Advances in Supportive Care for Multiple Myeloma

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Abstract
As patients with multiple myeloma live longer, helping them live better through improvements in supportive care is equally as vital. Intrinsic to the disease are bone-related complications at presentation and over the course of illness. Bisphosphonates have been an important therapy for ameliorating the risk of skeletal-related events, and work is ongoing to determine their optimal schedule. Patients with multiple myeloma also encounter several challenges related to their treatment, including peripheral neuropathy, thrombotic complications, and infections. These challenges are being addressed through a better understanding of the risk factors for developing these complications and by mitigating these risks through better dosing schemas and prophylaxis. (J Natl Compr Canc Netw 2014;12:502–511)

The past 2 decades have seen remarkable advances in the treatment of multiple myeloma (MM). These advances began with the use of high-dose melphalan and autologous stem cell transplant followed by the introduction of immunomodulatory drugs thalidomide and lenalidomide and the proteasome inhibitor bortezomib. These new treatments have yielded significant improvements in 5-year relative overall survival, from nearly 30% in the early 1990s to 40% in the previous decade. Although MM is not curable, increasingly more patients are living with MM for longer periods as survival improves. The focus has centered on maximizing quality of life for patients with MM. Improvements in supportive care will allow patients to gain the benefit of continuing with treatment, and understanding and managing toxicities will prevent premature discontinuation because of adverse reactions.

Supportive care for MM was reviewed in JNCCN 4 years ago and by the British Committee for Standards in Hematology and UK Myeloma Forum. This review focuses on advances in the management of bone-related complications, peripheral neuropathy, thrombosis, and risk of infection.

Bone Complications
Bone involvement is one of the pathognomonic and defining characteristics of MM, either as lytic lesions or osteopenia. At diagnosis, in 1 survey, 67% of patients had lytic bone disease and 20% had osteopenia, pathologic fractures, or compression fractures of the spine (many patients had both lytic bone lesions and other findings). Conventionally, skeletal surveys have been used to diagnose bone disease in MM. Newer modalities, such as MRI, CT, and PET/CT, have significantly higher sensitivity and should be considered in certain clinical situations (eg, back pain with normal plain films, cord compression).

Bone involvement is frequently associated with pain and skeletal-related events (SREs), such as pathologic fracture, cord compression, and hypercalcemia, which may lead to surgery or radiation. Pathologic fractures are associated with increased mortality by 20%, and in 1 series, overall survival was 57.3 months in patients without pathologic fracture compared with 17.6 months in patients with pathologic fracture.
Bisphosphonates

Bisphosphonates, such as pamidronate and zoledronate, play a fundamental role in minimizing and managing bone-related complications in MM.\(^{14,15}\) Bisphosphonates are drugs that share a phosphorus-carbon-phosphorus backbone and accumulate in the mineral phase of bone. They reduce osteoclast activity through inhibiting farnesyl pyrophosphate synthase.\(^{16}\) Bisphosphonates have a well-established role in the treatment of osteoporosis\(^{17,18}\) and metastatic bone involvement from solid tumors.\(^{19-21}\)

In MM, bisphosphonates palliate pain and prevent SREs. The Cochrane Collaboration has reported a comprehensive meta-analysis of bisphosphonate clinical trials,\(^{22}\) and the International Myeloma Working Group (IMWG) recently issued guidelines for the treatment of MM-related bone disease.\(^{23}\) Pamidronate, given intravenously, was one of the first bisphosphonates to show a significant reduction in SREs in MM. In patients with at least one osteolytic lesion, intravenous pamidronate (90 mg given every 4 weeks) significantly reduced SREs compared with placebo (24% vs 41%, respectively; \(P<.001\)) after 9 cycles.\(^{24}\) Time to first pathologic fracture or first radiation treatment was longer in the pamidronate-treated group. Moreover, pamidronate also significantly improved quality of life, with decreases in pain scores seen within a month.

