

Thrombocytopenia Following Bortezomib Therapy

For Relapsed Multiple Myeloma

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Thrombocytopenia is an important side effect of cytotoxic therapy and can limit treatment in patients with poor marrow reserve. Bortezomib (Velcade) is a novel first in class, proteasome inhibitor, that works through a variety of mechanisms including inhibition of NFκB and modulation of cyclin dependent kinases leading to an inhibition of IL6 secretion. Based upon its mechanism of action, and preclinical data suggesting a lack of toxicity on murine hemopoietic stem cells, we hypothesized that bortezomib-related thrombocytopenia may be due to inhibition of thrombopoiesis rather than direct marrow cytotoxicity.

Methods:

We evaluated pooled data from 228 patients in 2 phase II myeloma trials (SUMMIT and CREST) who received bortezomib at the approved dose of 1.3 mg/m² given days 1, 4, 8, and 11 on a 21-day cycle. We evaluated the frequency and severity of thrombocytopenia, max decrease in platelet (PLT) count compared to baseline, and pretreatment characteristics associated with the development of Gr 3/4 thrombocytopenia. We measured serum thrombopoietin (tpo) levels in a smaller subset of patients treated on another advanced myeloma study to determine the relationship between PLT count and serum tpo levels. Tpo levels were measured by ELISA.

Results:

13% of patients developed grade 3/4 thrombocytopenia with an initial platelet

Messages

- > Patients with baseline Plt count > 70K are unlikely to develop Grade 4 (<10K) thrombocytopenia
- > Patients with the greatest disease burden (and lowest baseline platelet counts) are the most likely to have significant thrombocytopenia
- > Platelet counts can rise with successive cycles
- > Nadir PLT count is about 40% of baseline
- > Thrombocytopenia is transient and returns to baseline during rest period
- > For patients with thrombocytopenia due to extensive disease, platelet transfusion support rather than holding doses may be appropriate

count >200k. 56% patients developed Gr 3/4 thrombocytopenia when the platelet count was between 200k and 100k (1% Gr 4), and 90% of patients developed Gr 3/4 thrombocytopenia when the PLTcount was 100k -70k (all Gr 3). When the initial plt count was below 70k the incidence of grade 4 thrombocytopenia increased markedly. When analyzed by cycle, most patients had recovery of the PLT count towards baseline during the rest period between cycles among patients without progression of their myeloma. Analysis of baseline factors associated with thrombocytopenia showed that patients with greater BM involvement

(>50% plasma cells in BM) or higher serum M-protein (above or below the median value of 31g/l) started therapy with a lower PLT count, and had a lower PLT nadir. However, all patients developed approximately a 60% reduction in their PLT count regardless of initial PLT count, serum protein, or degree of BM involvement. In patients with measured tpo levels, there was an inverse relationship between the PLT count and the serum tpo level. Patients receiving weekly maintenance therapy did not have a reduction in their PLT count or serum tpo levels.

Conclusion:

The development of Gr 3/4 thrombocytopenia associated with Bortezomib is dependent upon the initial PLT count, which is in turn dependent upon the severity of disease as reflected by the degree of BM involvement or the quantity of serum paraprotein. On average, most patients will develop a 60% reduction in their PLT count during their course of therapy, and it is uncommon to develop Gr 4 thrombocytopenia unless patients begin therapy with a PLT count <70k. Serum tpo levels are not reduced in response to Bortezomib therapy. Bortezomib does not appear to be directly cytotoxic to most normal BM cells, nor to destroy immature progenitors. As PLT budding from megakaryocyte progenitors is an NFκB dependent process, Bortezomib may temporarily suppress this process resulting in thrombocytopenia.