Original Article

Supportive Therapies in Multiple Myeloma

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Key Words

Myeloma, neuropathy, thrombosis, bisphosphonates

Abstract

The outlook for patients with myeloma has improved dramatically over the past few years largely because of improvements in supportive care, the use of high-dose therapy, and the introduction of the novel agents thalidomide, bortezomib, and lenalidomide. These new treatment options have changed the natural history for patients with myeloma, but clinicians must consider treatment-related toxicities. Some of the most common short- and long-term toxicities include the development of peripheral neuropathy, hematologic complications, thrombosis, and bone-related complications, such as fracture and osteonecrosis of the jaw. Careful consideration of patient-reported symptoms and appropriate dose modification or prophylaxis to prevent the development of toxicity are critical, and will result in improved quality of life and better tolerance of delivered therapy. (*JNCCN* 2009;7:971–979)

New treatments and combinations for patients with myeloma have resulted in improved overall survival,[1] higher rates of complete and overall response, and durations of remission, raising the importance of maximized quality of life considerations. However, treatment-related toxicity remains a concern, with some of the more common short- and long-term toxicities involving hematologic complications, peripheral neuropathy (PN), thrombosis, and bone health complications. This article briefly addresses these 4 areas of potential toxicity, and discusses how to best minimize these complications while still optimizing long-term outcomes for patients.

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Peripheral Neuropathy

PN is a common finding among patients with plasma cell dyscrasias and is a common side effect associated with the use of agents such as vincristine, thalidomide, bortezomib, and cisplatin.[2] A recent trial from Richardson et al.[3] evaluating the use of single-agent bortezomib for patients with previously untreated myeloma objectively documented the incidence of PN among patients before initiation of therapy. In their analysis, 50% of patients had evidence of small fiber neuropathy and 9% had evidence of large fiber neuropathy before any therapy was initiated.[3] Thus, patients with plasma cell disorders have pre-existing PN, which may influence the subsequent development of treatment-related symptoms.

Bortezomib

Bortezomib is a proteasome inhibitor with significant activity in patients with relapsed/refractory and newly diagnosed myeloma. Treatment with bortezomib can cause development of PN that is predominantly sensory in nature, although motor neuropathy was rarely reported (Table 1).

In the SUMMIT and CREST phase II trials, 35% of the 256 patients developed PN, including 13% with grade 3/4.[4] Dose reductions were required in 12% of patients, with 5% discontinuing bortezomib because of PN. Among patients with PN, 71% had improvement of symptoms at a median of 47 days (range, 1–529 days) after the last dose of bortezomib. Of 90 patients with

Table 1 Incidence of Bortezomib-Induced Peripheral Neuropathy

Study	N	Regimen	Median (Range) Cycles of Bort	Grade 1–2 (%)	Grade 3–4 (%)	Comments
Harousseau et al.[53]	50	Bort + dex		12 (24)	3 (6)	Bort as initial therapy for newly diagnosed MM
Rosinol et al.[54]	40	Bort + dex		10 (25)	–	Alternating bort and dex as induction regimen; only one grade 2 PN seen
Richardson et al.[5]	669	Bort		94 (28)	26 (8)	Bort vs. dex for refractory/ relapsed MM
Mikhael et al.[55]	638	Bort ± dex	5 (0–13)	119 (19)	38 (6)	Dex was added the day of and day after each bort dose for progressive disease after ≥ 2 cycles or for stable disease after ≥ 4 cycles
San Miguel et al.[34]	688	Bort + mel + pred	8 (–)	107 (31)	44 (13)	Bort/mel/pred as initial therapy for newly diagnosed MM
Orlowski et al.[56]	646	Bort ± PLD		61 (10)	13 (6)	PLD plus bort vs. bort alone in relapsed/refractory MM
Mateos et al.[9]	260	Bort + thal + pred			(15)	9% PN seen in VMP arm

Abbreviations: Bort, bortezomib; dex, dexamethasone; mel, melphalan; MM, multiple myeloma; PLD, pegylated liposomal doxorubicin; PN; peripheral neuropathy; pred, prednisone; thal, thalidomide; VMP, bortezomib, melphalan, prednisone.