More recently, the Nordic Myeloma Study group compared a 30-mg dose of pamidronate with the standard dose of 90 mg in a double-blind randomized study.\(^{25}\) The rates of SREs were similar, and a trend was seen toward fewer adverse events in the 30-mg dose group, with fewer episodes of osteonecrosis of the jaw and nephrotoxicity.

Zoledronate is a newer bisphosphonate that is more potent than pamidronate. For the treatment of hypercalcemia of malignancy (including MM), zoledronate is superior to pamidronate.\(^{26}\) In MM, the efficacy of zoledronate in preventing SREs was comparable to that of pamidronate (although in breast cancer, zoledronate was found to be superior).\(^{19}\) Compared with pamidronate, zoledronate has the practical advantage of a shorter infusion time.

In addition to playing an important supportive role, bisphosphonates may have an anti-MM effect. The MRC Myeloma IX trial compared zoledronate and oral clodronate in patients with newly diagnosed MM and found that zoledronic acid reduced mortality by 16% and increased median overall survival from 44.5 months to 50.0 months (\(P=.04\)).\(^{27}\) At a median follow-up of 3.7 years, a lower incidence of SREs was seen with zoledronate (27% vs 35%; \(P=.0004\)).\(^{28}\) Moreover, patients without bone lesions at baseline also derived benefit from zoledronate in terms of skeletal morbidity,\(^{29}\) although the benefit in survival was seen only in patients with bone disease on study entry.\(^{29}\) In a retrospective subset analysis of the MRC Myeloma IX data, in patients undergoing intensive treatment, the benefit in terms of SRE and overall survival with zoledronate was only seen in patients experiencing a VGPR (very good partial response) or less or a PR (partial response) or less, respectively, suggesting that the response to autologous stem cell transplant may influence the benefit of bisphosphonate therapy.\(^{30}\)

Osteonecrosis of the Jaw: Osteonecrosis of the jaw (ONJ) is one of the most serious complications of bisphosphonates.\(^{31,32}\) ONJ is traditionally defined as exposed, necrotic bone in the jaw that does not heal after 8 weeks and is generally painful. Zoledronate is associated with the highest risk of ONJ, attributed to its increased potency, and earlier studies suggested an incidence of 4% to 11%, correlating with duration of exposure.\(^{33,34}\) In the MRC Myeloma IX trial, the cumulative incidence of ONJ was 3% to 4% at a median follow-up of 3.7 years.\(^{35}\)

Dental extractions are a major risk factor for the development of ONJ.\(^{34,36}\) Attention to dental hygiene and minimizing invasive procedures (eg, tooth extractions, dental implants) may reduce the risk of ONJ.\(^{37}\) IMWG guidelines recommend suspending bisphosphonate therapy for 90 days before and after invasive dental procedures (although routine dental cleanings and procedures, including root canals, may proceed).\(^{23}\) Treatment of ONJ is supportive. The IMWG also recommends resuming bisphosphonates after healing has occurred. ONJ has also been reported with the use of other antiresorptives, such as denosumab, with an incidence of 1.8% noted in several phase III trials.\(^{38}\)

Renal Toxicity: Nephrotoxicity may occur with intravenous bisphosphonates, ranging from collapsing focal segmental glomerulosclerosis with pamidronate to acute tubular necrosis with zoledronate.\(^{39}\) An increase in serum creatinine was seen in fewer than 10% of cases, and severe renal toxicity was infrequent\(^{40}\) in long-term follow-up from clinical trials.\(^{21,41}\)
ASCO guidelines recommend dose adjustments in patients with impaired renal function.

**Treatment Duration:** The IMWG recommends that bisphosphonates be given until disease progression in patients not experiencing a complete response or very good partial response and further continued at relapse. This recommendation is motivated by the finding in the MRC Myeloma IX trial that improvements in overall survival and reduced SREs occurred in patients who received bisphosphonate treatment for more than 2 years. For patients experiencing complete response or VGPR, the optimal duration of bisphosphonates is an active area of investigation, because prolonged exposure to bisphosphonates may increase the risk of side effects, including ONJ. In the interim, the IMWG panel recommends at least 12 months and up to 24 months of treatment (timing from start of treatment), and thereafter at the discretion of the provider.

