Comment on Bringhen et al, page 4745

Improving the therapeutic index in myeloma

Paul G. Richardson  DANA-FARBER CANCER INSTITUTE

In this issue of Blood, Bringhen and colleagues report on the efficacy and safety of once-weekly bortezomib in multiple myeloma (MM) patients.1 The authors report on a post-hoc analysis which assessed the impact of schedule change on clinical outcomes as part of their randomized phase 3 trial, which compared the combination of bortezomib, melphalan, and prednisone with thalidomide followed by maintenance treatment with bortezomib and thalidomide, versus a current standard approach, namely bortezomib, melphalan, and prednisone.

The latter was established as an important option for transplant-ineligible patients as a result of the large, randomized, international phase 3 VISTA trial in which bortezomib, melphalan, and prednisone (VMP) was shown to be significantly superior to melphanal and prednisone, for all the assessed endpoints, including complete response, time to progression, and overall survival (OS).2 The superiority of the 3-drug combination approach was further demonstrated in a recent update with more than 3 years of follow-up.3 Arguably the most important toxicity encountered with VMP is peripheral neuropathy (PN); indeed, overall rates of 40%-64% for bortezomib-induced peripheral neuropathy (BiPN) are seen in the upfront setting, with changes of treatment through either dose reduction or discontinuation ranging from 14%-30%.2,4,5 Thus, strategies to significantly reduce BiPN are an obvious and urgent priority, with dose reduction and schedule change being the most effective approach to date.6

In this particular trial, the protocol was amended to evaluate whether the treatment regimens could be further optimized by decreasing the incidence of PN while maintaining efficacy through the reduction of bortezomib infusions from twice weekly to once weekly.

Remarkably, there was a substantial improvement in nonhematologic severe adverse event rates, while long-term outcomes appeared similar with 3-year progression-free survival rates of 50% in the once-weekly and 47% in the twice-weekly group (P = 1.00), and 3-year OS rates of 88% and 99%, respectively (P = .54), as well as CR rates of 30% in the once-weekly group and 35% in the twice-weekly group (P = .27). Specifically, a 35% significant toxicity rate was reported for once-weekly treated patients, as opposed to 51% for twice-weekly treated patients (P = .003). Moreover, the incidence of grade 3/4 PN was 8% in the once-weekly group and 28% in the twice-weekly arm (P < .001). This translated into discontinuation in 5% of the patients treated on the once-weekly arm versus 15% in the twice-weekly group (P < .001). The authors concluded that the weekly schedule resulted in a substantial improvement of safety, which did not impact on the efficacy of either regimen tested.

One of the correlates to this observation was overall bortezomib exposure and median cumulative dose delivered, which was similar...
in both groups at 39.4 mg/m² versus 40.1 mg/m² in the once-weekly versus twice-weekly groups (P = .65). In contrast, there was a substantial difference in the number of patients who received 90% or more of the planned dose, with 39% achieving this with the once-weekly bortezomib regimen versus just 13% in the twice-weekly regimen (P = .001). What is also interesting is the association between both patient and treatment characteristics with cumulative incidence of BiPN, where no relationship to thalidomide use as part of one of the regimens was seen. No other factor in the analysis (including age, creatinine clearance, presence of diabetes, or certain MM disease features) proved relevant. Conversely, once-weekly bortezomib was associated with a significant hazard ratio in favor of reducing both any grade of PN as well as grade 3/4 PN. Furthermore, when the authors compared grade 3/4 PN between the twice-weekly VMP used in the present study and the VISTA study, the rates were similar at 14% and 13%, respectively, with discontinuation rates comparable between the 2 trials.

It is also notable that adequate dose reductions resulted in a high proportion of patients having an improvement in their symptoms, with significant PN resolving or improving in more than two-thirds of patients in both groups after a median of 2–3 months, an observation consistent with previous studies.5,6

Thus, acting promptly with dose and schedule change, as well as providing patients with information regarding PN, is mandatory in the management of BiPN; informed patients can thus signal the worsening of symptoms, whereas less well-informed patients may delay. The authors correctly conclude that symptoms interfering with functions of daily living (including pain or motor PN, such as muscle cramps, tremor, or loss of strength) should require withholding of treatment, and once toxicities resolve then treatment can be reinitiated, but at a dose reduction.