treatment-emergent PN, 35 experienced grade 3 or higher neuropathy or neuropathy leading to discontinuation. PN was the reason for discontinuing treatment in 5% of patients (14 of 256). Dose reduction was required in 12% (31 of 256) because of PN, representing 34% of patients (31 of 90) who developed new or worsening neuropathy. At least one dose of bortezomib was held because of PN in 7% of patients (19 of 256), representing 21% (19 of 90) with new or worsening neuropathy. Higher incidence of grade 3 or 4 neuropathy was seen in patients with baseline evidence of neuropathy according to Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire. The development of treatment-emergent PN seemed to be independent of the type of prior neurotoxic therapy the patient received.[4]

Based on experience from phase II trials, a dose modification schema was developed and later validated in the phase III APEX trial. Use of this dose reduction schema reduced the incidence of grade 3/4 PN to 8%, with a 37% total incidence of PN.[5] In addition, and unlike PN noted with other agents, 64% of patients experienced either improvement or resolution of PN to baseline within a median of 110 days after bortezomib was stopped or dose reduced.[6] Dose modifications may be required in patients experiencing new or worsening PN as listed in the package insert for bortezomib. The use of this simple dosing algorithm has the ability to limit PN in the short term and improve long-term improved quality of life (Table 1). In a comprehensive review of the literature, Argyriou et al.[7] listed therapeutic options for PN and provided dose modification guidelines.

An alternative approach to reduce the incidence of PN is to administer bortezomib as a weekly instead of a biweekly regimen. Data presented by Palumbo et al.[8] from a phase III randomized trial evaluated the efficacy and toxicity between the biweekly and weekly trial arms. Among patients with newly diagnosed myeloma, efficacy between weekly and biweekly therapy with VMPT (bortezomib, melphalan, prednisone, thalidomide; complete response [CR], 36% vs. 39%) and VMP (bortezomib, melphalan, prednisone; CR, 27% vs. 20%) was similar; whereas the incidence of grade 3/4 neuropathy was significantly reduced (6% for VMPT vs. 2% for VMP, administered weekly).

A similar approach was taken by Mateos et al.[9] and the Spanish Myeloma Group, in which VTP (bortezomib, thalidomide, prednisone) was com-

pared with VMP, with a change to weekly bortezomib after 2 cycles of the VMP induction. This approach reduced the incidence of grade 3 PN to less than 2% and had a similar efficacy to standard VMP.

In summary, patients should be monitored for symptoms of neuropathy, such as burning, hyperesthesia, hypoesthesia, paresthesia, neuropathic pain, or weakness. Preexisting symptoms or signs of PN do not predict its occurrence during treatment with bortezomib, and trials have shown that bortezomib can be safely combined with other neurotoxic agents, such as thalidomide.[10] In the context of combination therapy, alternative schedules or doses may be a way to avoid or minimize neuropathy, thereby allowing for long-term therapy with less impact on quality of life.

Thalidomide-Related Neuropathy

PN can be a major issue associated with thalidomide that can limit long-term use among patients with myeloma (Table 2). However, objective data on incidence and resolution of PN associated with thalidomide therapy are somewhat limited. Palumbo et al.[11] has reported that PN typically starts with sensory symptoms such as paresthesias, hyperesthesias, motor neuropathy, and autonomic symptoms that often start distally and move proximally, with patients experiencing decreased pinprick sensations, numbness, and tingling.

A multicenter study evaluating dose escalation of thalidomide with or without interferon performed serial nerve electrophysiologic studies to detect onset of PN.[12] In the study, 39% of patients had abnormal PN at baseline and 31 of 75 (41%) developed PN during treatment; incidence of PN increased from 38% at 6 months to 73% at 12 months. Overall, 81% of patients who experienced response to treatment developed neurologic complications. The study concluded that duration of therapy is an important predictor for developing PN.

