



Evidence-based Series #6-18: Section 1

Bortezomib in Multiple Myeloma and Lymphoma: A Clinical Practice Guideline

*D. Reece, K. Imrie, C.A. Smith, A. Stevens,
and the members of the Hematology Disease Site Group*

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Question

1. In patients with multiple myeloma, Waldenstrom's macroglobulinemia, or lymphoma, what is the efficacy of bortezomib alone or in combination, as measured by survival, quality of life, disease control (e.g., time-to-progression), response duration, or response rate?
2. What is the toxicity associated with the use of bortezomib?
3. Which patients are more or less likely to benefit from treatment with bortezomib?

Target Population

This evidence-based series applies to adult patients with myeloma, Waldenstrom's macroglobulinemia, or lymphoma of any type, stage, histology, or performance status.

Recommendations

Based on the results of a large well conducted randomized controlled trial (RCT) (1), which represents the only published randomized study in relapsed myeloma, the Hematology Disease Site Group (DSG) offers the following recommendations:

- For patients with myeloma refractory to or relapsing within one year of the conclusion of initial or subsequent treatment(s) (including autologous stem cell transplantation) who are candidates for further chemotherapy, bortezomib is recommended as the preferred treatment option.
- Bortezomib is also a reasonable option for patients relapsing at least one year after autologous stem cell transplantation. The DSG is aware that thalidomide, alkylating agents, or repeat transplantation may also be options for these patients. However, evaluation of these other options is beyond the scope of this Practice Guideline.
- For patients with myeloma relapsing at least one year after the conclusion of alkylating agent-based chemotherapy who are candidates for further chemotherapy, further treatment with alkylating agent-based chemotherapy is recommended.
- There is insufficient evidence to support the use of bortezomib outside of clinical trials in patients with non-Hodgkin's lymphoma or Waldenstrom's macroglobulinemia.

Qualifying Statements

- There is limited evidence to support the appropriateness of a specific time-to-relapse period as being indicative of treatment-insensitive disease. The one-year threshold provided in the above recommendations is based on the opinion of the Hematology DSG.
- For specific details related to the administration of bortezomib therapy, the DSG suggests clinicians refer to the protocols used in the major trials. Some of those details are provided below for informational purposes:
 - Regarding dosage, bortezomib 1.3 mg/m² is given as a rapid intravenous bolus over 3-5 seconds on days 1, 4, 8 and 11 of a 21-day cycle; a minimum of 72 hours between doses is required to allow for the recovery of normal proteasome function. Vital signs should be checked before and after each dose. A complete blood count is recommended before each dose, with blood chemistries, including electrolytes and creatinine levels, monitored at minimum on days 1 and 8 of each cycle. The dose of bortezomib should be reduced or held immediately for the development of painful neuropathy, as described in the product monograph; dose modification may also be required for peripheral sensory neuropathy without pain, or other toxicities. Most toxicities are reversible if dose modification guidelines are followed.
 - Responses to treatment are usually apparent by six weeks (two cycles). For patients achieving complete remission (CR) (determined by negative electrophoresis and immunofixation), bortezomib should be given for two additional cycles beyond the date of confirmed CR. In patients with progressive disease after two cycles, or stable disease after four cycles, dexamethasone (20 mg po the day of, and the day after each bortezomib dose) added to the bortezomib regimen may produce an objective response. Bortezomib (with or without dexamethasone) should be continued in patients showing benefit from therapy (excluding those in CR), unless disease progression or significant toxicity is observed. Therapy should be discontinued in patients who do not respond to bortezomib alone if disease progression is seen within two cycles of the addition dexamethasone.
- The Hematology DSG recognizes that thalidomide is an active agent in treating patients with multiple myeloma who have relapsed after autologous stem cell transplantation or are refractory to alkylating agent-based chemotherapy. To date, there are no RCTs reporting evaluations of thalidomide in this role, and, specifically, no trials comparing thalidomide with bortezomib. With these limitations, members of the Hematology DSG regard thalidomide or bortezomib to be alternative therapies to dexamethasone.

Key Evidence

- In total, 20 publications of 16 trials in myeloma and lymphoma were identified. For myeloma, one RCT, one randomized phase II trial, four non-randomized phase II trials, and five dose-escalation trials were included. For lymphoma, four non-randomized phase II and one phase I/II trials were included.
- The RCT (1) compared bortezomib with high-dose dexamethasone in patients with relapsed myeloma and reported superior median time to progression (6.2 versus 3.5 months; $p < 0.001$) and greater one-year survival (80% versus 66%; $p = 0.003$) in the bortezomib arm. Grade 3 adverse events were more common in the bortezomib arm (61% versus 44%; $p = 0.01$).
- Two phase II trials, the SUMMIT (2) and CREST (3) trials, reported response rates of 33-44% with median response durations of 9.5-13.7 months. In both studies, the addition of dexamethasone in non-responders increased the response rate by 18-33%.

Treatment Alternatives

- For myeloma patients who relapse following autologous stem cell transplantation or who are refractory to alkylating agent-based chemotherapy, the principal alternative to bortezomib treatment is pulsed oral (po) high-dose dexamethasone (40 mg po days 1-4, 9-12, and 17-20 of each cycle). Thalidomide (100-400 mg/day) has a demonstrated activity in this setting and may be a better alternative; however, it has not been approved by the Health Protection Branch and is not routinely available. Multi-agent chemotherapy with vincristine, adriamycin, and prednisone (VAD) is an active regimen and is also a reasonable alternative in patients who have not received this regimen previously. Neither thalidomide nor VAD have been compared to high-dose dexamethasone or bortezomib in randomized trials.

Future Research

Studies of bortezomib in combination with other agents are underway.

Related Guidelines

- Practice Guideline Report #6-4: *The Role of Bisphosphonates in the Management of Skeletal Complications for Patients with Multiple Myeloma.*
- Practice Guideline Report #6-6: *Optimal Therapy for Patients Diagnosed with Multiple Myeloma and the Role of High-Dose Chemotherapy and Stem Cell Support.*

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Contact Information

For further information about this series, please contact **Dr. K. Imrie**, Chair, Hematology Disease Site Group, Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5; Phone: 416-480-4757; Fax: 416-480-6002

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