Evidence-Based Series 6-18 Version 2 [REQUIRES UPDATING]

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Bortezomib in Multiple Myeloma and Lymphoma


June 13, 2016

| Section 1: | Guideline Recommendations [REQUIRES UPDATING] |
| Section 2A: | Updated Evidentiary Base [REQUIRES UPDATING] |
| Section 2B: | Original Evidentiary Base |
| Section 3: | EBS Development Methods and External Review Process |
| Section 4: | Guideline Summary and Review Tool |

Evidence-Based Series 6-18 was reviewed and the Hematology Cancer Disease Site Group determined it REQUIRES UPDATING. (See Section 4: Document Review Summary and Tool for details.)

This Evidence-based Series (EBS) consists of 4 sections and is available on the CCO website on the PEBC Hematology Cancer DSG page.

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:

Phone: 905-527-4322 ext. 42822  Fax: 905-526-6775  E-mail: ccopgi@mcmaster.ca


Guideline Report History

<table>
<thead>
<tr>
<th>GUIDELINE VERSION</th>
<th>SYSTEMATIC REVIEW</th>
<th>PUBLICATIONS</th>
<th>NOTES and KEY CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Search Dates</td>
<td>Data</td>
<td></td>
</tr>
</tbody>
</table>

Table of Contents

Section 1: Guideline Recommendations ................................................................. 1
Section 2A: Updated Evidentiary Base ................................................................. 9
Section 2B: Original Evidentiary Base ................................................................. 164
Section 3: EBS Development Methods and External Review Process ...................... 188
Section 4: Document Review and Summary Tool .................................................... 206
Bortezomib in Multiple Myeloma and Lymphoma: Guideline Recommendations


Original Report Date: March 18, 2013

The 2013 guideline recommendations

REQUIRE UPDATING

This means that the recommendations require additional evidence but are relevant for decision-making.

GUIDELINE OBJECTIVE

The purpose of this guideline is to provide recommendations for the use of bortezomib alone or in combination with other agents in patients with multiple myeloma, or lymphoma, including Waldenström’s macroglobulinemia.

QUESTIONS

1. In patients with multiple myeloma (MM), or lymphoma, including Waldenström’s macroglobulinemia (WM), what is the efficacy of bortezomib alone or in combination as measured by survival, quality of life, disease control (e.g., time-to-progression (TTP)), 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?

INTENDED USERS

• Healthcare practitioners treating patients with MM, or lymphoma, including WM.
• Policy makers involved in the planning of treatment and the financing of drugs for MM, or lymphoma (including WM).

TARGET POPULATION

This evidence-based series applies to adult patients with MM or lymphoma of any type, stage, histology, or performance status.
RECOMMENDATIONS AND KEY EVIDENCE

Question 1. Efficacy of bortezomib

Multiple Myeloma: Previously Untreated Patients

<table>
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<tr>
<th>Patients who are ineligible for autologous stem cell transplantation (ASCT)</th>
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<tr>
<td>For patients with previously untreated MM who are ineligible for ASCT, the combination of bortezomib, melphalan, and prednisone is a recommended first-line treatment option and preferred over treatment with melphalan and prednisone alone. The recommended dose and schedule of bortezomib is 1.3 mg/m² given as a rapid intravenous bolus over 3-5 seconds on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9. Melphalan 9 mg/m² and prednisone 60 mg/m² are to be given on days 1 through 4 of a six-week cycle. A total of nine cycles is given.</td>
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<th>Key Evidence</th>
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<td>One RCT compared bortezomib plus melphalan and prednisone (n=344) to melphalan and prednisone (n=338) in patients with ASCT ineligible, previously untreated, MM (1-3). The authors reported a significantly higher median time-to-progression for the bortezomib/melphalan/prednisone arm (24.0 versus [vs.] 16.6 months; hazard ratio [HR], 0.48; p&lt;0.001). Overall survival for patients who received bortezomib plus melphalan and prednisone was also higher compared to melphalan and prednisone only (at 24 months, 84% vs. 70%; HR, 0.61; p=0.008).</td>
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<th>Patients who are candidates for autologous stem cell transplantation</th>
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<td>In patients with previously untreated MM, a recommended option is the use of bortezomib in combination with dexamethasone or other immunomodulatory or alkylating agents as induction therapy prior to ASCT and it is preferred over induction therapy without novel agents (i.e., dexamethasone alone or vincristine, doxorubicine and dexamethasone [VAD]). The recommended dose and schedule of bortezomib should be 1.3 mg/m² given as a rapid intravenous bolus over 3-5 seconds days 1, 4, 8, and 11 of four 3-week cycles.</td>
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<td>Three randomized controlled trials (RCTs) of bortezomib as an induction prior to ASCT in previously untreated MM patients have been reported: two full publications (4,5) and one in abstract form (6). Harousseau et al (7) compared induction therapy with bortezomib plus dexamethasone to vincristine, doxorubicin, and dexamethasone (VAD) prior to ASCT and found a statistically significant, better complete response and a trend toward significance in progression-free survival in the bortezomib arm. Cavo et al (4) compared induction therapy with bortezomib plus dexamethasone and thalidomide to dexamethasone and thalidomide followed by a double ASCT. These authors also reported a significant and better CR and a better progression-free survival in the bortezomib arm.</td>
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**Multiple Myeloma: Patients with Relapsed/Refractory Disease**

