Bortezomib (Velcade®) is the first of a new class of drugs known as proteasome-inhibitors. Its efficacy has been established in phase II trials SUMMIT and CREST and phase III trial APEX has demonstrated the superiority of Bortezomib (Velcade®) over high-dose dexamethasone in relapsed/refractory multiple myeloma (MM) patients.

Although generally well tolerated, several side-effects are correlated to the administration of Bortezomib (Velcade®). The most common adverse events are listed in Figure 1.

**Non-hematologic toxicity**

**Peripheral neuropathy**

Bortezomib (Velcade®) usually induces a sensory, axonal polyneuropathy affecting small and large fibers. The clinical picture is characterized by paresthesias, numbness and pain affecting lower more than upper extremities. The overall rate of peripheral neuropathy (PN) reported in phase II studies SUMMIT and CREST was 35%, with 5% of patients discontinuing Bortezomib (Velcade®) because of PN. In this latter trial, the incidence of PN was lower in patients receiving 1 mg/m² compared to those receiving 1.3 mg/m², supporting the hypothesis of a dose-dependent effect. In the APEX trial, 36% (120/331) of patients receiving Bortezomib (Velcade®) developed a PN, which led to treatment discontinuation in 9% (31/331). Although a higher incidence of PN could be expected in patients previously treated with other neurotoxic agents commonly used in MM such as Vin-cristine and Thalidomide, the number and types of prior therapies did not appear to affect the incidence and severity of PN.

According to NCI Common Toxicity Criteria (version 2), 27% (91/331) of patients had a PN of grade ≥2. In about two-thirds of these patients PN was reversible, with complete resolution or partial improvement in 55% and 9% of cases respectively after a median time of 110 days. In the APEX trial specific recommendations for the management of Bortezomib (Velcade®)-related PN were provided (Table 1). Complete resolution or at least an improvement of PN was observed in 70% of patients undergoing dose reduction or schedule modification and in 61% of patients requiring Bortezomib (Velcade®) discontinuation. When these guidelines were not followed the outcome of PN was more disappointing (Table 2). Dose adjustments appeared to help resolution of PN without compromising treatment efficacy.

Besides an early recognition of signs and symptoms of PN with subsequent dose modifications, the use of some drugs may be helpful in the management of Bortezomib (Velcade®)-induced PN. Even though no standard treatment is still available, gabapentin, pregabalin, nortryptiline and duloxetine along with vitamin supplements are currently used with variable efficacy.

**Other non-hematologic toxicities**

Gastrointestinal disorders are commonly reported during therapy with Bortezomib (Velcade®) and may consist of nausea (57%), vomiting (35%), diarrhea (57%) or constipation (42%) (Figure 1). These adverse events are usually mild and easily manageable with hydration, dietary modifications and specific drugs. Furthermore, some cases of paralytic ileus resulting from autonomic neuropathy have been reported.

Another common side effect is represented by fatigue, reported by 65% of patients enrolled in the SUMMIT and CREST trials and in 42% of those receiving Bortezomib (Velcade®) in the APEX trial. Fatigue is usually of mild or moderate severity and may benefit of low-dose steroids.

In the APEX Trial, the overall incidence of cardiovascular disorders was 15% in the Bortezomib (Velcade®) group (similar to that seen in the dexamethasone group) and there were 3 deaths from cardiac causes that were considered possibly related to study drug by the investigators. Postural
hypotension was observed in 12% of patients (4% of grade 3) in phase II studies.\(^1,2\) Hydration, corticosteroids with mineralcorticoid effect and adjustment of antihypertensive therapy in patients on treatment may be required to manage hypotension.

Infections seem not to be a common event during treatment with Bortezomib (Velcade\(^{\circledR}\)), with the exception of herpes zoster, which has been reported in 13% of patients receiving Bortezomib (Velcade\(^{\circledR}\)) as compared to 5% of patients receiving dexamethasone in the APEX Trial (\(p<0.001\)).\(^3\) Despite this, there is not a definite agreement about prophylactically giving acy-
clovir during treatment. Skin rashes with features typically consistent with a hypersensitivity reaction have been reported in about 20% of patients treated with Bortezomib (Velcade®). Recently, rashes with peculiar clinical and histological features have been reported in some patients receiving Bortezomib (Velcade®). Knops et al. described a case of Sweet’s syndrome with neutrophilic infiltration of the dermis, leukocytoclasis and subepidermal edema. More recently, in a series of patients with non-Hodgkin’s lymphoma on treatment with Bortezomib (Velcade®), Gerecitano et al. described 18 cases of asymptomatic erythematous maculopapular rash. In the 6 patients undergoing punch biopsy, the histologic examination revealed a perivascular lymphocytic infiltrate sometimes associated with small vessel necrotizing vasculitis.

**Hematologic toxicity**

**Thrombocytopenia**

Bortezomib (Velcade®) has been associated with a cyclic thrombocytopenia, with decrease of approximately 60% in platelet counts during cycle and recovery to baseline values during the 10-day rest period between cycles. In phase II studies SUMMIT and CREST, thrombocytopenia was the most common grade 3 adverse event. In the APEX Trial grade ≥3 thrombocytopenia was observed in 30% of patients (Figure 2). The kinetics of Bortezomib (Velcade®)-associated thrombocytopenia is different from that seen with standard cytotoxic drugs, with shorter times of recovery and absence of cumulative effect over time. Preclinical studies demonstrated the absence of a lethal cytotoxic effect on megakaryocytes, suggesting that different mechanisms are involved in Bortezomib (Velcade®)-induced thrombocytopenia. It has been hypothesized that Bortezomib (Velcade®) induces thrombocytopenia by preventing the activation of NF-kB, which is necessary for platelet budding from megakaryocytes. The strongest predictor of severe thrombocytopenia is the platelet count at baseline. In phase II studies, all patients with a baseline platelet count ≤70x10^9/L developed a grade 3-4 thrombocytopenia. Grade 4 thrombocytopenia was rare in patients beginning treatment with higher counts (Table 3). In patients responding to bortezomib, the lowest platelets counts are observed early, usually during the first cycle, and platelet nadirs progressively increase during subsequent cycles. Attention must be paid to prolonged thrombocytopenia, which could be related to a progression of the disease. Approximately 15% of patients treated with Bortezomib (Velcade®) in the APEX trial required platelet transfusions, the majority of which were delivered during the first two cycles of treatment. Anyway, the incidence of major bleeding complications reported in patients with severe thrombocytopenia was low.

**Other hematologic toxicities**

A grade 3-4 neutropenia associated with Bortezomib (Velcade®) has been reported in 14% and 15% of patients in phase II SUMMIT trial and in phase III APEX trial respectively (Figure 2). In both studies, febrile neutropenia was rare with a limited requirement of growth factors. As thrombocytopenia, also neutropenia follows a cyclical biphasic pattern, with decrease dur-

<table>
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<th>Baseline platelet count (x10^9/L)</th>
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