Recommended Therapy for PN

Treatment of PN remains a major challenge, and is the reason that much effort should be put into prevention rather than treatment. Much of the pharmacologic intervention data are derived from nonmyeloma studies treating diabetic PN and postherpetic neuralgia. First-line therapies include opioids, gabapentin, pregabalin, tricyclic antidepressants, topical lidocaine, topical capsaicin cream, and vitamin supplements.[13] Vitamin C for preventing or treating PN is not recommended, however, because it can block the effects of bortezomib in vitro and in vivo.[14] The use of pyridostigmine (vitamin B_6) may also be a potential problem in patients who have renal impairment, and can cause additional sensory neuropathy in association with a protein-deficient diet.[15]

Narcotics remain a mainstay of therapy, and if short-acting therapy offers some benefit, then long-acting agents should be used to provide more general and longer-lasting effects. Patients should be monitored frequently for potential neuropathy symptoms when on thalidomide or bortezomib, because early intervention with prompt dose modification or delay is essential to prevent permanent damage.[2]

Hematologic

Bortezomib

The exact mechanism through which bortezomib causes thrombocytopenia is unclear. Lonial et al.[16] reviewed the risk factors and kinetics of thrombocytopenia associated with bortezomib in patients

Table 2 Incidence of Thalidomide-Induced Peripheral Neuropathy

Study	n	Response	PN	Other
Offidani et al.[57]	59	44%	39%	Incidence higher with doses > 150
Tosi et al.[58]	40	All responders for > 12 mo	75% (27.5% grade 3)	Related to duration of disease
Richardson et al.[59]	30	33%	37%	Treatment duration and dose
Mileshkin et al.[12]	75	39%	41%	Increased incidence with longer follow-up

Abbreviation: PN, peripheral neuropathy.

from SUMMIT and CREST trials. The cyclical pattern of transient decrease in platelets followed by quick recovery during the rest period suggests a possible different pathogenesis than that seen with conventional chemotherapeutic agents. Specifically, the effect of bortezomib on platelet production was hypothesized to be related to the inhibition of nuclear factor-κβ, which may prevent platelet budding and result in transient inhibition of thrombopoiesis, rather than the traditional marrow ablative effect seen with conventional chemotherapy.

Among patients treated in the phase II trials, the mean baseline platelet count was 165 × 10^9/L (standard deviation [SD], 91.3), and the mean cycle 1, day 11 platelet count was 107 × 10^9/L (SD, 65.7). Mean platelet concentrations in all patients of each treatment cycle followed a biphasic and cyclic pattern, decreasing at administration of bortezomib (by approximately 60%) and recovering during the periods of rest with each cycle. Absence of cumulative or persistent thrombocytopenia is corroborated by the fact that platelet count actually increased over the course of continued therapy, despite repeated dosing.[16] This further shows that the effect of bortezomib in causing thrombocytopenia is transient, and that overall improvement of the baseline possibly relates to improvement in the hematopoietic reserve among patients experiencing response.

In a separate but similar analysis, Lonial et al.[17] analyzed platelet kinetics from the APEX study and reported grade 3/4 thrombocytopenia among 30% of patients receiving bortezomib compared with 5% receiving dexamethasone. However, the percentage of clinically significant bleeding episodes associated with grade 3 thrombocytopenia was similar in both treatment groups. Management of bortezomib-induced thrombocytopenia occurring early during therapy should include the use of platelet transfusions and close monitoring until the effectiveness of the therapy can be determined. Alternative approaches include suspending therapy and dose reduction, although these strategies may not be needed if the underlying cytopenias are from myelomatous marrow involvement.

Transient neutropenia and anemia are seen with bortezomib administration and with a similar kinetics curve to that noted for platelets. Few cases of febrile neutropenia causing death have been reported. White blood cell growth factors are rarely needed.

Lenalidomide

The most common adverse effect reported with lenalidomide is myelosuppression, mainly manifested as thrombocytopenia and neutropenia.[18] Lenalidomide was initially investigated in a phase I study from the Dana-Farber Cancer Institute, where grade 3 and 4 myelosuppression was observed in 12 of 13 patients treated with the highest dose, 50 mg daily.[19] The most common adverse effects were grade 3 neutropenia in 15 patients (60%) and grade 4 in 4 patients (16%). Grade 3 thrombocytopenia was noted in 5 patients (20%), and a dose reduction of 25 mg daily was concluded to be the desired dose.