The combination of bortezomib and pegylated liposomal doxorubicin (PLD) is a recommended treatment option for patients with MM that has relapsed or is refractory to previous treatment who are candidates for further chemotherapy; who have no clinically significant cardiac disease; who have received less than 240 mg/m², or the equivalent cumulative dose of doxorubicin; who have a left ventricular ejection fraction in the normal range; and who would be expected to tolerate the myelosuppression of combination therapy. The recommended dose and schedule of bortezomib is 1.3 mg/m² given as a rapid intravenous bolus over three to five seconds on days 1, 4, 8, and 11 of an every-21-days cycle. PLD 30 mg/m² is administered as a one-hour infusion on day 4 of each cycle. Treatment should be continued for eight cycles unless disease progression or unacceptable treatment-related toxicity occurs. Patients who are still responding and who are tolerating therapy well may continue until the criteria of progressive myeloma are met, i.e., at least a 25% increase in the serum monoclonal protein level (which must be an absolute minimum increase of 5 g/L). The treatment can be discontinued two to four cycles after the achievement of complete remission (CR) (as determined by negative electrophoresis and immunofixation).

**Key Evidence**

One RCT compared bortezomib plus PLD (n=324) to bortezomib alone (n=322) in patients with relapsed or refractory MM (8) and reported that overall survival at 15 months was superior for the combination compared to bortezomib monotherapy (76% vs. 65%; p=0.03). The median time-to-progression was also significantly higher in the PLD plus bortezomib arm (9.3 months vs. 6.5 months, respectively; HR, 1.82; 95% confidence interval [CI], 1.41 to 2.35; p=0.000004). The Hematology Disease Site Group (DSG) opinion is that the treatment can be discontinued two to four cycles after the achievement of CR.

For patients with MM refractory or relapsed to previous treatment, who are candidates for further chemotherapy but are not candidates for the combination of bortezomib and PLD, bortezomib monotherapy is recommended as a preferred treatment option. The recommended dose and schedule of bortezomib is 1.3 mg/m², given as a rapid intravenous bolus over three to five seconds on days 1, 4, 8, and 11 for eight three-week cycles, and then on days 1, 8, 15, and 22 for three five-week maintenance cycles.

**Key Evidence**

One RCT compared bortezomib monotherapy (n=333) to dexamethasone (n=336) in patients with relapsed or refractory MM (9,10) and reported that the median overall survival was significantly higher for patients who received bortezomib (29.8 months vs. 23.7 months; HR, 0.77; p=0.027). The median time-to-progression was also significantly higher in the bortezomib arm (HR, 0.55; p<0.001). Of note, grade 3 adverse events were more common in the bortezomib arm (61% vs. 44%; p<0.01).

**Qualifying Statement**

Since the seminal studies on which the recommendations for patients with MM are based were published, practice has evolved to include a weekly dosing of bortezomib. Practice has also evolved to include subcutaneous dosing of bortezomib. The Working Group considers this practice acceptable.

Consideration should be given to the use of antiviral prophylaxis against herpes zoster (shingles) during bortezomib therapy in patients with MM. In fact Chanan-Khan et al (11), in a
secondary analysis of the study by Richardson et al (10) showed that the incidence of herpes zoster events in patients treated with bortezomib was significantly higher than in the controls who received dexamethasone alone (13% vs. 5%, p=0.0002).

Lymphoma (including Waldenström’s macroglobulinemia)

For patients with relapsed or refractory mantle cell lymphoma, bortezomib monotherapy is a reasonable treatment option. Bortezomib should be administered at a dose of 1.3 mg/m$^2$ given as a rapid intravenous bolus over three to five seconds on days 1, 4, 8, and 11 of a 21-day cycle. Treatment should continue until disease progression or intolerance, or until two to four cycles after maximal response has been achieved.

**Key Evidence**

One large single-arm phase II trial was identified that investigated the use of bortezomib monotherapy in 155 patients with relapsed or refractory mantle cell lymphoma (12,13). The authors reported a median TTP of 6.7 months after a median follow-up of 26.4 months and a one-year survival of 69%.

**Qualifying Statement**

The evidence provided by a phase II trial, although large, is normally considered a weak basis for recommendations. However, this group of patients has a particularly poor prognosis and have limited treatment options. Therefore, these data are considered of clinical utility.

