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**Evidence-based Series #6-18: Section 1**

# Bortezomib in Multiple Myeloma and Lymphoma: A Clinical Practice Guideline

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*and the members of the Hematology Disease Site Group*

A Quality Initiative of the
Program in Evidence-based Care, Cancer Care Ontario
Developed by the Hematology Disease Site Group

**Report Date: April 3, 2006**

## 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/m$^2$ 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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**Evidence-based Series #6-18: Section 2**

# Bortezomib in Multiple Myeloma and Lymphoma: A Systematic Review

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A Quality Initiative of the
Program in Evidence-based Care, Cancer Care Ontario
Developed by the Hematology Disease Site Group

**Report Date: April 3, 2006**

## QUESTION(S)

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 (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?

## INTRODUCTION

Multiple myeloma is a cancer characterized by a malignant proliferation of clonal plasma cells in the bone marrow; these cells typically produce a monoclonal immunoglobulin molecule that can be detected in the serum or urine. Common manifestations include fatigue, anemia, and bone damage related to osteopenia and/or lytic bone lesions; the resulting bone pain, pathologic fractures, or, in some cases, spinal cord compression leads to substantial morbidity. Renal failure, frequent infections, and hypercalcemia also occur in a significant proportion of patients.

Treatment of myeloma can result in reductions in levels of monoclonal immunoglobulins and can lead to symptomatic benefit and delay or improve end-organ complications. The role of chemotherapy and stem cell transplantation in myeloma is summarized in the Program in Evidence-Based Care (PEBC) Practice Guideline Report #6-6 (1). Patients ≤ 65-70 years of age are generally treated with several cycles of high-dose dexamethasone-based induction therapy such as VAD (vincristine, doxorubicin, and dexamethasone) followed by stem cell collection and autologous stem cell transplantation (ASCT). ASCT represents the current standard of care in this patient group and has demonstrated higher remission rates (including about 20-30% complete remissions) and improved progression-free and overall survival rates than conventional chemotherapy alone. Older patients generally receive less aggressive therapy with oral regimens such as melphalan and prednisone. Partial remissions are seen in approximately 50% of cases, but complete remissions are rare. Despite either treatment approach, virtually all

myeloma patients eventually relapse and require further therapy. Options for the management of recurrent myeloma include reinstitution of the initial treatment if the duration of response was prolonged, alternative alkylating agent therapy with oral cyclophosphamide plus prednisone, high-dose dexamethasone, or thalidomide alone or in combination with corticosteroids. Therapeutic options become progressively limited as the disease progresses. At the present time, the disease is not considered curable, and overall survival rates average from three to five years.

Over the last few years, a better understanding of the biology of myeloma cells and the relationship between the tumour cells and bone marrow microenvironment has stimulated efforts to develop other novel agents in this disease. Bortezomib (Velcade™, PS-341), a first-in-class proteasome inhibitor, is the best studied of the next generation of anti-myeloma drugs. Bortezomib blocks the action of the 29S proteasome, a multicatalytic enzyme that has been nicknamed the "housekeeper" of the cell as it degrades abnormal or misfolded proteins targeted for destruction, particularly those involved in cell cycling and gene transcription. Clinical evidence suggesting that this agent is active in myeloma and lymphoma has begun to emerge. For this reason, the Hematology DSG determined that a systematic review assessing the currently available evidence was a high priority, in order to guide the appropriate use of this agent.

## METHODS

This systematic review was developed by Cancer Care Ontario's PEBC. Evidence was selected and reviewed by two member of the PEBC Hematology DSG.

This systematic review is a convenient and up-to-date source of the best available evidence on bortezomib in multiple myeloma and lymphoma. The body of evidence in this review is primarily comprised of randomized controlled trial (RCT) data. That evidence forms the basis of a clinical practice guideline developed by the Hematology DSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

### Literature Search Strategy

MEDLINE (Ovid) (1966 through October 2004), Medline Daily Update (October 22, 2004), Medline In-Process & Other Non-Indexed Citations (October 22, 2004), HealthStar (1975 through September 2004), CINAHL (1982 through October 2004), EMBASE (Ovid) (1982 through 2004 Week 42), and the Cochrane Library (2004, Issue 4) databases were searched. The search strategy for MEDLINE is shown in Appendix 1; searches in other databases were similar. Literature searches were not restricted for publication type or study design.

In addition, conference proceedings of the American Society of Clinical Oncology (1995-2004) and the American Society of Hematology (1996-2004) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp), and the National Institute for Clinical Excellence (http://www.nice.org.uk/) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials. Personal files were also searched.

### Study Selection Criteria

#### *Inclusion Criteria*

Articles of study designs of any type (including systematic reviews, meta-analyses, and evidence-based practice guidelines) were selected for inclusion in this systematic review of the

evidence if they were published full report articles or published meeting abstracts in the English language of:

1. Studies including adult patients with myeloma, Waldenstrom's macroglobulinemia, or lymphoma (any histologic subtype, stage, performance status, or disease type).
2. Studies evaluating bortezomib as a single agent or in combination with other regimens.
3. Comparative trials, in which bortezomib could be compared with any agent, any combination of agents, or placebo.
4. Results reporting one or more of the following outcomes: survival, quality of life, disease control (e.g., time-to-progression [TTP]), response duration, response rate, or adverse effects.