Richardson et al.[20] performed a single-agent trial evaluating the efficacy of 2 different dosing schedules for lenalidomide: once-daily versus a twice-daily dose. The most common adverse effects were neutropenia and thrombocytopenia. Grade 4 neutropenia occurred in 4 (11%) of 35 patients receiving twice-daily lenalidomide and in 8 (12%) of 67 on once-daily dosing. Grade 4 thrombocytopenia occurred in 6 patients (17%) receiving twice-daily dosing and in 11 (16%) of 67 on once-daily dosing. The time to first occurrence of grade 3 or 4 myelosuppression was shorter in the twice-daily dosing arm, and occurred in a higher proportion of patients whose prior therapy included high-dose chemotherapy and stem cell transplantation.

Phase III trials by Dimopoulos et al.[21] involving patients with relapsed or refractory multiple myeloma compared lenalidomide, 25 mg daily, on days 1 through 21 with dexamethasone, 40 mg daily, on days 1 to 4, 9 to 12, and 17 to 20 for the first 4 cycles versus placebo/dexamethasone. Grade 3 and 4 thrombocytopenia was twice as frequent in the lenalidomide/dexamethasone arm as the placebo arm (11.4% vs. 5.7%, respectively). Incidence of grade 3 neutropenia was 25% in the treatment compared with 2.3% in the placebo group, with grade 3 or 4 febrile neutropenia occurring in 3.4% of patients treated with lenalidomide versus none treated with placebo.

In a separate but parallel trial, Weber et al.[22] randomized patients to receive either lenalidomide, 25 mg daily, on days 1 through 21 plus dexamethasone, 40 mg daily, on days 1 through 4, 9 through 12, and 17 through 20 for the first 4 cycles, or placebo/dexamethasone. Grade 3 or 4 hematologic toxic effects occurred in 52.5% of patients in the lenalidomide

arm versus 13.7% for the placebo. Grades 3 or 4 neutropenia was more common in the lenalidomide arm (41.2%) versus the placebo arm (4.6%), as was thrombocytopenia (14.7% vs. 6.9%). Notably, granulocyte colony-stimulating factor (GCSF) was administered if grade 3 or 4 myelosuppression occurred without other adverse events; with development of additional grade 3 or 4 events, the dose of lenalidomide was reduced.

Mateos et al.[23] also looked at lenalidomide-induced neutropenia in 3 patients treated with lenalidomide and dexamethasone with grade 3 or 4 events, and concluded that GCSF can prevent further neutropenia-related dose reductions.

Clinical studies have shown lenalidomide and bortezomib to be effective alone or in combination with dexamethasone. Some hematologic toxicity can be reduced with concomitant administration of steroids and lenalidomide, and no stem cell suppressive effect is seen with either agent. Supportive care, dose modification, growth factor support, and transfusion support can be used to keep patients on therapy and reduce toxicities. Erythropoiesis stimulating agents (ESAs) should be used with caution in patients with myeloma as Katodritou et al.[24] reported that they may have a detrimental effect on outcomes.

A systematic review by Shehata et al.[25] found no evidence supporting the use of ESAs in improving overall survival in hematologic malignancies, and the impact on quality of life was hard to assess.

The effect of lenalidomide on stem cell mobilization has been described in the International Myeloma Working Group (IMWG) on mobilization.[26] Early data identified patients from several centers who did not experience mobilization after induction with lenalidomide and dexamethasone when growth factors alone were used.[27] Data from the randomized E4A03 trial did not show a significant number of failed mobilizations,[28] with myeloma investigators reaching consensus that collections should occur within the first 4 to 6 months of induction therapy with a lenalidomide-based treatment.[26]

Infections

Herpes zoster reactivation has been reported with bortezomib-containing regimens. No clear mechanism for reactivation was suggested; however, this may be related to impaired T-cell responses while on bortezomib.[29,30] In a phase II study using induction therapy for multiple myeloma with PS-341, Adriamycin, and dexamethasone (PAD), Oakervee et al.[31] reported that 3 of 21 (14%) patients had shingles. In the follow-up study by Popat et al.,[32] induction with PAD using a lower dose of bortezomib (1.0 mg/m^2) did not show any herpes zoster reactivation, suggesting that it is dose-dependent.