Responses to treatment are usually apparent by six weeks (two cycles). For patients achieving CR, 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 orally 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 of dexamethasone.

**Question 2. Toxicity**

A complete blood count is recommended with blood chemistries, including electrolytes and creatinine levels, all to be 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.

In lymphoma, a weekly bortezomib (alone or in combination) schedule is preferable to a bi-weekly schedule to prevent excess toxicity.

Because bortezomib is fatal if administered intrathecally, the recommendation is to administer it only by the approved intravenous or subcutaneous routes.
Key Evidence

Multiple myeloma: In all patients, bortezomib drug combinations were associated with an increased incidence of peripheral neuropathy and hematologic events, as well as nausea and diarrhea, in contrast to non-bortezomib-containing regimens (2,4,5,8,10) (see Table 7 in Section 2 for details). The DSG opinion is that blood count, blood chemistries, and creatinine levels should be monitored on days 1 and 8 of each cycle.

Lymphoma: Several phase II RCTs of a weekly versus bi-weekly bortezomib schedule have shown an increased incidence of toxicities in the bi-weekly schedule (14-16). Cases of accidental intrathecal administration of bortezomib have been reported, and Health Canada issued an alert on January 26, 2012 (17).

Qualifying Statement
Consideration should be given to the use of antiviral prophylaxis against herpes zoster (shingles) during bortezomib therapy in patients with MM. In fact Chanan-Khan et al (11), in a secondary analysis of the study by Richardson et al (10) showed that the incidence of herpes zoster events in patients treated with bortezomib was significantly higher than in the controls who received dexamethasone alone (13% vs. 5%, p=0.0002).

Lymphoma: DeVos et al (14) suggested that bortezomib given with rituximab was better tolerated on a weekly schedule, while Gerecitano et al (15) showed that, although bortezomib given alone proved to be less toxic on a weekly schedule, it provided a lower overall response than did the bi-weekly schedule. The greater ease of giving bortezomib once weekly is one more factor the DSG Working Group (Section 2: Appendix 1, A) considered when choosing this schedule.

Question 3: Patient subgroups that are more or less likely to benefit from the use of bortezomib.

In MM, treatment with bortezomib combinations (i.e., bortezomib with melphalan and prednisone for newly diagnosed patients, or either bortezomib and dexamethasone or bortezomib and pegylated liposomal doxorubicin for those with relapsed or refractory disease) is recommended for all patient subgroups (i.e., patients who are older, patients with impaired renal function, patients with an high-risk cytogenetic profile, patients exposed to multiple previous lines of therapy and ASCT, and patients with an elevated level of β2-microglobulin).

Key Evidence

Multiple myeloma: In newly diagnosed patients, melphalan, prednisone, and bortezomib was superior in all patient subgroups to melphalan and prednisone alone (2,18). In refractory MM patients, bortezomib and dexamethasone has been shown to be superior to dexamethasone alone in patients 65 years or older (response rate p=0.0004; TTP p=0.002) and patients with International Staging System (ISS) stage II and III disease (response rate p<0.0004; TTP p=0.0002) and patients refractory to the most recent therapy or patients who have previously received great than one prior line of therapy (response rate p<0.0001 and TTP p<0.0001 for both subgroups) (19), as well as in patients with renal impairment (20). Bortezomib plus pegylated liposomal doxorubicin was also more efficacious than bortezomib alone in most subgroups analyzed (8,21). An advantage of bortezomib and pegylated liposomal doxorubicin compared to bortezomib alone was observed in patients with cytogenetic abnormalities, except for deletion 13q (8).

Qualifying Statement
Multiple myeloma: Prognostic factors (or markers) provide information about a likely disease...
outcome, independent of the treatment used, and can be used for risk stratification. For example, high-risk myeloma patients who do poorly with conventional treatments can be treated more aggressively, based on this risk stratification. Factors (or markers) that provide information on a disease outcome based on a specific treatment are known as predictive factors (or markers). Predictive markers can be used to identify which patients should be treated with a specific treatment. Studies on markers are under way (22), and the results will help in targeting specific groups of patients in the future.

FUTURE RESEARCH

Studies of bortezomib in combination with other agents are underway.

RELATED GUIDELINES

- PEBCEBS 6-21: Thalidomide in Multiple Myeloma.
- PEBCEBS 6-5: Lenalidomide in Multiple Myeloma.
- PEBCEBS 6-4: The Role of Bisphosphonates in the Management of Skeletal Complications for Patients with Multiple Myeloma.
- PEBCEBS 6-6: Optimal Therapy for Patients Diagnosed with Multiple Myeloma and the Role of High-Dose Chemotherapy and Stem Cell Support.
- PEBCEBS 6-4: The Role of Bisphosphonates in the Management of Skeletal Complications for Patients with Multiple Myeloma.
- PEBCEBS 12-12: Safe Administration of Systemic Cancer Therapy.
REFERENCES