### *Exclusion Criteria*

Studies were excluded if they were:

1. Letters, comments, books, notes, or editorial publication types.
2. Studies reporting fewer than 20 patients (all disease types combined).

### Article Selection

Citations in the initial search of the literature were reviewed by two independent reviewers for inclusion. Citations were not blinded for the selection process. Each citation was scored as "Yes" (inclusion criteria were met, no exclusion criteria were met), "No" (one or more exclusion criteria were met), or "Maybe" (unclear from the citation if article meets any criteria). All discrepancies were resolved by consensus between the two reviewers and, if necessary, scored by a third reviewer. Interobserver kappa coefficients were calculated using GraphPad QuickCalcs © (GraphPad Software, Inc.) (http://graphpad.com/quickcalcs/kappa1.cfm). Any subsequent exclusions of selected articles were documented.

### Synthesizing the Evidence

Data appropriate for pooling or meta-analysis are not expected but will be investigated if the possibility exists. For planned analyses, the primary outcome of interest is progression-free survival, secondary outcomes of interest are response rate and overall survival, and subset analyses will be conducted by histology.

## RESULTS

### Literature Search Results

A total of 344 database citations and conference proceedings were evaluated in the original literature search. Agreement between the two reviewers in scoring of the database and conference publications for inclusion was kappa=0.84. Thirteen studies were excluded, after retrieval, for the following reasons: one did not report information separately for the patient populations of interest, one did not meet the sample size criterion, seven were previous reports of included trials, and four were abstracts reporting combined data of included trials. From the original and update literature searches, 20 publications of 16 trials were located. Two trials were located by searching personal files. An overview of the 16 trials is provided in Tables 1, 2, and 3. Intervention details are provided in Appendix 2.

Of the 16 trials meeting inclusion, 11 dealt with myeloma, five with lymphoma, and no reports were located for Waldenström's macroglobulinemia. For myeloma, one randomized controlled trial (APEX) abstract (2) (the full-report (3) was retrieved later), one randomized phase II trial (CREST) (4), four non-randomized phase II trials (SUMMIT, an abstract and full-report (5,6), and three other trials abstracts (7-9)), and five dose escalation trial abstracts (10-14) were located. One additional abstract (15) reporting toxicity data of an included trial (9) was also located. One previous reporting (16) of an included trial (12) provided toxicity data for that trial. Of those, seven trials were in relapsed or refractory myeloma and four were in previously

untreated patients. For lymphoma, four non-randomized phase II trials (one abstract and full-report of the same trial (17,18), and three other abstracts (19-21)) and one phase I/II trial (22) were located. Relapsed or refractory patients were evaluated in three trials (17,20,22), and a mix of previously treated and untreated were evaluated in two trials (18,19,21).

**Table 1: Summary of the 12 myeloma trials meeting inclusion criteria.**

| Study | Patient Characteristics | Treatment | N[a] |
|---|---|---|---|
| **RELAPSED/REFRACTORY MYELOMA** | | | |
| Phase III Randomized Controlled Trials | | | |
| Richardson 2004 (3) (APEX) | Relapsed MM (1-3 prior regimens); D refractory disease excluded | B 1.3 mg/m$^2$<br>vs.<br>D 40 mg | 315 (95%)<br><br>312 (93%) |
| Phase II Extension Study Trials | | | |
| Jagannath 2004 (4) (CREST) | MM in relapse or refractory to first-line therapy, incl. ASCT | B 1.0 mg/m$^2$<br>*B+D 20 mg*<br>vs.<br>B 1.3 mg/m$^2$<br>*B+D 20 mg* | 27 (96%)<br>*16*<br><br>26 (100%)<br>*12* |
| Richardson 2003 (6) (SUMMIT) | Relapsed MM and refractory to salvage chemotherapy | B 1.3 mg/m$^2$<br>*B+D 20 mg* | 193 (96%)<br>*74* |
| Combination therapy & Dose Escalation | | | |
| Berenson 2004 (10) abs | Previously treated refractory/relapsed MM | B 0.7 mg/m$^2$ [b] +<br>M 0.025-0.25 mg/kg dc | 24 (92%) |
| Hollmig 2004 (11) abs | High-risk, advanced MM | B 1.0 or 1.3 mg/m$^2$ +<br>M 100-250 mg/m$^2$ +<br>ASCT | 27 (73%) |
| Zangari 2004 (12) abs | Refractory MM after transplant and salvage treatment[e] | B 1.0 mg/m$^2$ [c] +<br>T 50-200 mg/d dc[d] | 79 |
| Orlowski 2003 (13) abs | Refractory MM | B 0.9-1.5 mg/m$^2$ +<br>PD 30 mg/m$^2$ | 22 (92%) |
| **NEWLY DIAGNOSED MYELOMA** | | | |
| Phase II Monotherapy | | | |
| Richardson 2004 (7) abs | Previously untreated, symptomatic MM | B 1.3 mg/m$^2$ | 22 (79%) |
| Combination therapy & Dose escalation | | | |
| Wang 2004 (14) abs | Newly diagnosed MM | B 1.0-1.9 mg/m$^2$ +<br>T 100-200 mg/d +<br>D 20 mg/m$^2$ | 25 (100%) |
| Combination therapy before ASCT | | | |
| Jagannath 2004 (8) abs | Newly diagnosed MM patients; ASCT at physician discretion | B 1.3 mg/m$^2$<br>*B+D 20 mg* | 23 (61%)<br>*14* |
| Barlogie 2004 (9) abs | Newly diagnosed MM | B,T,D + PACE +<br>PBSC collection,<br>M-based ASCT | 57 (100%) |

