Peripheral Neuropathy Experience in Patients With Relapsed and/or Refractory Multiple Myeloma Treated With Carfilzomib

The adverse event profile of single-agent carfilzomib suggests that the agent is an important treatment option for patients with advanced multiple myeloma, particularly those with pre-existing peripheral neuropathy or those who are at risk for the development of peripheral neuropathy.

Introduction

Multiple myeloma (MM) is a devastating disease that is associated with significant morbidity and uniform mortality. Only recently has the median survival of patients with MM surpassed 5 years, and many patients can live more than 10 years. Throughout the course of their disease, patients with MM experience numerous complications as a result of patient-, disease-, and treatment-related factors. The uncontrolled proliferation of plasma cells can lead to substantial end-organ damage, resulting in an increased susceptibility to infections, bone destruction with significant pain, renal and neurologic dysfunction, and hematologic complications.[1-6] In addition, because most patients with MM are > 70 years of age,[7] comorbidities such as cardiac risk factors or baseline renal disease commonly predispose patients to subsequent complications.[1,8,9]

The morbidity associated with MM is also influenced by the tolerability of current anti-MM treatment options. The most common treatments include immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide) and/or proteasome inhibitors (bortezomib and carfilzomib). These drugs can be used in combination with each other and with other effective but potentially toxic drugs, including dexamethasone and traditional chemotherapeutic agents such as cyclophosphamide.[7] All of these drugs can be associated with adverse events, including myelosuppression, thrombosis, gastrointestinal events, and peripheral neuropathy (PN), although the rates of each adverse event can vary depending on the agent being used.[10-18] Therapy selection for patients with relapsed and/or refractory MM must therefore reflect current comorbidities, patient age, and treatment history, because subsequent therapies may exacerbate pre-existing comorbidities and toxicities.

PN is common in patients with MM. It is predominantly sensory or sensorimotor and may present as numbness (paresthesia), burning (dysesthesia), pain, or sensory loss.[17,19] Approximately 20% of patients with MM have symptoms indicative of PN at diagnosis. Possible mechanisms by which MM leads to the development of PN include the occurrence of amyloid deposition in the peripheral nerves, the production of antibodies that target myelin-associated glycoprotein, the existence of cytokine-mediated injury, and the incidence of radiculopathy from direct compression by tumor.[19,20-22]

PN is also frequently associated with anti-MM treatment, occurring in as many as 75% of patients receiving anti-MM therapies, most notably in those receiving thalidomide- or bortezomib-based therapies.[17,19] Carfilzomib is a selective proteasome inhibitor with lower observed rates of neurotoxicity relative to other agents. This article reviews the current clinical trial experience of carfilzomib with respect to PN in 526 patients with relapsed and/or refractory MM. The use of carfilzomib—including its use in patients with a history of PN and the incidence of new-onset PN in carfilzomib-treated patients—is considered, and a clinical perspective on the management of PN in these patients is provided.

Treatment-Induced PN

Patients in whom treatment-induced PN develops often require dose reductions or treatment withdrawal, which may limit the potential benefit of these agents.[17,19,23] In addition, the symptoms of treatment-induced PN can be debilitating and may negatively affect a patient’s quality...
of life (Table 1).[17,24-27] For example, a study that monitored the pain intensity associated with bortezomib-induced PN reported an average daily maximum pain rating of 7.8, on a scale of 1 to 10.[25] The patients with pain associated with PN had a significantly elevated touch detection threshold and slotted peg board time, impaired sharpness detection, elevated thresholds for the detection of skin warming and heat pain, and increased pain with skin cooling. Patients achieved only modest levels of pain relief with opioids, which was indicative of the refractoriness of treatment-associated neuropathic pain.

**Immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide)**

Patients who receive thalidomide are at increased risk for PN, yet the etiology of this toxicity remains unclear. It is believed that thalidomide may have direct effects on the dorsal root ganglia (DRG), leading to DRG degeneration.[28] Other studies suggest that thalidomide can downregulate tumor necrosis factor-alpha, leading to Wallerian degeneration and the loss of myelinated fibers.[29] The contribution of each of these effects or other factors to the development of PN is still undefined. The clinical manifestations of thalidomide-induced PN include sensory symptoms (distal paresthesia and hyperesthesia), motor symptoms, and autonomic dysfunction.[18]

In a meta-analysis of 1,674 patients receiving single-agent thalidomide for relapsed or refractory MM, the incidence of severe grade 3/4 PN was 6%, while PN of any grade was reported in 28% of patients.[30] PN occurs more frequently in elderly patients receiving thalidomide and is closely related to the cumulative dose and the duration of treatment.[18,30] PN develops in about 70% of patients treated with thalidomide for > 12 months, and symptoms can occur after treatment has stopped.[18,31] It is recommended that patients with PN induced by thalidomide discontinue therapy before the neuropathy becomes painful or interferes with daily activities, because the PN may become aggravated and irreversible.[17,18]

In general, lenalidomide and pomalidomide are considered much less neuropathic than thalidomide; thus, few data are available on the etiology of PN associated with either agent. Pomalidomide in combination with dexamethasone has been associated with low rates of PN when evaluated in phase II/III studies of patients with relapsed or refractory MM (< 1%-2% grade 3/4 PN).[32,33] A low incidence of treatment-emergent neuropathy has also been reported in lenalidomide-treated patients. In a prospective trial designed specifically to evaluate treatment-emergent neuropathy in patients with relapsed MM who are receiving lenalidomide, only 2 of 30 had worsening neuropathy with lenalidomide. Both had pre-existing neuropathy, and both had resolution of neuropathic symptoms over time without cessation of therapy.[34] In a larger study examining lenalidomide and dexamethasone in patients with relapsed and refractory MM, grade 3/4 neuropathy developed in only 1.7% (3 of 177) of patients.[35] Similar data exist for lenalidomide in the treatment of patients with newly diagnosed MM: the incidence of neuropathy was < 25% overall, and the rate of grade 3/4 events was < 5%.[36]

**Bortezomib**

Treatment-induced PN has been particularly problematic with intravenous bortezomib; PN developed in as many as two out of three patients during treatment for MM in phase II/III clinical trials.[14,23,27] Multivariate analysis has identified risk factors for bortezomib-induced PN, including the number of cycles of treatment and a history of thalidomide therapy.[37] A pooled analysis of two phase II studies (Clinical Response and Efficacy Study of Bortezomib in the Treatment of Refractory Myeloma [CREST] and Study of Uncontrolled Myeloma Management With Proteasome Inhibition Therapy [SUMMIT]) revealed a 35% incidence of PN, with PN leading to dose reductions in 12% of patients and treatment discontinuation in 5% of patients.[27] PN was rated as grade 3/4 in severity for 13% of patients, and a higher incidence of grade 3/4 PN was reported among patients with baseline neuropathy (14%) compared with those without baseline neuropathy (4%). In a later multicenter phase II study that specifically examined the prevalence of PN in patients treated with bortezomib, sensory polyneuropathy developed in 64% of patients with newly diagnosed MM who were treated with single-agent bortezomib (N = 64).[23] There was a lower rate of grade ≥ 3 PN than reported in the CREST and SUMMIT trials (grade 3 sensory PN in 3% of patients and no grade 4 PN), which the authors suggested could be attributed to the establishment of dose-modification guidelines and more rigorous monitoring.

Ordinarily, PN induced by bortezomib occurs early in treatment (usually by cycle 5) and does not worsen with cumulative exposure to the drug.[27] Studies have suggested that decreasing the dosing frequency or administering bortezomib by the subcutaneous route may help to reduce the incidence of PN.[38,39] In a study of once-a-week vs twice-a-week bortezomib, the overall incidence...
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of grade 3/4 PN was significantly decreased from 28% to 8% in the once-a-week treatment group, and only 5% of patients discontinued therapy because of PN compared with 15% in the higher-dose group.[38] Progression-free survival and overall survival (OS) did not differ significantly between treatment groups. In a phase III study, the rate of PN was significantly lower in patients given bortezomib via the subcutaneous route compared with intravenous administration (all grades: 38% vs 53%, respectively, \(P = .044\); grade \(\geq 3\): 6% vs 16%, respectively, \(P = .026\).[39] This suggests that patients at high risk for bortezomib-induced PN may experience more favorable outcomes by changing to either subcutaneous or weekly administration of bortezomib. Clinical studies have reported a reversal of PN in most patients once bortezomib is discontinued,[23,27] although results from one case study of 12 patients with ongoing pain after treatment with bortezomib have indicated that patients can have persistent and severe impairment of nerve fibers.[40] Patients who experience improvement in neuropathy often note relief after approximately 3 to 4 months of treatment discontinuation or dose reduction, and improvements can be seen as many as 6 to 9 months later. In the phase III study that compared subcutaneous and intravenous bortezomib administration, patients in both treatment arms experienced improvement or resolution of PN at similarly high rates; 83% of PN events in the intravenous arm had resolved or improved in a median of 2.5 months vs 74% of PN events in the subcutaneous arm that had resolved or improved in a median of 1.5 months.[39] Preclinical studies suggest that the inhibition of nonproteosomal targets by bortezomib leads to PN via the accumulation of ubiquitinated proteins in the cytoplasm of the DRG of primary sensory neurons.[41-44] Thus, therapies with fewer off-target effects may offer lower incidences of toxicity related to PN, allowing for a longer duration of treatment and improved efficacy.