To optimize the duration of bisphosphonate therapy, the Z-MARK study evaluated whether patients with 1 to 2 years of prior intravenous bisphosphonate therapy could be treated safely long-term with less-frequent zoledronate, based on markers of bone turnover.

Patients with urinary N-telopeptide of type 1 collage (uNTX) levels less than 50 nmol/mmol of creatinine received zoledronate 4 mg every 12 weeks versus every 4 weeks for higher levels of uNTX. uNTX levels were monitored over the course of treatment, and the dosing of zoledronate was adjusted as a result. Additionally, patients who developed an SRE or experienced disease progression were treated on the every-4-week schedule thereafter, regardless of uNTX levels. Most patients (79 of 121) were on the every-12-week schedule throughout the study. Of these 79 patients, only 7 (8.9%) had an SRE in year 1, and 5 had an SRE in year 2. The low incidence of SREs overall in the study compared with prior studies with zoledronate suggests that less-frequent dosing of zoledronate beyond 1 to 2 years may continue to reduce the risk of SREs. Furthermore, it also suggests that more-effective treatment of MM with novel therapies may have protective effects on the bone. Importantly, the overall incidence of ONJ in this study was 3%.

**Vertebral Compression Fractures**

Painful vertebral compression fractures are a common source of morbidity in patients with MM. These fractures can be palliated through vertebroplasty (injection of methyl methacrylate or bone cement) and kyphoplasty (use of an inflatable balloon followed by instillation of bone cement), with rapid pain relief. A randomized study of 134 patients investigated the role of kyphoplasty versus noninvasive management for patients with cancer and painful vertebral body compression fractures; approximately 38% of these patients had MM. The kyphoplasty arm had significant improvements in functional outcome, with less back pain and improvement in quality of life a month after the procedure, and the benefits continued until the end of the study at 12 months. The superiority of kyphoplasty over vertebroplasty remains to be determined, although one recent meta-analysis found comparable efficacy.

**Palliative Radiation Therapy**

Radiation plays a key role in managing painful bony lesions in MM, with roughly 38% of patients expected to receive radiation over the disease course. Although bone pain is frequently the primary reason for radiation therapy, other indications include impending fracture, cord compression, or relief of symptoms associated with a mass (eg, cranial nerve palsies, cosmesis, organ or joint dysfunction).

Doses of 20 to 35 Gy are typically used for palliative radiation. Ability to retreat is important to consider when designing treatment fields, particularly of the spine. At the authors’ institution, doses of 20 Gy delivered in either 5 or 10 fractions provide adequate symptom relief. Furthermore, the need to preserve bone marrow reserve as much as possible is another consideration when planning a course of radiotherapy.

**Denosumab**

As an osteoclast inhibitor, denosumab may play a role in the supportive care of MM-associated bone disease. Denosumab is a monoclonal antibody, given subcutaneously, that inhibits osteoclast activity through targeting RANKL (receptor activator of nuclear factor κB ligand). RANKL is a cytokine produced by osteoblasts that activates the RANK receptor present on osteoclast precursors and osteoclasts.

Denosumab is approved for increasing bone density in patients with osteoporosis and for preventing SRE in patients with metastatic bone disease. In MM, although denosumab was comparable to zoledronate with respect to SREs, an ad hoc subset analysis...
showed inferior survival in a phase III trial. However, interpretation is limited based on the small numbers in the trial and imbalances in baseline disease characteristics. Denosumab is not currently FDA-approved for use in patients with MM; a larger, ongoing phase III study (ClinicalTrials.gov identifier: NCT01345019) is comparing it with zoledronate in this disease setting.