Notes: abs=abstract; ASCT=autologous stem cell transplantation; B=bortezomib; d=day; D=dexamethasone; dc=dose cohorts; M=melphalan; mo=month; PACE=four day infusion of cisplatin 10 mg/m$^2$, doxorubicin 10 mg/m$^2$, cyclophosphamide 400 mg/m$^2$, and etoposide 40 mg/m$^2$; PBSC= peripheral blood stem cell; T=thalidomide; vs.=comparison between arms, y=year.

[a]Number of patients evaluable, (% evaluable).

[b]In absence of dose-limiting toxicity, B increased to 1.0 mg/m$^2$.

[c]B increased to 1.3 mg/m2 in absence of grade 3 neurotoxicity.

[d]To-date accrual done to B 1.3 + T 150 mg.

[e]One patient did not receive a transplant as per a previous reporting of this trial (14).

**Table 2. Trials evaluating bortezomib regimens in multiple myeloma.**

| Trial | Treatment | ORR[a] (%) | CR (%) | PR (%) | Median TTP | Overall Survival[b] |
|---|---|---|---|---|---|---|
| **RELAPSED/REFRACTORY MYELOMA** | | | | | | |
| | | Phase III Randomized Controlled Trials | | | | |
| Richardson 2004 (3) (APEX) | B (1.3 mg/m$^2$) | 38 | 6 | 32[c] | 6.2 mo | 80% at 1y |
| | D (40 mg) | 18 | 1 | 17[c] | 3.5 mo | 66% at 1y |
| | | Phase II Extension Study Trials | | | | |
| Jagannath 2004 (4) (CREST) | B 1.0 mg/m$^2$ [d] | 33 | 4 | 26[c] | NR | NR |
| | *B+D* | *44* | *7* | *30*[c] | *7 mo*[e] | *26.7 mo*[f,e] |
| | B 1.3 mg/m$^2$ | 50 | 4 | 35 | NR | NR, |
| | *B+D* | *62* | *4* | *46* | *11 mo*[e] | *Not Reached*[f,e] |
| Richardson 2003 (6) (SUMMIT) | B 1.3 mg/m$^2$ | 35 | 4 | 24[c] | 7 mo[g] | 16 mo[e] |
| | *B+D* | *18* | *0* | *N/A* | *6.6 mo* | *NR* |
| | | Combination therapy & Dose Escalation | | | | |
| Berenson 2004 (10) abs | B 0.7 mg/m$^2$ [h] + M dc | 67 | 4 | 29 [c,i,j] | 1-18 mo | NR |
| Hollmig 2004 (11) abs | B 1.0 or 1.3 mg/m$^2$ + M + ASCT | 39 | 26 | 13 | NR | NR |
| Zangari 2004 (12) abs | B 1.0 mg/m$^2$ [k] + T dc | 60[H] | 0 | ~60[c,l] | 7 mo (EFS) | 21 mo |
| Orlowski 2003 (13) abs | B 0.9-1.5 mg/m$^2$ + PD | 68 | 23 | 45[c] | NR | NR |
| **NEWLY DIAGNOSED MYELOMA** | | | | | | |
| | | Phase II Monotherapy | | | | |
| Richardson 2004 (7) abs | B 1.3 mg/m$^2$ | 64 | 5 | 36 | NR | NR |
| | | Combination therapy & Dose escalation | | | | |
| Wang 2004 (14) abs | B (1.0-1.9 mg/m$^2$) + T + D | 84 | NA | 84 | NR | 100% at 6 mo |
| | | Combination therapy before ASCT | | | | |
| Jagannath 2004 (8) abs | B 1.3 mg/m$^2$ | 96 | 13 | 70[c] | NR | NR |
| | *B+D* | | 0 | [m] | | |
| Barlogie 2004 (9) abs | B,T,D + PACE + PBSC collection, M-based ASCT | 26[n] | 26[n] | 0 | NR | NR |

Notes: ASCT=autologous stem cell transplantation; B=bortezomib; CR=complete response rate; D=dexamethasone; EFS=event-free survival; M=melphalan; mo=month; NR=not reported; PACE=four-day infusion of cisplatin 10 mg/m2, doxorubicin 10 mg/m2, cyclophosphamide 400 mg/m2, and etoposide 40 mg/m2; ORR=overall response rate; PBSC=peripheral blood stem cell; PD=pegylated doxorubicin; PR=partial response rate; T=thalidomide; TTP=time-to-progression; y=year.