**Carfilzomib**

The proteasome inhibitor carfilzomib has demonstrated significant durable activity in patients with advanced MM and was recently approved in the United States for use as a single-agent treatment for patients with relapsed and refractory MM. Approval by the US Food and Drug Administration of carfilzomib was based, in part, on efficacy results from the phase II study PX-171-003-A1, which demonstrated an overall response rate (partial response or better) of 23%, with a median duration of response of 7.8 months in patients with relapsed and refractory MM.[45] Carfilzomib, unlike bortezomib, has minimal off-target effects on non-proteasome, serine proteases.[46] In preclinical studies, the proteases HtrA2/Omi, cathepsin A, cathepsin G, chymase, and dipeptidyl peptidase II were inhibited by bortezomib, leading to reduced neurite growth. In contrast, carfilzomib did not inhibit these serine proteases, yet it still achieved an equivalent level of proteasome inhibition compared with bortezomib.[46] This may, in part, explain the decreased incidence of PN observed in the clinic in patients with MM who receive carfilzomib,[9,47-50] as the neurotoxicity of bortezomib is thought to be caused by off-target activity.[46]

**Cross-trial safety analysis of phase II carfilzomib trials: key adverse events related to PN.**

A cross-trial safety analysis from four phase II clinical trials (PX-171-003-A1, PX-171-003-A0, PX-171-004, and PX-171-005) further evaluated the tolerability of single-agent carfilzomib in patients with relapsed and/or refractory MM, including an assessment of the incidence of baseline and treatment-emergent PN.[9] The majority of patients (84.8%) enrolled in the clinical trials of single-agent carfilzomib had a history of PN, most attributable to previous therapy. The patterns of PN and adverse events related to PN were comparable across the four studies and are summarized in Table 2.

The overall incidence of adverse events related to PN with single-agent carfilzomib was 13.9%. Most patients (71.9%) had active grade 1/2 PN at baseline (higher grades were not eligible for study treatment), but the majority of these patients (330/378; 87.3%) did not report a worsening adverse event related to PN while receiving carfilzomib. Grade 3 PN was reported in only 1.3% of patients overall, and there were no cases of grade \(\geq 4\) PN. These results suggest that single-agent carfilzomib is associated with a low rate of new-onset PN and does not exacerbate previous or existing PN. The majority of adverse events related to PN occurred early in the course of single-agent carfilzomib treatment (prior to cycle 6), suggesting that the induction of PN is not cumulative. Importantly, PN accounted for a very low rate of carfilzomib discontinuation (one patient [0.2%]) and dose reduction (four patients [0.8%]), despite the fact that 47.1% of patients had discontinued a previous treatment because of PN. Thus, PN does not appear to be dose-limiting during single-agent carfilzomib therapy.

**Clinician Perspective**
In general, the treatment of MM and the number of effective agents have significantly improved in the past 5 to 10 years. These novel agents have increased median OS, and many patients are now living more than 10 years from diagnosis. In addition, the toxicity profiles of the newer agents differ, thus allowing for a more “personalized” selection of treatment for individual patients. The hope is that with better-tolerated treatments, patients can receive the maximum benefit from “full-dose” and sustained treatment. To that end, some centers have adopted a continuous-therapy model for the treatment of MM with maintenance therapy being used for patients with newly diagnosed disease and in the relapsed and refractory setting.[51] Overall, since patients with MM are living longer, better-tolerated agents affording improved quality of life are essential. One of the most significant causes of debility in patients with MM is disease- and treatment-induced neuropathy. Thus, strategies aimed at limiting neuropathy and the use and development of agents that induce less neuropathy are strongly encouraged. Patients with MM—particularly those with relapsed and/or refractory disease—should be closely monitored for symptoms of PN at diagnosis and throughout treatment. Many of these patients have pre-existing neuropathy, and it is important to evaluate PN before selecting and starting new treatment. One must establish a baseline that will allow longitudinal assessment of PN. Periodic and dedicated neurologic assessments throughout treatment are recommended to determine whether a regimen change or other intervention is needed. Patients and the clinical staff should be educated on the signs of PN and encouraged to promptly report these signs to the care team.