Peripheral Neuropathy

Peripheral neuropathy is one of the principal dose-limiting side effects of MM treatments, particularly with thalidomide and bortezomib, and is associated with significant effects on quality of life. Before treatment, the percentage of newly diagnosed patients experiencing symptomatic sensory peripheral neuropathy ranges from, for example, 1% to 2% to 11% to 20% in more recent studies depending on the criteria used. Similar to neuropathy related to diabetes mellitus or paclitaxel, MM treatment–related peripheral neuropathy typically involves the longest axons in the extremities, following a distal-to-proximal, stocking and glove distribution. Symptoms generally include numbness, tingling, and pinprick sensations, beginning with the toes and fingers. The neuropathy can be painful, with a sharp or burning sensation. Effects on motor strength are uncommon.

Bortezomib

In the SUMMIT and CREST phase II trials of bortezomib in patients with relapsed MM, in which bortezomib was given on a conventional schedule of twice per week, intravenously, on a 21-day cycle, peripheral neuropathy was common, occurring in 35% of patients, including 13% in whom it was grade 3 or higher. Dose reductions occurred in 12% of patients, and 5% of patients discontinued therapy because of neuropathy. Similar rates of peripheral neuropathy have been seen in newly diagnosed patients, such as in the VISTA trial, which studied bortezomib combined with melphalan and prednisone versus melphalan and prednisone alone in older patients with MM. Because of the frequency of peripheral neuropathy seen in initial studies of bortezomib, a dose-modification schedule was adopted in the phase III APEX trial of bortezomib (Table 1). This dose-modification schedule resulted in a reduction in the frequency of grade 3 or higher peripheral neuropathy to 9%.

Bortezomib-induced peripheral neuropathy is reversible. In the APEX study, 64% of patients experienced improvement or resolution of neuropathy to baseline at a median of 110 days, and the reversibility was higher when dose modifications were used. The effectiveness of bortezomib did not seem to be affected by this dose modification schedule.

Weekly Versus Twice-Weekly Schedule: To improve the tolerability of treatment, bortezomib has been given on a weekly schedule rather than twice weekly. In older patients with newly diagnosed MM who were not considered eligible for autologous stem cell transplant, a phase III study compared the combination of bortezomib, melphalan, prednisone, and thalidomide followed by maintenance bortezomib and thalidomide versus bortezomib, melphalan, and prednisone alone. In this trial, bortezomib was initially given twice weekly intravenously for the first 4 cycles and then weekly in subsequent cycles. Later in the trial, to reduce the incidence of peripheral neuropathy, the schedule was modified to weekly. The patients receiving twice-weekly bortezomib had a significantly higher incidence of grade 3 or greater peripheral neuropathy (28% vs 8%; P.<.001), along with a higher discontinuation rate due to neuropathy (15% vs 5%; P.<.001). Efficacy was similar between the groups with respect to progression-free survival, complete response rate, and 3-year overall survival rate. A phase II study of bortezomib combined with cyclophosphamide and dexamethasone (CyBorD) also found a lower rate of grade 3 or higher peripheral neuropathy when bortezomib was given weekly versus twice weekly (0% vs 6%).

Subcutaneous Route: Conventionally, bortezomib has been given intravenously as a bolus. Changing the route of administration from intravenous to subcutaneous was investigated in a randomized study of patients with relapsed disease. Peripheral neuropathy was significantly less common in patients receiving bortezomib subcutaneously, with a 6% rate of grade 3 or higher neuropathy compared with 12% among patients treated intravenously (P=.026). An updated analysis of the trial showed comparable outcomes between the routes. Pharmacokinetic studies showed that systemic exposure was equivalent with subcutaneous and intravenous routes, although the peak drug concentration was lower with the subcutaneous route. Given the remarkably improved tolerability of the subcutaneous route, it is now
FDA-approved and increasingly used in the relapsed and newly diagnosed settings. An ongoing phase II trial of subcutaneous bortezomib combined with lenalidomide and dexamethasone in newly diagnosed, transplant-ineligible patients will provide additional data on the efficacy of subcutaneous bortezomib (ClinicalTrials.gov identifier: NCT01782963).