[a]Sum of all measured response rates (e.g. CR+nCR+PR+MR).

[b]% value indicates percent patients surviving, time value indicates median survival time for patients.

[c]PR and near CR.

[d]One patient not evaluable for response.

[e]Patients continuing on in the extension study known or assumed to be included in these analyses.

[f]Data assumed to be for patients receiving B ± dexamethasone.

[g]Discrepancy within article whether 202 or 196 patients included in the analysis.

[h]B increased to 1.0 mg/m2 in absence of DLT

[i]CR and near CR occurred in B 1.0 + melphalan 0.025 mg/kg cohort.

[j]PR or better observed in those with prior B or melphalan treatment.

[k]B increased to 1.3 mg/m$^2$ when no grade 3 neurotoxicity

[l]A small number of MR assumed based on definition of response.

[m]64% improved.

[n]40% after first transplant.

**Table 3. Trials evaluating bortezomib therapy in malignant lymphoma.**

| Trial | Treatment and Patients | N[a] | ORR[b] (%) | CR (%) | PR (%) | Median Remission (months) |
|---|---|---|---|---|---|---|
| | | Phase II (Non-randomized) | | | | |
| O'Connor 2004 (18) | B 1.5 mg/m$^2$ | 51 (100%)[c] | 55 | NR | NR | NR |
| | Relapsed, refractory, or untreated | *FL: 19* | *60* | *5* | *5*[d] | *NYR* |
| Multi-centre | indolent NHL and mantle cell | *MCL: 23* | *56* | *NR* | *NR* | *6-19* |
| | lymphoma | *SLL/CLL: 5* | *20* | *0* | *20* | *NR* |
| | | *MZL: 4* | *100* | *0* | *100* | *NR* |
| Goy 2002 (19) abs | B 1.5 mg/m$^2$ | 24/30 (80%) | 38 | 13 | 25 | NR |
| | Relapsed/refractory lymphoma; | *SLL: 1* | *0* | | | |
| | Median age 63y; Median 4 prior | *FL: 2* | *0* | | | |
| | treatments; Entry: ≤ grade 1 | *MCL: 15/18* | *53* | *20* | *33* | *cr:2-7*[e]*, pr:3* |
| | sensory neuropathy | *DLBCL: 6/8* | *17* | *0* | *17* | |
| | | *tFL: 0/1* | *NE* | | | |
| Strauss 2004 (20) abs | B 1.3 mg/m$^2$. | 32/32 (100%) | 19[f] | 3 | 16 | NR |
| | Relapsed/refractory lymphoma | *MCL: 11* | *36* | *9* | *27* | |
| | subset; Median 3.5 prior | *FL: 10* | *0*[g] | *na* | *na* | |
| | treatments | *WM: 4* | *50* | *0* | *50* | |
| | | *LL: 1* | *0* | *N/A* | *N/A* | |
| | | *DLBCL: 1* | *0* | *N/A* | *N/A* | |
| | | *ATL: 1* | *0* | *N/A* | *N/A* | |
| | | *DFCL: 1* | *0* | *N/A* | *N/A* | |
| | | *HD: 3* | *0* | *N/A* | *N/A* | |
| Belch 2004 (21) abs | B 1.3 mg/m$^2$ | 24/30 (80%) | 33[h] | 0 | 33[h] | NR |
| | Mantle cell lymphoma; advanced | *PT: 14* | *36*[h] | *0* | *36* | |
| | stage previously untreated or ≤2 | *UT: 10* | *30* | *0* | *30* | |
| | prior chemo regimens; Median 67y; | | | | | |
| | All stage III/IV disease | | | | | |
| Dunleavy 2004 (22) abs | B 1.3 mg/m$^2$ | B+chemo: 25/26 (96%) | 24 | 8 | 16 | NR |
| Phase I/II | Relapsed/refractory aggressive B-cell lymphoma (activated B-cell DLBCL); Median age 54y; Median 4 prior therapies | B: 15/16 (94%) | 7 | 0 | 7 | NR |

Notes: abs=abstract; ATL=adult T-cell leukemia/lymphoma; B=bortezomib; chemo=chemotherapy; CLL=chronic lymphocytic leukemia; cr=complete remission; CR=complete response ;CRu=unconfirmed CR; d=day; DFCL= diffuse follicle centre lymphoma; DLBCL=diffuse large B-cell lymphoma; EPOCH= etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone; FL= follicular lymphoma; HD=Hodgkin's disease; max=maximum; LL=lymphoplasmacytic lymphoma; LR=late response; MCL= mantle cell lymphoma; MZL= marginal zone lymphoma; N=number of patients; na=not assessable; N/A=not applicable; NE=not evaluable; nr=no response; NR=not reported; NYR=not yet reached; pr=partial remission; PR=partial response; q=every; SLL=small lymphocytic lymphoma; tFL=transformed FL; WM=Waldenstrom's macroglobulinemia; y=year.

[a]Subgroups indicated by italics.

[b]Sum of all measured response rates (e.g. CR+nCR+PR+MR).

[c]One patient was untreated.

[d]CRu/ PR not reported.

[e]Lower end represents one patient with autologous stem cell transplantation.