In the phase III APEX study, bortezomib treatment was associated with a significantly higher incidence of herpes zoster infection than dexamethasone (13% [42 of 331] vs. 5% [15 of 332]; P = .0002).[33] No grade 3/4 reactivations were reported. In the phase III VISTA trial, patients receiving VMP had a higher incidence of herpes zoster reactivation than those receiving melphalan and prednisone (13% vs. 4%).[34] The incidence of herpes zoster was reduced to 3% in patients in the bortezomib group who received antiviral prophylaxis, suggesting the beneficial role of prophylaxis. Therefore, the risk for herpes zoster reactivation should be monitored and routine use of antiviral prophylaxis is recommended in patients treated with bortezomib or bortezomib-containing regimens.

Intravenous immunoglobulin is used by some groups to treat patients with recurrent upper respiratory infections or chronic sinusitis. However, no randomized clinical trials support this practice. Currently, there is no consensus on the timing or duration of IVIG replacements.

Thrombosis

Thrombosis is a complication associated with all cancer and cancer therapy, particularly myeloma. This may be partly due to high levels of circulating paraprotein, endothelial damage that can be a result of therapy with agents such as anthracyclines, or antiangiogenic properties of agents, such as thalidomide and lenalidomide.[35] Several retrospective studies have shown that the risk for thrombosis or deep vein thrombosis (DVT) is higher among patients with newly diagnosed multiple myeloma than among those with relapsed disease, and the incidence of DVT during induction treatment is between 5% and 10%.[35]

Among the agents commonly used in myeloma therapy, the 2 with the highest incidence of DVT are thalidomide and lenalidomide. When used alone, however, the rate of DVT is less than 5%, as shown in early trials.[36] The incidence of thrombosis increases when dexamethasone is added. Trials evaluating thalidomide and dexamethasone have thrombosis rates ranging from 10% to 15%;[37] when an anthracy-

cline is added, the incidence rises to 25%, suggesting some interaction between the endothelial damage induced by anthracyclines and antiangiogenic properties of thalidomide.[38] Thus, based on a preliminary view of thrombotic risk with thalidomide, risk may be assessed based on host factors such as induction versus relapse and therapy factors such as the concomitant use of dexamethasone or an anthracycline.

In the setting of lenalidomide-based thrombosis, early studies noted that patients have a low risk for DVT with lenalidomide alone,[20] this incidence increases when dexamethasone is added. From the MM009[22] and MM010[21] studies, the incidence of DVT in the lenalidomide dexamethasone (LenDex) cohorts was 8.5% to 16% compared with less than 5% for the dexamethasone alone arm. When the incidence of DVT was evaluated in the 2 induction therapy studies performed in the United States (ECOG E4A03, lenalidomide and high-dose dexamethasone vs. lenalidomide low-dose dexamethasone; and SWOG S0232, lenalidomide and high-dose dexamethasone vs. high-dose dexamethasone), the incidence of DVT was also high. In the SWOG trial, 9 of the first 12 patients randomized to receive LenDex developed a DVT.[39] In the ECOG trial, incidence of DVT was 26% in the lenalidomide plus high-dose dexamethasone arm versus 12% in the lenalidomide plus low-dose dexamethasone arm.[40] When prophylaxis was mandated in both arms, the rate of DVT in the lenalidomide plus high-dose dexamethasone arm decreased to 14%, again confirming the role of high-dose dexamethasone in facilitating DVT when immunomodulatory drugs (IMiDs) are used.

A recent consensus paper published by the IMWG provided guidance on how DVT prophylaxis is approached in patients with either newly diagnosed or relapsed disease. In the guidelines, physicians are encouraged to evaluate risk based on the number inciting or risk factors,[41] including patient-specific factors such as functional status, disease burden, and history of prior thrombosis, and treatment-related factors, such as the use of high-dose dexamethasone, use of an anthracycline (with an IMiD), use of ESAs, and whether concomitant bortezomib is used. For patients with 1 or no risk factors, the risk for thrombosis is low enough that an aspirin is sufficient (5%–7%), but those with multiple risk factors may need more intense therapy to lower this risk. Anticoagulation has attendant risks and therefore should be performed in the context of evaluating risk and benefit to each patient and of each individual treatment.

