Bortezomib for Myeloma — Much Ado about Something

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Multiple myeloma is a neoplastic plasma-cell dyscrasia that will cause more than 11,000 deaths in 2005 in the United States alone. The usefulness of the many therapies for multiple myeloma is limited, and virtually all patients eventually die from the disease. When thalidomide was shown to be effective against relapsed myeloma in 1999, more than 30 years had elapsed since a clinical response to any single agent had been reported in at least 25 percent of treated patients. By the early 2000s, it had become clear that another two agents — lenolidomide and bortezomib — had activity against malignant plasma cells. Bortezomib is the first of a new class of drugs, proteasome inhibitors, that have been shown to be cytotoxic to several tumor types. Because of the benefit observed in patients with relapsed or refractory myeloma in phase 1 and 2 trials, the drug was fast-tracked by the Food and Drug Administration (FDA), making it available to patients with this kind of advanced myeloma in May 2003. The Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial, which is reported by Richardson et al. in this issue of the Journal, supports the FDA’s decision.

The APEX trial randomly assigned 669 patients...
with relapsed or refractory myeloma who had received one to three previous regimens to receive either high-dose dexamethasone or bortezomib. Patients were stratified according to the number of previous regimens they had received, the time since the last therapy, and levels of serum beta-2-microglobulin. The primary end point was the time to disease progression. Secondary end points included response rates and overall survival. Patients who were randomly assigned to receive bortezomib had both a significantly longer median time to disease progression than those assigned to receive dexamethasone (6.22 months vs. 3.49 months, \( p < 0.001 \)) and higher response rates (complete response, 6 percent vs. less than 1 percent; partial response, 32 percent vs. 17 percent; \( p < 0.001 \) for both comparisons). Follow-up was truncated at the interim analysis because the results favored bortezomib.

In order to interpret the results of this trial in the context of other myeloma therapies, potential limitations of the trial — including the study design and deleterious effects of the therapies — must be considered. The choice of dexamethasone, a potent synthetic corticosteroid, as a control drug for the phase 3 trial was reasonable, since it is commonly used either as a single agent or in combination with other drugs to treat all phases of myeloma. When dexamethasone is given as a single agent, the response rate ranges from 25 to 44 percent.\(^{11,12}\) However, the first potential limitation of the APEX study was that only 1 percent of patients had not received any corticosteroids, whereas no patients had received bortezomib. The authors initially addressed this issue by restricting enrollment to patients who did not have disease that had shown previous “resistance” to dexamethasone. However, in a post hoc subgroup analysis, 60 participants were found to have disease that was possibly refractory to dexamethasone and were excluded. The observed superiority of bortezomib persisted, but the lower-than-expected response rate in the dexamethasone group (18 percent vs. the expected 25 to 44 percent) is not explained.\(^{11,12}\)

A second limitation of the trial design was the intended dose intensity of drugs to be delivered. The choice of a dexamethasone schedule of 40 mg on days 1 to 4, 9 to 12, and 17 to 20 every five weeks\(^{11}\) rather than every four weeks\(^{12}\) for induction resulted in a slightly lower dose-intensity schedule (by a factor of 0.6 to 0.8) than that used by others.\(^{12-14}\) A more striking disparity between the two groups, however, was the duration of induction for bortezomib as compared with that for dexamethasone (1.2 times as long) and the difference in dose intensity during maintenance in favor of bortezomib. Whether these design choices affected the end points cannot be known, but the intensity of the dose could certainly have influenced both response and toxicity.

The third potential limitation of the trial is the short follow-up period — 8.3 months for surviving patients. The positive findings in favor of bortezomib at the interim analysis and the subsequent recommendation of the data monitoring committee that patients in the dexamethasone group be offered premature elective crossover to the bortezomib group resulted in exorbitant censoring and truncation of follow-up. Less than 20 percent of patients were followed for one year, yet the one-year overall survival is reported as 80 percent versus 66 percent (\( p = 0.003 \)). This short follow-up and a loss to follow-up of 22 percent of patients make it uncertain that this survival benefit will withstand the test of time. Similarly, data on approximately 50 percent of patients were censored in the analysis of the time to disease progression: for the bortezomib and dexamethasone groups, respectively, data on 23 percent and 14 percent of patients were censored because of the use of alternative therapy or loss to follow-up, and data on 28 percent and 19 percent because of the mandate of the data-monitoring committee. Once again, how these censoring events affected the overall results is not known.

The difference in the overall tolerability of the therapies is not emphasized by the authors but is not inconsequential. Nearly a third of patients discontinued a study drug because of side effects. Bortezomib was associated with more serious adverse events than dexamethasone (grade 3, 61 percent vs. 44 percent; \( p < 0.01 \)) and a higher rate of drug discontinuation due to adverse events. Most striking was the relative incidence of peripheral neuropathy (all grades, 36 percent in the bortezomib group vs. 9 percent in the dexamethasone group; grade 3, 7 percent vs. <1 percent; \( p < 0.01 \)). Patients who were receiving bortezomib had significantly more fatigue, gastrointestinal symptoms, fever, myelosuppression, headache, anorexia, cough, rash, and pain. The cause of the differences is probably multifactorial. First, the dose intensity of bortezomib was higher than that of dexamethasone. Second, since
the trial was not double-blinded, there may have been a reporting bias against the “new intravenous” therapy as compared with the “old oral” therapy. Third, patients in the bortezomib group had a longer time to disease progression and thus received their assigned therapy for a longer period. This may have caused more cumulative toxicity, though similar numbers of patients in the two groups completed approximately five months of treatment (nearly 30 percent) and nine months of treatment (about 10 percent). Fourth, bortezomib may be more toxic than dexamethasone at the present dose schedules.

The final consideration of “tolerability” is one of cost. The charge by the pharmacy at my center (Mayo Clinic, Rochester, Minn.) to a patient with a body-surface area of 2 m² for the nine months of therapy as outlined in the APEX trial would be $45,760 for bortezomib and $170 for dexamethasone. Though no price can be placed on the value of an effective drug to a patient or his or her family and doctor, this differential is sobering.

So where does this leave us? The take-home message of the APEX study is that bortezomib is an effective therapy against relapsed myeloma, a fact to which anyone who has used the drug can attest. It is a much-needed additional tool against this devastating disease. Though other drugs have similar overall response rates as monotherapy, aside from high-dose melphalan, no other single agent has resulted in complete response rates of 6 percent in patients with the relapsed or refractory disease. Moreover, bortezomib markedly enhances the sensitivity of myeloma cells to other chemotherapeutic agents both in vitro and in vivo. At this year’s meeting of the American Society of Hematology, there were many preliminary reports of high rates of response to bortezomib, given either as a single agent or in combination with other agents — including dexamethasone, melphalan, doxorubicin, and thalidomide — and radiation.

After a generation without a new agent to treat myeloma, the future is bright. In the past five years, two new classes of drugs have been shown to have activity in patients with myeloma. As we move forward, we cannot ignore effective old therapies. We must determine the optimal sequence and combinations of these agents. Well-designed, randomized trials will guide our understanding, but we must be cognizant of the limitations of such studies. What is a meaningful end point? How does quality of life fit into the analysis? Despite the caveats in the APEX study, the time to disease progression was nearly doubled — albeit in absolute terms, it was a difference of three months at a price of 1.2 times as many serious adverse events and a higher dollar investment. The trial emphasizes the dire need to decipher the molecular basis of myeloma, with subsequent development of rational targeted therapies, since only these steps will lead us to substantial improvements in outcome.

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