[f]+ 6% LR.

[g]"late response" was recorded by authors in two patients (7%).

[h]CRu+PR.

### Critical Appraisal

#### *Myeloma*

Of eleven myeloma trials included in this systematic review, four were reported as multicentre trials (3,4,6), and pharmaceutical authorship or sponsorship was noted in six (3,4,6,8,10,13). A formal critical appraisal of the majority of studies included in this systematic review was not possible because many are phase I or II data trials reported in abstract form.

The one RCT located in the literature search (3) was a multicentre phase III trial. The trial was unblinded, and information on allocation concealment was not provided in the article. Randomization was stratified by various prognostic factors, including the following: number of previous treatments, TTP after last treatment, and β2-microglobulin values. A retrospective review of those subgroups indicated that 4-7% of patients were placed in incorrect subgroups; however, those patients were analysed as part of their intention-to-treat populations. The authors reported that the two arms were balanced in terms of baseline characteristics (demographics, type of myeloma, performance status, and prior treatments). The protocol allowed patients who progressed on dexamethasone to cross over and receive bortezomib. In addition, the trial was ended early following interim analyses for efficacy. As a result of that analysis, patients initially randomized to dexamethasone were immediately offered bortezomib. Details of withdrawals and dropouts were provided in a supplementary appendix (online), and analyses were conducted based on intention-to-treat populations. Of enrolled patients, 627/669 (94%) were included in the analyses, and median follow-up was 8.3 months. The trial was funded by the pharmaceutical company that manufactures bortezomib, and final analyses were conducted by the company in collaboration with the principal investigators.

In the randomized phase II CREST study (4), the authors stated that a power calculation was performed for response data but they were unable to accrue the target enrolment. The authors, appropriately, did not compare the dose groups in their analyses. The dose groups represented slightly different populations; more women, patients with IgG myeloma, and abnormal cytogenetics were present in the higher dose group, and there were more patients with a lower platelet count in the lower dose group.

#### *Lymphoma*

Of the five lymphoma trials included in this systematic review, one expanded study was reported as a multicentre trial (18). Pharmaceutical authorship or sponsorship was noted in three trials (18-20). A formal critical appraisal of the lymphoma studies included in this systematic review was not possible because they were phase II trials, mainly reported in abstract form.

## Outcomes

**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. , TTP), response duration, or response rate?**

#### *Multiple Myeloma*

*Survival*

Survival data have been reported in five studies, the RCT, the randomized phase II trial, and three non-randomized studies. The RCT (3), which compared bortezomib with dexamethasone, reported a 14% greater one-year survival in the bortezomib arm (Table 2), with a hazard ratio of 0.57 for patients in the bortezomib group (p=0.001). In other trials, median survival ranged from 16 to 26.7 months (4,6,12), with the longest survival being seen in the CREST trial (4) and performed in less extensively pre-treated patients

*Quality of Life*

No published analysis compares quality of life with bortezomib to other agents. In the phase II non-randomized SUMMIT trial, quality-of-life data was reported to have improved in incomplete and partial responders to bortezomib but not in minimal or non-responders (7).

*Disease control*

(i) Time to progression (TTP): Four trials reported data on TTP (3,4,6,10). The median TTP reported in two phase II trials (one randomized and one non-randomized) ranged from seven to 11 months. In the RCT, median TTP was significantly longer with bortezomib than with dexamethasone (median 6.2 versus [vs.] 3.5 months, $p<0.001$).

(ii) Event-free survival (EFS): Event-free survival data were reported in one dose-escalation trial (12); the median EFS for combined bortezomib and thalidomide was seven months. Twelve-month event-free survival for the two dose cohorts was 20% for the bortezomib 1.0 mg/m$^2$ plus thalidomide 150 mg/d cohort and 26% for the bortezomib 1.0 mg/m$^2$ plus thalidomide 200 mg/day cohort.

(iii) Response duration: Response duration was reported in the RCT (3) and was eight months for the bortezomib arm compared with 5.6 months for dexamethasone (p=NR). The SUMMIT and CREST trials (4,6) also reported response duration, with values ranging from 9.5-13.7 months.

(iv) Response: The overall response rates to bortezomib alone, or in combination with other agents, are summarized according to disease status in Table 2. Reporting varied among trials—only complete and partial responses were reported in some trials, and others included minimal responses. In the RCT, the response rate to bortezomib was significantly greater than to dexamethasone (38% vs. 18%; $p<0.001$). Responses to bortezomib as a single agent range from 33-96%. Response rates reported for bortezomib in combination with other agents ranged from 18-84%.

***Lymphoma***

Data for the use of bortezomib in malignant lymphoma are shown in Table 3. All trials evaluated single-agent bortezomib, and one trial included an arm combining bortezomib and chemotherapy. Response rates ranged from 7-55% (Table 3).

