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Practical issues involved with the use of bortezomib

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The use of proteasome inhibition as a therapeutic target against human cancers represents an exciting new target either alone, or in combination with other agents. The use of single agent bortezomib in relapsed myeloma resulted in a 43% response rate, improved time to progression, and superior overall survival when compared with high dose dexamethasone in the randomized phase III APEX trial. This survival benefit continues to hold despite the cross-over use of bortezomib for patients initially randomized to receive dexamethasone, further solidifying the use of bortezomib as a standard approach for the management of relapsed myeloma. Additional studies combining bortezomib with novel agents or cytotoxic agents in the relapsed disease setting or the induction setting has the potential to change the natural history of this disease in a manner previously only seen with the use of high dose therapy and autologous transplant.

As bortezomib is used more frequently, it is important to revisit the expected side effects, and strategies that can be undertaken to potentially reverse or minimize these effects in order to maximize the objective benefit and quality of life for our patients.

Based upon the 2 large phase II trials in myeloma, the most common adverse events using the standard 1.3 mg/m^2 dose include asthenia, gastrointestinal toxicity (including nausea, vomiting, constipation, diarrhea), thrombocytopenia, and peripheral neuropathy (PN). Asthenia and GI toxicity are managed expectantly, and often benefit from the use of hydration, anti-emetics, and in certain situations may benefit from the use of anti-motility agents.

Management of hematologic toxicity

Hematologic toxicity associated with the use of bortezomib is most frequently noted to be associated with thrombocytopenia. Anemia was often noted at the time of initiation of therapy, and among responders to bortezomib thearpy, the requirements for PRBC transfusions reduced with subsequent cycles. A similar finding was noted with leucopenia as well, and significant grade 4 neutropenia was only noted in <5% of patients, and is more likely a reflection of plasma cell infiltration of the marrow rather than a drug related event.

Early into the use of bortezomib, the cyclic pattern of thrombocytopenia was noted, with a recovery phase that did not parallel what is usually noted following cytotoxic injury to the bone marrow. An in depth analysis of predictors for the development of significant thrombocytopenia demonstrated that all patients in the phase II trials developed a similar 60% reduction in platelet count during the first 2 cycles of therapy, independent of the marrow plasma cell infiltration or serum paraprotein. Interestingly, the best predictor for the development of significant thrombocytopenia (grade 3 or 4) was the baseline platelet count at the time of bortezomib initiation. For patients who started with a platelet count of >70k, the likelihood of grade 4 thrombocytopenia was <2%, compared to 14% for patients who start with a platelet count of <70k.

A mechanistic study into the etiology of bortezomib induced thrombocytopenia demonstrated that there was no change in marrow cellularity, megakaryocyte content or ploidy among mice that received bortezomib or placebo, though the same 60% reduction in circulating platelet count was noted. Currently it is thought that the effect of bortezomib on the circulating platelet count is related to impaired platelet release from megakaryocytes, that resumes quickly following recovery of proteasome function accounting for the rapid platelet recovery, and kinetically different from the recovery phase noted following chemotherapy.

Management and incidence of peripheral neuropathy

Peripheral neuropathy (PN) is a common finding among patients with plasma cell

dyscrasias as well as a common side effect associated with the use of agents such as vincristine, thalidomide, and cisplatin. A recent trial from Richardson *et al.* evaluating the use of single agent bortezomib for patients with previously untreated myeloma objectively documented the incidence of PN among patients before the initiation of therapy. In their analysis, 50% of patients had evidence of small fiber neuropathy, and 9% of patients had evidence of large fiber neuropathy prior to the initiation of any therapy. This is important, as management and the subsequent development of PN may in part depend upon the baseline severity of PN. From the phase I and II experience with bortezomib, it is clear that the overall incidence of treatment emergent PN (PN that worsens from baseline per patient or physician reporting) was 34% with only 14% grade 3 or higher. It should be noted that over 50% of patients in the phase II experience already had PN before study entry. Based upon the experience gleaned from the phase II trials, a dose reduction schema was developed, and later used in the phase III APEX trial. Use of this dose reduction schema reduced the incidence of grade 3/4 PN to 8% with a total incidence of PN of 37%. In addition, unlike the PN noted with other agents, once bortezomib was stopped or dose reduced, over 50% of patients experienced either improvement or resolution of PN back to their baseline. Thus, the use of this simple dosing algorithm has the ability to limit PN in the short term and long term.

It is clear based on the results from several clinical trials, that the addition of bortezomib to our list of active agents in myeloma has had a major impact on the treatment approach. Understanding the toxicities, and management of these toxicities will clearly be important as bortezomib based combinations are used more in the setting of relapsed disease as well as induction therapy for patients with myeloma.