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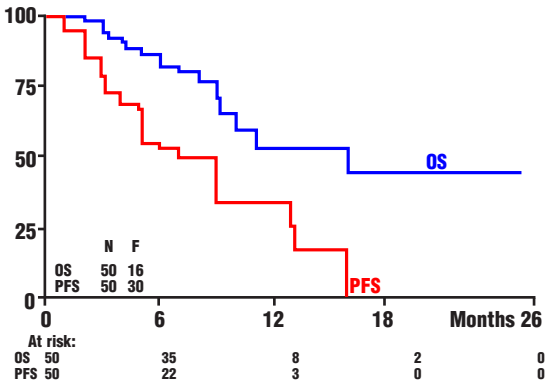

Figure 1. Overall survival and progression-free survival.

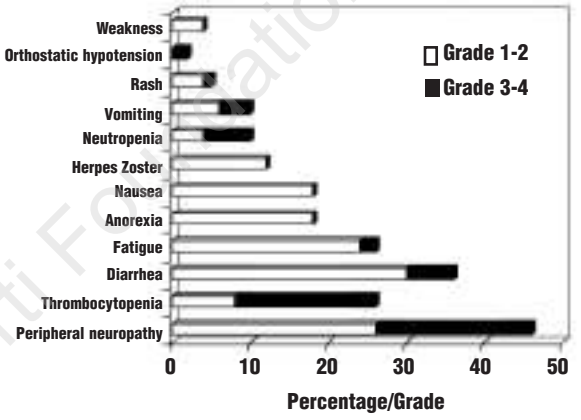

Figure 2. Observed toxicity of bortezomib.

Multiple Myeloma

Analysis of the efficacy and toxicity of bortezomib for treatment of relapsed or refractory multiple myeloma in community practice

The clinical data on the efficacy and toxicity of bortezomib as treatment for multiple myeloma patients are restricted to prospective phase II studies in expert myeloma centers. Here we report a multi-institutional analysis of the efficacy and toxicity of bortezomib in patients with relapsed or refractory multiple myeloma who were treated in community centers in a compassionate need program.

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Between November 2002 and December 2004, 50 patients with relapsed or refractory multiple myeloma were treated with bortezomib in centers in the Netherlands. The clinical data of these patients were obtained by means of case research. The mean age of the patients was 59 years (range 37–87); 33 patients had IgG, 10 patients IgA, 6 patients light-chain and 1 patient non-secretory myeloma. The median number of prior treatments was 3 (range 1-5). Twenty-nine patients were treated with high-dose melphalan with autologous stem cell support and 8 patients had received an allogeneic stem cell transplant.

Patients treated in the compassionate need program received up to eight 3-weekly cycles of bortezomib. Within each cycle, bortezomib 1.3 mg/m^2 was administered as an intravenous bolus twice weekly on days 1, 4, 8 and 11. Treatment was withheld in case of any grade ≥3 non-hematologic toxicity or grade 4 hematologic toxicity considered to be drug-related. Treatment was resumed at a dose of 1.0 mg/m^2 after resolution of the non-hematologic toxicity to grade 2 or better and for hematological toxicity to an absolute neutrophil count ≥0.5×10^9/L and platelet count ≥20×10^9/L. Responses were evaluated based on the EBMT criteria.[1] NCI Toxicity Criteria (version 2.0) were used to grade the non-hematologic toxicity. At the time of analysis, 33 patients (66%) were still alive. The median follow-up from the start of bortezomib treatment was 7 months (range 2-26 months). A clinical response was observed in 23 patients (46%), including complete response in 2 patients, partial response in 15 and minimal response in 6 patients. The median time to response was 6 weeks and the median duration of response was 9 months. The median progression-free survival was 7 months and the median overall survival was 15 months. (Figure 1). Response to bortezomib occurred in 5 of the 15 patients with a complete or partial deletion of chromosome 13.