**Question 2: What is the toxicity associated with the use of bortezomib?**

***Multiple Myeloma***

A variety of grade 3 or 4 adverse events in varying frequencies were reported among ten trials (3,4,6,8-11,14), including neutropenia (eight trials); thrombocytopenia (five trials); neuropathy (five trials); diarrhea or fatigue (three trials each); abdominal pain, anemia, dyspnea, hyponatremia, pneumonia with no other symptoms (NOS)/pneumonia/sepsis, or vomiting, (two trials each); and anorexia, bone pain, constipation, cough, deep vein thrombosis (DVT), dizziness, fever, headache, insomnia, lymphopenia, mucositis, nausea, non-neutropenic infection, orthostatic hypotension, pain in limb, paresthesia, pyrexia, rash, syncope, or weakness, (one trial each).

Grade 3 neuropathy was reported in four trials (3,4,6,8); of those, grade 4 neuropathy was reported in two (3,4). One trial explicitly stated no grade 3 or 4 neuropathy was observed (11). In the RCT (3), a higher proportion of patients in the bortezomib arm had one or more grade 3 adverse events compared to patients in the dexamethasone arm ($p<0.01$). Patients experienced one or more of the following grade 3 adverse events: anorexia, diarrhea,

neuropathy, neutropenia, and thrombocytopenia. Grade 4 adverse events were more common in the bortezomib arm compared to the dexamethasone arm for thrombocytopenia (4% vs. 1%, p=0.05) and neutropenia (2% vs. 0%, p=0.01). Of 21 reported adverse events of any grade, 17 occurred in a statistically significant greater proportion of patients in the bortezomib arm compared with the dexamethasone arm. One additional study (9) reported toxicity data but did not state whether any were grades 3 or 4. One abstract (15) reporting DVT data for two trials reported 0% DVT occurrence in a trial evaluating bortezomib combination therapy before transplant (9). Toxicity was not reported in one trial (13). The earlier report (16) of Zangari et al. 2004 (12) provided the toxicity data for that trial.

The discontinuation of treatment because of toxicity was reported in four trials (3,4,6,8) and ranged from 5-37% of patients. Discontinuation because of bortezomib treatment-related toxicity in the RCT was 37% (compared with 29% for the dexamethasone arm), and in the phase II trials ranged from 15-18% (4,6). A subset of patients in three trials discontinued treatment because of neuropathy (3,4,6). Another trial reported one grade 3 neuropathy event leading to discontinuation (8).

The RCT (3) reported four possible bortezomib treatment-related deaths (three from cardiac causes, one from sudden death of unknown cause). The SUMMIT trial (6) reported two possible treatment-related deaths, and the Barlogie et al. trial (9) reported one treatment-related death in a patient with renal failure at baseline. The CREST trial reported one death due to pneumonia in a patient receiving bortezomib at 1.3 mg/m$^2$ (4). One trial (11) explicitly stated that no toxicities were fatal.

***Lymphoma***

The majority of trials in lymphoma evaluated bortezomib monotherapy in relapsed or refractory patients. Five trials reported toxicities. In the full report by O'Connor et al. (18), the grade 3 toxicities observed were lymphopenia (14 patients); thrombocytopenia (seven patients); hypokalemia, hyponatremia, infection without neutropenia, neuropathy, and prothrombin time (two patients each); and alanine aminotransferase, alkaline phosphatase, hemoglobin, hyperkalemia, leukocytes, nausea, neutrophils, anorexia, constipation, and fatigue (one patient each). Only one grade 4 event was observed, hyponatremia. The abstract update of that trial reported similar data.

Among three trials published in abstract form (19,20,22), similar grade 3 or 4 toxicities were reported (thrombocytopenia, gastrointestinal, neuropathy, fatigue, anemia, and neutropenia). The fourth trial, in abstract form also, (21) evaluated bortezomib in previously treated and untreated patients and reported grade 2 or higher toxicities, attributed to the study drug and similar to the above (anorexia, gastrointestinal, fatigue, dizziness, sensory neuropathy, edema, hypotension, vascular leak syndrome, arthralgia, myalgia, neuropathic pain, dyspnea, and rash).

In the trial that evaluated bortezomib plus EPOCH chemotherapy (22), grade 4 neutropenia, grade 4 thrombocytopenia, fever/neutropenia (grade not given), grade 2 or higher gastrointestinal toxicities, and grade ≥3 sensory neurotoxicity were observed. The authors of that trial also compared the toxicities in the combination-therapy arm with those in a historical cohort of patients receiving fixed-dose EPOCH. Results were similar for fever/neutropenia (grade not given), grade 4 neutropenia, and grade 3/4 thrombocytopenia but higher, in the fixed-dose EPOCH group, for grade 2 or higher gastrointestinal toxicity (statistical analysis not provided). Grade 2 or higher neurotoxicity was also more frequent with fixed-dose EPOCH, but the authors stated that fewer treatment cycles were received by the combination-therapy patients.

In the full report by O'Connor et al. (18), two patients were taken off the study because of toxicity. Thirteen patients (50%) missed at least one dose of bortezomib; thrombocytopenia was the most common reason for missing doses, and occurred most frequently at the beginning of

the study before investigators changed the platelet count requirements (≥100,000/μL to ≥50,000/μL for the first dose of every cycle). Thrombocytopenia was the only dose-limiting hematologic toxicity. In the trial by Goy et al. (19), one patient with herpes zoster died of encephalitis. In the trial by Belch et al. (21), toxicity led to discontinuation in nine patients, of which six was because of neuropathy or myalgia. Amendment of eligibility criteria to exclude patients with edema, dyspnea, or effusion at baseline eliminated the occurrence of serious toxicities.