Bone Complications

Skeletal Events

Myeloma bone disease is one of the most clinically important manifestations of disease activity, and can result in significant morbidity and mortality for patients with symptomatic disease. The hallmark of myeloma bone disease is a loss of the normal bone homeostatic process that balances bone formation and removal. This occurs as a result of an interweaving cytokine network secreted by malignant plasma cells that include RANKL, MIP-1α, and SDF-1. The net result is enhancement of osteoclast differentiation and survival, suppression of osteoblast maturation, and inhibition of new bone formation, resulting in bone destruction that manifests as osteopenia and lytic bone disease.[42,43]

The introduction of bisphosphonates in the 1990s dramatically changed the landscape of myeloma bone disease, although it has not completely eliminated the problem. Studies performed using the oral bisphosphonate clodronate[44,45] or the intravenous agent pamidronate[46] showed that bisphosphonate use was able to significantly reduce the incidence of skeletal-related events. The newer, more potent intravenous agent zoledronic acid was shown to be more effective in the setting of hypercalcemia of malignancy, and to have similar efficacy to pamidronate and a shorter infusion time.[47]

Osteonecrosis of the Jaw

As bisphosphonates are increasingly used, osteonecrosis of the jaw (ONJ), a complication previously only seen among patients who underwent local radiotherapy to the mouth or oropharynx, was observed (Table 3). *ONJ* is defined as exposed bone in the jaw that does not heal or become covered with tissue after an 8-week period of interventions and that is not associated with a known lytic lesion or radiation therapy.[48] Several largely retrospective series of data have tried to quantify the incidence of ONJ and correlate its incidence with precipitating factors. The most significant risk factor for patients taking bisphosphonates is undergoing an invasive dental procedure, whereas other factors include duration of therapy and, in some studies, the choice of bisphosphonate.

Table 3 Incidence of Osteonecrosis of the Jaw

Reference	Total #	# ONJ	Risk Factors
Durie et al.[60]	1203 (904 MM)	75 (6.2%) 62 (6.8%)	Zoledronic acid
Bamias et al.[61]	252 (111 MM)	17 (6.7%) 11 (9.9%)	Dental extraction
Badros et al.[62]	340	11 (3%)	Dental extractions
Dimopoulos et al.[63]	202	15 (7.4%)	
Zervas et al.[64]	254	28 (11%)	Thalidomide Increased duration of bisphosphonates
Hoff et al.[50]	3994 548 (MM)	29 (0.73%) 13 (2.4%)	Longer duration of therapy
Tosi et al.[65]	259	9 (3.47%) 6.6% at 24 mo	Duration of exposure

Abbreviations: MM, multiple myeloma; ONJ, osteonecrosis of the jaw.

Symptoms of ONJ include bleeding, infection, and jaw pain, and should be managed by an oncologist and experienced oral surgeon or dentist, because often conservative management and antibiotics are the mainstay of treatment.[49] To minimize the risk for developing this complication, patients should have a thorough dental examination before they start therapy with bisphosphonates whenever possible. For patients who need emergent dental care while on therapy, care should be taken to minimize the risk for infection after the procedure, because this may be one of the inciting factors.[50]

The use of oral rinses and oral antibiotics after any dental procedure may limit the severity of incidence of ONJ among patients treated with bisphosphonates, but this has not been confirmed in randomized trials.[51] ASCO published a summary of guidelines for bisphosphonate use in patients with myeloma, including recommendations for treatment for those with renal impairment and appropriate dose modifications.[52]

Conclusions

Despite major therapeutic advances, complications of therapy remain an important factor influencing treatment choice. Special attention to minimizing PN allows patients to be treated or retreated with all available options in the future, and maintains overall performance status and quality of life. Antiviral and thrombosis prophylaxis also can have a major impact on minimizing complications of therapy. Minimizing hematologic toxicity is important when considering possible treatments that may be needed later in the disease course. These parameters should be carefully considered when treating patients with symptomatic newly diagnosed or relapsed myeloma to maximize long-term outcome and quality of life.

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