

Bortezomib at First Relapse is Superior to High-Dose Dexamethasone and More Effective Than When Given Later in Relapsed Multiple Myeloma

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Introduction

- Bortezomib (VELCADE®): novel first-in-class proteasome inhibitor
 - Downregulates growth and survival pathways in multiple myeloma (MM)¹
 - Upregulates proapoptotic pathways and disrupts adhesion¹
 - Antiangiogenic effects
 - Prolonged survival in a murine model of MM²
 - Approved in the U.S. for MM patients who have received at least 1 prior therapy
- SUMMIT phase 2 study in relapsed, refractory patients (N = 202)³
 - Overall response rate (complete response [CR] + partial response [PR] + minor response) 35%
 - Median overall survival ~ 17 months
 - Manageable toxicity
- CREST phase 2 study in patients who relapsed after or were refractory to front-line therapy (N = 54)⁴
 - Overall response rate 50% with bortezomib 1.3 mg/m²
- APEX: the largest randomized phase 3 study to date in relapsed MM⁵
 - Bortezomib achieved a significantly longer median time to progression (TTP), higher response rates, and improved overall survival compared with dexamethasone (dex) in the entire study population at the final analysis
 - In this prospective subgroup analysis, outcomes in patients treated with bortezomib or dex as second-line versus ≥ third-line therapy were compared to determine the potential benefit of starting bortezomib at first relapse

Study Design

- International, randomized, open-label study of bortezomib versus high-dose dex in patients with relapsed MM
 - 669 patients enrolled at 93 centers (42% North America, 58% Europe and Israel)
- End points
 - Primary: TTP
 - Secondary: overall and 1-year survival, response rate, duration of response, time

to response, time to skeletal events, incidence of grade ≥ 3 infections, and safety

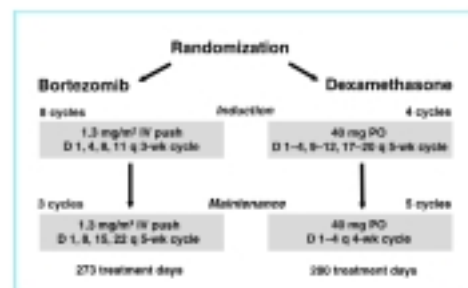
- Companion crossover study (M34101-040): bortezomib for patients progressing on dex
- Randomization to each arm stratified by number of prior treatments (1 vs > 1), refractory disease, β₂-microglobulin
- Efficacy and safety
 - Disease assessment every 3 weeks (central laboratory)
 - Progression and response per EBMT criteria,⁵ with the addition of a near CR (nCR) category for patients meeting all criteria of CR except that the immunofixation test was positive
 - For this analysis, outcomes were compared in patients who had received only 1 versus > 1 prior treatment regimen
 - Adverse events (AE) were graded according to National Cancer Institute Common Toxicity Criteria version 2.0 Major Eligibility Criteria

Methods

Major Eligibility Criteria

- Inclusion
 - Relapsed or refractory MM following 1–3 prior lines of therapy
 - Measurable disease (M-protein or plasmacytoma)
 - Platelets ≥ 50,000/μL
 - Creatinine clearance ≥ 20 mL/min
- Exclusion
 - Refractory to high-dose dex (> 500 mg over 10 weeks)
 - < PR or progressive disease within 6 months after discontinuation of dex
 - Grade ≥ 3 dex-related toxicity leading to discontinuation
 - Peripheral neuropathy (PN) grade ≥ 2

Treatment Plan



Conclusions

- Bortezomib was superior to high-dose dex at first relapse and beyond
 - Regardless of number of lines of prior therapy
 - Regardless of type of prior therapy
 - Response rates at first relapse appeared somewhat lower in patients who received prior thalidomide
- Bortezomib appeared to produce superior outcomes when used at first relapse versus as later salvage therapy, supporting its use during earlier stages of re-treatment
 - CR + PR rate 45% with bortezomib as second-line treatment
 - 43% improvement in median TTP with bortezomib as second-line treatment versus as later salvage therapy
 - The probability of death in the dex arm was 2.56 times that of the bortezomib arm
- AE profile was as expected

References

1. Hideshima et al. *Cancer Res.* 2001; 61:3071-3076.
2. LeBlanc et al. *Cancer Res.* 2002; 62:4996-5000.
3. Richardson et al. *N Engl J Med.* 2003; 348:2609-2617.
4. Jagannath et al. *Br J Haematol.* 2004; 127:165-172.
5. Bladé et al. *Br J Haematol.* 1998; 102:1115-1123.

Visit www.oagpo.com to view the complete study online and access the following additional poster sessions from the International Multiple Myeloma Workshop in Sydney, Australia:

- > Bortezomib Therapy Alone and in Combination With Dexamethasone for Patients With Previously Untreated Multiple Myeloma
- > Bortezomib Demonstrates Superior Efficacy Compared With High-Dose Dexamethasone, With Predictable Toxicity
- > Phase I Study of the Safety and Efficacy of Bortezomib (VELCADE®) in Combination With Lenalidomide (REVLIMID®) in Relapsed and Refractory Multiple Myeloma: The RevVel Study
- > Bortezomib (VELCADE®) Plus Dexamethasone as Induction Treatment Prior to Autologous Stem Cell Transplantation in Patients With Newly Diagnosed Multiple Myeloma: Results of an IFM Phase II Study
- > Bortezomib and Pegylated Liposomal Doxorubicin as Initial Therapy for Adult Patients With Symptomatic Multiple Myeloma: CALGB Study 10301