**Question 3: Which patients are more or less likely to benefit from treatment with bortezomib?**

***Multiple Myeloma***

In the SUMMIT trial, the factors reported to predict for higher response rates (complete/partial [CR/PR]) with bortezomib monotherapy were age <65 years and bone marrow plasmacytosis ≤50% ($p<0.05$ by multivariate analysis) (6). Known adverse prognostic factors such as beta-2-microglobulin, the number of prior therapies, and chromosome-13 abnormalities were not found to predict for response. In the abstract update of that trial, a partial least-square regression analysis detected that high serum protein, bone marrow plasma cells, and β2-microglobulin and low platelet count, serum albumin, hemoglobin, Karnofsky score, body surface area, weight, and quality of life at baseline predicted for mortality (5). In the APEX trial (3), the authors stratified the randomization along prognostic factors, such as the number of prior therapies, and conducted subgroup analyses. Time-to-progression, one-year survival, response rate (CR/PR), and duration of response were higher in patients with one prior line of therapy than in those with more than one prior line of therapy, although the study design did not permit statistical comparisons of the effect of prognostic factors. One trial (12) evaluating bortezomib combination therapy in refractory myeloma analyzed 17 factors by multivariate analysis and concluded that treatment more than five years previously was associated with superior survival ($p=0.03$), previous thalidomide treatment was associated with inferior survival after combination treatment ($p=0.05$), and bortezomib at the 1.3 mg/m$^2$ dosage reduced the risk of death ($p=0.02$).

***Lymphoma***

Although the numbers of patients treated were small, and no statistical analyses have been performed to date, the highest response rates to bortezomib have been observed in mantle cell and follicular lymphoma.

**DISCUSSION**

The standard first-line therapy for myeloma has been established through a series of large randomized trials. This topic is addressed in the PEBC Practice Guideline #6-6: *Optimal Therapy for Patients Diagnosed with Multiple Myeloma and the Role of High-Dose Chemotherapy and Stem Cell Support* (1). Autologous stem cell transplantation is recommended as the first-line of therapy for patients with advanced-stage myeloma and good performance status. For patients not eligible for autologous stem cell transplantation, oral alkylating agent-based chemotherapy with regimens such as melphalan, or prednisone and cyclophosphamide, represent the standard of care. While neither approach is curative therapy, both are associated with moderate to high rates of remission, effective palliation of symptoms, and acceptable toxicity profiles. Bortezomib has not been compared to standard treatment options in RCTs in first-line treatment. Until evidence of its superiority to currently available treatment options becomes available, the Hematology DSG does not recommend that bortezomib be used as first-line therapy outside the setting of a clinical trial.

The optimal therapy for patients beyond first-line therapy is not well established. Available options include additional alkylating agent-based chemotherapy, or regimens of high-dose dexamethasone, thalidomide, or, more recently, bortezomib. In relapsed patients, of these options, only bortezomib has been tested in RCTs.

Alkylating-agents (e.g., melphalan, cyclophosphamide, and prednisone) as second-line therapy may produce successful re-induction in cases of relapsed myeloma. Where relapse occurs following the use of alkylating agents as first-line therapy, additional therapy with alkylating-agents may effectively palliate symptoms and induce remissions, while offering the advantage of convenient oral administration and a relatively favourable toxicity profile (23). Fewer data are available on the use of alkylating agents for relapse following autologous stem cell transplantation or high-dose therapy. A reasonable expectation is that toxicity, particularly myelosuppression, would be greater in this setting, given the limited marrow reserve following transplantation.

High-dose oral dexamethasone alone has modest activity in relapsed and refractory myeloma, and is an appropriate comparator for tests of new agents or regimens (either as a single agent or in combination with vincristine and adriamycin in the VAD regimen) (24,25). Because of the lack of myelosuppression, this regimen is commonly used in patients with compromised bone marrow reserves. VAD has not been compared to high-dose dexamethasone alone in randomized trials but is generally believed to be modestly more effective, at the cost of increased toxicity and inconvenience. The VAD regimen must be administered intravenously through a central venous catheter and is associated with myelosuppression, alopecia, nausea, and peripheral neuropathy.

Thalidomide is also an active agent in relapsed and refractory myeloma (26). Data from uncontrolled trials report a response rate of 30-40%, with a proportion of patients remaining disease-free for a prolonged period. The addition of corticosteroids appears to improve the response rates (27). Thalidomide is administered orally and is not associated with myelosuppression but does have significant toxicities, particularly neurotoxicity, that may cause the discontinuation of therapy in some patients. Thalidomide is also highly teratogenic. Thalidomide has not been compared to other agents in randomized trials in relapsed and/or refractory patients. It is approved for use by the US Food and Drug administration, although under a special program to safeguard against birth defects. However, it has not been approved by the Canadian Health Protection Branch and is therefore not widely available in Canada.

