strengthen bones, early treatment with antibiotics and antivirals during treatment with PIs or on signs of infection, and growth factor and transfusional support for myelosuppression [85]. Personalized survivorship and management plans can also be effective in addressing patient-specific vulnerabilities (e.g., age, frailty, comorbidities, disabilities). To achieve the deepest possible response for a given patient, survivorship strategies may include planned administration of lower doses for elderly patients or other tailored doses or modifications [85, 86].

The average age of patients with MM is ≈70 years, and inherent age-associated comorbidities can hinder the ability of healthcare providers to prescribe and administer the most effective MM treatments [85]. As such, an emphasis on overall health maintenance is important, as survival is prolonged after MM diagnosis [85]. In addition to receiving disease-related care, patients with MM should continue to see primary care physicians at regular healthcare and dental checkups, receive regular vaccines and flu shots, and undergo routine health screenings (e.g., mammograms, prostate screening).

Conclusions

The recent development of PIs and IMiDs, alone or in combination with other agents, has improved survival in patients with MM, with a concomitant increase in susceptibility to disease- and treatment-related symptoms. Effective management of the patient with MM requires knowledge of the disease and of treatment-associated AEs, in addition to preventative measures, supportive care strategies, and management of comorbidities. Patient education and individualized survivorship plans can play a role in achieving maximal patient responses to treatment. As patient survival continues to improve after MM diagnosis, optimal symptom management will be important in maximizing QOL in addition to disease control and survival.

Acknowledgments William H. Fazzone, PhD, Amanda L. Kauffman, PhD, and Peter J. Simon, PhD, provided medical editorial assistance with this manuscript that was financially supported by Novartis Pharmaceuticals Corporation.

Conflicts of interest Kathleen Colson consults and serves in an advisory role for Celgene, Millenium, Novartis, and Onyx.

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