**Carfilzomib**
In contrast to bortezomib, carfilzomib is a new proteasome inhibitor that is associated with a very low incidence of peripheral neuropathy. It was recently approved in July 2012 for patients with MM experiencing disease progression after prior therapy with bortezomib and an immunomodulatory drug. An analysis of 4 phase II trials of carfilzomib in patients with relapsed MM showed a 13.9% rate of peripheral neuropathy, with a 1.3% rate of grade 3 peripheral neuropathy. In newly diagnosed patients, a phase I/II trial of the combination of carfilzomib with lenalidomide and dexamethasone showed low rates of peripheral neuropathy (17% for grade 1; 6% for grade 2; and 0% for grade 3 or higher).

**Treatment**
The effective treatment of peripheral neuropathy from bortezomib and other treatments continues to be an unmet need. Early recognition of neuropathy is important so that dose modifications can be made to increase the chances of reversibility. Once present, treatment is supportive and primarily based on consensus guidelines and extrapolation of treatments used in other settings, such as peripheral neuropathy from diabetes or postherpetic neuralgia. The IMWG recently presented guidelines on managing peripheral neuropathy. Conventional treatments for neuropathy include opioids; gabapentin or pregabalin; tricyclic antidepressants; and topical agents such as capsaicin cream or menthol, or emollients such as cocoa butter. However, results have been inconsistent, such as with gabapentin. Recently, a randomized study showed that duloxetine was effective for treating painful peripheral neuropathy caused by chemotherapy. However, this patient population received oxaliplatin or a taxane, and did not include patients with MM who received bortezomib.

Nutraceuticals, such as vitamin E and glutamine, have also been used, although the findings regarding their use is conflicting. Vitamin C is not recommended, because, in vitro, vitamin C inactivates bortezomib. Furthermore, some of these approaches, although initially attractive, did not show efficacy when studied more rigorously in larger patient populations. These approaches include α-lipoic acid to prevent platinum-induced polyneuropathy and intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity.

**Venous Thromboembolic Complications**
Patients with MM have an increased risk of venous thromboembolism (VTE). In a survey of US military veterans (before the introduction of immunomodulatory drug therapy), patients with MM had a 9.2-fold increased risk of developing deep venous thrombosis (DVT) compared with all other patients. The highest risk of DVT was in the first year after diagnosis. The risk of VTE is significantly increased with the use of oral immunomodulatory drugs, such as thalidomide and lenalidomide, which are associated with the highest risk of thrombosis of all the therapies used in MM. Thrombotic events are predominantly venous, although occasionally arterial events have been observed.

In patients treated with older therapies, the

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<tr>
<th>Severity of Peripheral Neuropathy</th>
<th>Modification of Dose and Schedule</th>
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<tbody>
<tr>
<td>Grade 1 (paresthesias or loss of reflexes) without pain or loss of function</td>
<td>No action</td>
</tr>
<tr>
<td>Grade 1 with pain or grade 2 (interferes with function but not with ADLs)</td>
<td>Reduce to 1 mg/m²</td>
</tr>
<tr>
<td>Grade 2 with pain or grade 3 (interferes with ADLs)</td>
<td>Withhold treatment until toxicity resolves, then reinitiate at a dose of 0.7 mg/m² once weekly</td>
</tr>
<tr>
<td>Grade 4 (permanent sensory loss that interferes with function)</td>
<td>Discontinue treatment</td>
</tr>
</tbody>
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Abbreviations: ADLs, activities of daily living.
Data from Refs. 59, 62

Table 1: Dose Modification Guidelines for Bortezomib-Related Neuropathy
incidence of VTE ranges from 3% with high-dose dexamethasone to 2% to 4% with melphalan and prednisone. As single agents, the risk of VTE with thalidomide or lenalidomide is less than 5%. A consistent finding is that this thrombotic risk increases with the addition of dexamethasone, anthracyclines, or erythropoietin. Two phase III trials of lenalidomide with dexamethasone in patients with relapsed MM showed that the VTE rate was significantly higher with the combination than with dexamethasone alone (11%–15% vs 4%–5%).