Univariate and multivariate analyses of variables such as number of prior treatment regimens, treatment with thalidomide or dexamethasone, abnormalities of chromosome 13, serum β2 microglobulin and serum albumin levels did not show any statistically significant differences in progression-free survival and overall survival. This could be partly due to the small sample size involved. Seven patients who had no response after two treatment cycles of bortezomib alone continued treatment and received oral dexamethasone (20 mg) on the day of and the day following each bortezomib dose. One of these patients, who was previously refractory to corticosteroids, had an additional response on the combination therapy. Further investigations into the possibility of synergy between

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bortezomib and dexamethasone are warranted.[2,3] The most common toxicities were gastrointestinal symptoms, thrombocytopenia, neutropenia, fatigue and peripheral neuropathy (Figure 2). The majority of the side effects were low grade. The thrombocytopenia was transient, with recovery within the 10-day rest period in each cycle, and was not associated with bleeding complications. Six patients had herpes zoster. The dose of bortezomib was reduced in 18 patients and the drug was discontinued in 12 patients because of side effects: peripheral neuropathy (n=6), gastrointestinal symptoms (n=4), skin rash (n=1) and orthostatic hypotension (n=1).

In our observational analysis, the response rate to bortezomib was comparable to those in two prospective clinical studies, CREST and SUMMIT, which reported response rates of 35-50%.[4,5] The median duration of response was 9 months. In the CREST study, the median duration of response was 9.5 months and 13.7 months in the 1.0 mg/m^2 and 1.3 mg/m^2 groups, respectively, while in the SUMMIT study the median response duration was 12 months. A possible explanation for the shorter duration of response in our series may be that dose reduction was performed more frequently by local physicians in our study than in CREST and SUMMIT, which were conducted in expert myeloma centers. Therefore, the clinical practice in community hospitals of reducing doses in patients with treatment-related toxicity without adherence to well-defined guidelines may jeopardize the outcome of the efficacy of bortezomib in multiple myeloma.

A remarkable observation in our series was the high incidence of herpes zoster. Six patients developed a herpes zoster infection during treatment with bortezomib. The transcription factor NF-κB has been demonstrated to play a pivotal role in cytokine signaling and the generation of cell-mediated immune response in numerous models.[6,7] Therefore, inhibition of NF-κB may increase the risk of reactivation of the varicella zoster virus. Prophylactic antiviral medication should be considered in predisposed patients who receive bortezomib.

In conclusion, bortezomib can induce marked and durable response in advanced multiple myeloma. Overall, bortezomib was well tolerated and the toxicity was acceptable.

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Key words: bortezomib, multiple myeloma, toxicity, herpes zoster.

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Disorders of Hemostasis

Exon skipping partially restores factor VIII coagulant activity in patients with mild hemophilia A with exon 13 duplication

Ectopic mRNA was analyzed by reverse transcriptase polymerase chain reaction (RT-PCR) in patients with duplication of *F8* gene exon 13, a mutation which has been demonstrated to be a cause of mild hemophilia A in 32% of Northern Italian subjects. Two different transcripts originate from mutated genomic DNA, due to alternative splice processes. The larger-sized transcript contains both duplicated exons 13, the smaller one contains only one exon 13. The residual FVIII:C activity which accounts for the mild hemophilia A phenotype derives from the latter transcript.

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We described the duplication of exon 13 as a disease causative mutation in a cohort of Northern Italian patients with hemophilia A (HA).[1] The association of the alteration with a residual FVIII coagulant activity >8% suggested that a certain amount of normal protein was being produced. We could, therefore, hypothesize: (i) that an elongated form of mRNA is generated and that it somehow ends up in the translation of a partially functioning normal protein; or (ii) that alternative splicing processes produce two forms of RNA , but that only one of them is able to translate a correct protein.

To verify these working hypotheses, we undertook a study on ectopic mRNA obtained from the only available tissue, peripheral blood. mRNA was obtained from the lymphocytes of 6/10 patients and from 40 healthy controls, following informed consent. cDNA, reverse transcribed (Reverse Transcription kit - Clontech, Palo Alto,