Beyond the fact that once-weekly infusion of bortezomib in combination with melphalan and prednisone with or without thalidomide is a valuable treatment for newly diagnosed patients aged at least 65 years, the principle of combination therapy allowing active but potentially toxic agents to be dose reduced and continued to maintain efficacy is exemplified. Not only was bortezomib administered with less frequency, but thalidomide was also given at a lower dose at 50 mg per day in those patients assigned to the 4-drug combination. The correct partners for various combination approaches thus become particularly pertinent. The emerging role of lenalidomide as a newer immunomodulatory agent in combination with bortezomib is of particular interest, recognizing that neurotoxicity remains a challenge, although the extent and severity of PN with this combination appears substantially less.7

This raises the question that melphalan itself, as a potent alkylator, may contribute to the neurotoxicity seen. This becomes important because there is emerging data to suggest that the mechanisms of BiPN are complex, and include oxidative (as a part of free radical-mediated injury) as well as inflammatory processes in the mechanisms underlying the neurotoxicity encountered including a contribution from the underlying disease itself (please see figure).8 It is then perhaps not surprising when bortezomib is combined with conventional chemotherapy, be it alkylator-based or anthracycline-derived, that increased rates of higher-grade PN are seen.4 This further supports the development of rational combination strategies to minimize toxicity but maintain therapeutic efficacy.

Finally, with second-generation proteasome inhibitors having substantially less neurotoxicity, such as carfilzomib, and indeed newer boronate peptides (such as MLN 9708) also being less neurotoxic, the opportunity for further improvements in therapeutic index emerge, especially when combined with immunomodulatory agents including lenalidomide.8 Some caution has to be exercised, as illustrated by experience to date with the second-generation proteasome inhibitor NPI-0052: it appears devoid of significant PN but, as an irreversible and highly potent inhibitor, does appear to have some renal toxicity, a feature also occasionally seen with carfilzomib.10 Therefore, as is the case in all effective drugs, potentially challenging side effects of different forms will likely remain with the clinical application of these various agents.

However, these should be surmountable as not only dose, combination, and schedule are examined but also the risk profiles of the respective patients in whom each treatment is explored are characterized. Provocative work regarding gene-expression profiling and potential genomic vulnerability to specific toxicities is emerging,8 and will facilitate a risk-stratified approach to management. This in turn may meaningfully complement existing methods that center on dose reduction and the use of supportive care.

In aggregate then, and as reflected by this important study, the ability to develop and deliver effective combination treatments to our MM patients, young and old, continues to evolve. The clear recognition is that side-effects matter, such that our ability to continue treatment and so maintain disease control, while preserving quality of life, remains paramount.

Conflict-of-interest disclosure: P.G.R. is on the advisory boards of Millennium, Celgene, and Johnson & Johnson.

REFERENCES

1. Bringhen S, Lannec A, Rosi D, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood. 2010;116(23):4745-4753.
2. San Miguel JF, Schlag R, Khaguaeva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359(9):906-917.
3. Mateos MV, Richardson PG, Schlag R, et al. Bortezomib plus melphalan-prednisone versus melphalan-prednisone in previously untreated multiple myeloma: an updated follow-up and impact of subsequent therapy in the phase 3 VISTA trial. J Clin Oncol. 2010;28(13):2259-2266.
4. Mateos MV, Richardson PG, Schlag R, et al. Peripheral neuropathy with VMP resolves in the majority of patients and shows a rate plateau [abstract]. Clin Lymphoma Myeloma. 2009;9(suppl 1):S30. Abstract A172.
5. Richardson PG, Xia W, Mitsiades C, et al. Single-agent bortezomib in previously untreated multiple myeloma: efficacy, characterization of peripheral neuropathy, and molecular correlations with response and neuropathy. J Clin Oncol. 2009;27(21):3518-3525.
6. Richardson PG, Briemberg H, Jagannath S, et al. Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. J Clin Oncol. 2006;24(19):3113-3120.
7. Richardson PG, Weller F, Jagannath S, et al. Multi-center, phase I, dose-escalation trial of lenalidomide plus bortezomib for relapsed and refractory multiple myeloma. J Clin Oncol. 2009;27(34):5713-5719.
8. Broyl A, Corthals SL, Jongen JL, et al. Mechanisms of peripheral neuropathy associated with bortezomib and vincristine in patients with newly diagnosed multiple myeloma: a prospective analysis of data from the HOYON-65/GMMG-HD4 trial [published online ahead of print September 21, 2010]. Lancet Oncol. doi:10.1016/S1470-2045(10)70206-6.
9. Niezgoda R, Wang L, Orlovski RZ, et al. The Multiple Myeloma Research Consortium (MMRC). Phase II multi-center dose escalation study of carfilzomib plus lenalidomide and low dose dexamethasone (CRd) in relapsed and refractory multiple myeloma (MM). Blood (ASH Annual Meeting Abstracts). 2009;114(22):Abstract 304.
10. Chauhan D, Singh AV, Ciccarilli B, Richardson PG, Palladino MA, Anderson KC. Combination of novel proteasome inhibitor NPI-0052 and lenalidomide trigger in vitro and in vivo synergistic cytotoxicity in multiple myeloma. Blood. 2010;115(4):834-845.
Improving the therapeutic index in myeloma

Paul G. Richardson