Prophylaxis with aspirin or low-molecular-weight heparin can effectively lower the risk of VTE. In one trial of lenalidomide with dexamethasone, before the routine use of aspirin, 9 of 12 patients receiving this combination developed VTE. Once aspirin at 325 mg was mandated, the VTE rate was 19% with modification of the protocol. A similar benefit was seen with enoxaparin for prophylaxis. Guidelines from the IMWG recommend risk stratification; patients with 0 or 1 risk factor, such as prior VTE, should receive 81 to 325 mg of aspirin once daily. For patients who are receiving high-dose dexamethasone, prophylactic doses of low-molecular-weight heparin or therapeutic warfarin are recommended.

Using lower doses of dexamethasone with lenalidomide attenuates the risk of VTE. In the ECOG E403 study, patients with newly diagnosed MM were randomized to lenalidomide with traditional, high-dose dexamethasone versus lenalidomide with low-dose weekly dexamethasone. The rate of VTE was significantly lower with the low-dose dexamethasone regimen than in the traditional high-dose regimen (12% vs 26%; P=.0003). Notably, in this study, prophylaxis was recommended but not mandated initially in the study.

The current rate of VTE events with the newest immunomodulatory drug, pomalidomide, has been low, because prophylaxis has been used upfront. For example, in the MM-003 phase III trial comparing pomalidomide with low-dose dexamethasone versus high-dose dexamethasone, the VTE event was 2% versus 1%, respectively.

**Infection**

Infections are a major cause of morbidity and mortality in patients with MM, stemming from both the adverse effects of MM on humoral and cellular immunity and myelosuppression from treatment. Patients with MM have functional hypogammaglobulinemia coupled with decreased diversity in the antibody repertoire. Older data described a biphasic pattern for bacterial infections, with encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* early in the course of illness and *Staphylococcus aureus* and gram-negative organisms in later months. A recent survey of the Swedish cancer registry from 1998 through 2004 found a 6-fold risk of any infection among patients with MM compared with the general population, with the highest risk during the first year after diagnosis.

With the use of newer agents such as bortezomib, the types of infections have changed compared with older melphalan-based regimens and historical induction chemotherapy regimens. Bortezomib is associated with a significantly higher risk of herpes zoster. In the phase III APEX trial, the incidence of herpes zoster was 13% among patients treated with bortezomib compared with 5% in the control arm among those treated with dexamethasone (P=.0002). Using a lower dose of dexamethasone, when combined with lenalidomide, is associated with significantly decreased risk of infections, including pneumonia (9% vs 16%; P=.04).

**Prophylaxis**

The use of antibiotics for prophylaxis of infection is an area of evolving research. An older randomized study of 57 patients with newly diagnosed MM investigated prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) versus placebo for the first 2 months of chemotherapy. During the 3-month observation period after the start of chemotherapy, a significantly reduced rate of bacterial infection was seen among patients treated with prophylaxis: 2 patients in the TMP-SMX arm versus 11 in the control arm (P=.004). A subsequent larger phase III study randomized 221 patients with newly diagnosed MM to receive either ciprofloxacin, TMP-SMX, or observation, and evaluated them for grade 3 or higher infections during the first 2 months of treatment. The rates of infection were comparable (20% vs 23% vs 22%, respectively). Notably, most of these patients were on regimens that are no longer commonly used (eg, vincristine, doxorubicin, and dexamethasone).

In clinical practice, because of the high risk of
herpes zoster associated with bortezomib, the authors routinely prescribe antiviral agents, such as acyclovir (eg, 400 mg orally twice daily). They also use TMP-SMX (eg, 1 single-strength oral tablet daily, or alternatives in patients with sulfa allergy) for patients on corticosteroid-containing regimens to prevent Pneumocystis jirovecii pneumonia.