Treatment-induced PN is common in patients with MM and can have a marked effect on their quality of life. Severe PN can lead to increased resource utilization and healthcare expenditures, since each event of treatment-related grade 3/4 PN can result in supportive care costs of more than $1,000 (in 2011 United States dollars).[52] Severe PN can also lead to costs from loss of productivity, the effects of which have yet to be fully understood. In addition, dose reductions and discontinuations are recommended and necessary for patients with treatment-induced PN. These dosing changes may reduce the clinical benefit derived from these agents and may lead to increased healthcare resource utilization from suboptimal therapy. Thus, newer agents that have increased specificity and lower rates of associated PN, such as carfilzomib, could offer significant advantages to the treatment of patients with MM. Additional studies are needed to fully elucidate the effect of treatment-induced PN on quality of life, healthcare resource utilization, and individual patient productivity. These studies would help define the emerging role of new proteasome inhibitors and immunomodulatory agents in the treatment of patients with MM. Future studies would be informative in evaluating whether carfilzomib treatment reduces the complications and costs associated with managing PN, especially compared with rates experienced with bortezomib- or thalidomide-based treatment. It is notable that carfilzomib-associated PN is rare. When PN occurs, it is typically grade 1/2, and is unlikely to be dose-limiting. Therefore, patients with PN may have the ability to continue receiving the target dose of carfilzomib, deriving the full benefits of treatment without dose interruptions or reductions. However, in the event of severe treatment-induced PN (ie, grade 3/4 PN), carfilzomib should be withheld until the PN is resolved or returns to baseline.[45] Carfilzomib may be restarted at the target dose used before the event or may be given at a reduced dose (eg, from 27 mg/m² to 20 mg/m², or from 20 mg/m² to 15 mg/m²) as clinically appropriate; if tolerated at the reduced dose, carfilzomib may also be escalated to the target dose, if appropriate.

Patients with MM frequently receive multiple lines of therapy, including front-line treatment with neurotoxic agents. Thus, it is important to understand the safety profile of each agent to determine appropriate combinations and sequencing of therapies. Because single-agent carfilzomib does not aggravate pre-existing neuropathy, this agent may be a good treatment option for patients with disease- or treatment-induced PN or for use after or in combination with agents associated with an increased risk of PN. Although both lenalidomide and carfilzomib are associated with low rates of PN as single agents, a recent phase II trial of carfilzomib, lenalidomide, and dexamethasone in patients with relapsed and refractory myeloma surprisingly reported treatment-emergent neuropathy in 24% of patients.[53] This may suggest a synergistic effect when carfilzomib is combined with lenalidomide; however, it is noteworthy that only 1.2% of patients experienced grade 3/4 toxicity, and that these data are favorable in relation to the combination of bortezomib, lenalidomide, and dexamethasone in the relapsed and refractory setting, in which PN of any grade has been reported in 42% of patients.[54] Further studies are needed to more fully define the effect of carfilzomib treatment on PN when used in combination treatment.

**Conclusion**
Patients with MM are at increased risk for the development of PN as a consequence of the disease itself and of anti-MM therapy. Encouragingly, the recently approved proteasome inhibitor carfilzomib is associated with low rates of new-onset PN. In addition, results from an integrated safety analysis of single-agent carfilzomib indicate that treatment-emergent PN is mild to moderate in intensity and very rarely results in dose reductions or discontinuations. Although most patients in the phase II studies of single-agent carfilzomib had active PN at baseline, the drug did not exacerbate pre-existing PN. In conclusion, the adverse event profile of single-agent carfilzomib suggests that the agent is an important treatment option for patients with advanced MM, particularly those with pre-existing PN or those who are at risk for the development of PN.

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