**Intravenous Immunoglobulin**

Because of the functional hypogammaglobulinemia associated with MM, immunoglobulin replacement (intravenous immunoglobulin [IVIG]) has been considered. An older randomized study of IVIG in newly diagnosed patients did not find benefit. In patients with stable, plateau-phase disease, a randomized, placebo-controlled trial studied the use of IVIG given monthly for 1 year in 82 patients with MM. No episodes of septicemia or pneumonia were seen in the IVIG arm compared with 10 events in the placebo arm (P = .002). Although the findings in the latter study showed benefit, the use of IVIG as a prophylaxis has not been generally adopted. However, IVIG may be considered in selected patients with severe, recurrent infections and hypogammaglobulinemia.

**Conclusions**

Over the past decades, the treatment of MM has become increasingly more effective with the incorporation of novel therapies such as bortezomib and lenalidomide, and now carfilzomib and pomalidomide. An imperative exists to develop better supportive strategies that match the effectiveness of these newer anti-MM agents. Bisphosphonates have been a major advance in the management of bone disease, and the challenge remains to optimize the frequency and duration of therapy. Newer agents such as denosumab and other bone anabolics are under investigation and may be incorporated as therapy for bone disease in the near future. The tolerability of anti-MM regimens with peripheral neuropathy and thrombotic complications has improved with a better understanding of dosing schedules, thromboprophylaxis, and infectious complications. Ultimately, advances in supportive care will translate to better quality of life and survival as patients are able to continue on treatment longer. A summary of current recommendations for supportive care is provided in Table 2.

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**Table 2  Summary of Recommendations for Supportive Care**

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<tr>
<th>Bone Disease</th>
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<tr>
<td>• Intravenous bisphosphonate monthly for 1 to 2 years</td>
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<tr>
<td>• Note: zoledronate has shown overall survival benefit in MRC Myeloma IX trial</td>
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<tr>
<td>• Reinitiate intravenous bisphosphonate monthly at time of relapse</td>
</tr>
<tr>
<td>• Hold bisphosphonate for invasive dental procedures (eg, tooth extractions; cleanings and root canals are not contraindications) for 3 months before and after procedures, if possible</td>
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<tr>
<td>• Monitor for osteonecrosis of the jaw</td>
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<tr>
<td>• Monitor for renal dysfunction</td>
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<tr>
<th>Peripheral Neuropathy</th>
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<tbody>
<tr>
<td>• Risk of peripheral neuropathy higher with bortezomib</td>
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<tr>
<td>• With bortezomib, close surveillance for peripheral neuropathy</td>
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<tr>
<td>• Dose-reduce bortezomib with grade 1 neuropathy with pain or grade 2 neuropathy (moderate symptoms or limiting instrumental activities of daily living, such as preparing meals, shopping for groceries or clothes, using telephone, and managing money)</td>
</tr>
<tr>
<td>• Administer bortezomib subcutaneously instead of intravenously (when clinically appropriate)</td>
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<tr>
<td>• Schedule bortezomib weekly instead of twice weekly (when clinically appropriate)</td>
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<tr>
<th>Venous Thromboembolism</th>
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<tbody>
<tr>
<td>• Risk of venous thromboembolism higher with immunomodulatory drugs, such as lenalidomide in combination with dexamethasone</td>
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<tr>
<td>• Combination of lenalidomide (or other immunomodulatory drug) with dexamethasone warrants routine thromboprophylaxis with aspirin at 81 to 325 mg daily</td>
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<tr>
<td>• In patients with additional risk factors (obesity, trauma), consider low-molecular-weight heparin at prophylactic dosage (eg, enoxaparin, 40 mg subcutaneously daily) or full-dose warfarin</td>
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<tr>
<td>• With high-dose dexamethasone or doxorubicin, use low-molecular-weight heparin at prophylactic dose or full-dose warfarin</td>
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<th>Infection</th>
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<tr>
<td>• In patients on bortezomib-based therapies, use oral acyclovir at 400 mg twice daily (or equivalent) to decrease risk of herpes zoster</td>
</tr>
<tr>
<td>• Patients on corticosteroid-containing regimens should take 1 single-strength oral tablet daily of trimethoprim-sulfamethoxazole (or equivalent) to decrease risk of Pneumocystis jirovecii pneumonia and other infections</td>
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**References**


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