In patients with relapsed myeloma, the DSG emphasized the importance of sensitivity to alkylating agents in defining the optimal therapeutic regimen. Patients who remain sensitive to alkylating agents may be effectively re-treated with alkylators. There is no consensus definition for alkylator sensitivity, but the DSG thought the commonly used relapse threshold of one year or more after alkylating-agent–based chemotherapy was a reasonable definition. No other regimen has been compared to re-treatment with alkylating agents in this group of patients.

In view of the favourable toxicity profile and greater ease of administration of alkylating-agent–based regimens, the DSG recommends treatment or re-treatment with alkylating-agent chemotherapy for patients with relapsed myeloma whose disease is sensitive to alkylating-agents, including those whose first-line treatment was autologous stem cell transplantation or high-dose therapy, and who are candidates for further chemotherapy. The oral regimen of cyclophosphamide (250-300 mg/m$^2$, usually 500 mg) per week and prednisone (50-100 mg) every second day is commonly used and produces less cumulative myelosuppression than melphalan and prednisone (28). Thalidomide-based therapy is also an option under these circumstances.

For patients with myeloma refractory (i.e., relapse within one year of treatment) to first-line treatment who are candidates for chemotherapy, the use or re-use of alkylating agents is not a reasonable option. Treatment options under these circumstances include high-dose dexamethasone, thalidomide, and bortezomib. In the APEX trial, bortezomib was associated

with a 14% improvement in one-year survival when compared with high-dose dexamethasone, without increased severe toxicity. The DSG considers this difference to be important. While thalidomide has demonstrated activity in this population of patients in uncontrolled studies, it has not been compared to either bortezomib or dexamethasone. For this reason, the DSG considers that bortezomib is the preferred treatment option for this group of patients.

The place of bortezomib in the management of lymphoma and Waldenstrom's macroglobulinemia was also considered. Only preliminary results from small studies are available for these cancers. Until such time as more mature data are available, the DSG does not recommend that bortezomib be used outside of clinical trials in patients with these diagnoses.

## TREATMENT ALTERNATIVES

For patients with myeloma relapsing following autologous stem cell transplantation or who are refractory to alkylating-agent–based chemotherapy, the principal alternative to bortezomib treatment is pulsed oral high-dose dexamethasone (40 mg po days 1-4, 9-12, and 1-20 of each cycle). Thalidomide (100-400 mg/day) has 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.

## ONGOING TRIALS

The National Cancer Institute (NCI) (http://www.cancer.gov/search/clinical_trials/), United Kingdom Coordinating Committee on Cancer Research (UKCCCR) (http://212.219.75.230/scripts/ ukcccr/ibmhpj/bin/DisText.exe), National Institute of Health (NIH) Clinical Trials (http://clinicaltrials.gov/), the European Organization for Research and Treatment of Cancer (EORTC) (http://www.eortc.be/), BioMed Central (http://www.biomedcentral.com/home/), and the Ontario Cancer Trial (http://ontariocancertrials.ca/) databases were searched for reports of new or ongoing trials. Personal files were also searched. The ongoing trials located are detailed in Appendix 3.

## CONCLUSIONS

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, the evaluation of these other options is beyond the scope of this systematic review. 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 in patients with non-Hodgkin's lymphoma or Waldenstrom's macroglobulinemia.

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. The Hematology DSG recommends the same dose of bortezomib used in the RCT (1)—bortezomib 1.3 mg/m$^2$, 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 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 upon 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 the dose modification guidelines are followed. Responses to treatment are usually apparent by six weeks (two cycles). For patients achieving CR (determined by negative electrophoresis and immunofixation), bortezomib should be given for two additional cycles beyond the date of the 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 a 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.

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, the members of the Hematology DSG regard thalidomide or bortezomib to be alternative therapies to dexamethasone.

## CONFLICT OF INTEREST

The working group members for this topic and the Chair of the Hematology DSG disclosed potential conflicts of interest relating to the topic of this evidence-based series. The lead author of this evidence-based series was the principal investigator or the local investigator and received research funding for four trials, including the RCT (3) reported here. That author was also a consultant for the manufacturer of bortezomib, received honoraria, and was an advisory board participant for a future trial.

## JOURNAL REFERENCE

Reece D, Imrie K, Stevens A, Smith CA. Bortezomib in multiple myeloma and lymphoma: a systematic review and clinical practice guideline. Curr Oncol. 2006;13(5):162-72.

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For a complete list of the Hematology Disease Site Group members, please visit the CCO Web site at http://www.cancercare.on.ca/

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**Appendix 1. MEDLINE search strategy.**

1 bortezomib:.mp,kf.
2 bortez##id:.mp,kf.
3 bortez##ib:.mp,kf.
4 velcade:.mp,kf.
5 ps?341:.mp,kf,kw.
6 ldp?341:.mp,kf,kw.
7 mln?341:.mp,kf,kw.
8 bortezomib.rn.
9 bortezomib.rw.
10 or/1-9
11 multiple myeloma/
12 myeloma:.mp,kf.
13 MM.mp,kf,kw.
14 lymphoma:.mp,kf.
15 exp lymphoma/
16 exp lymphoma, large-cell/
17 (DLBCL or FCL or MCL or NHL).mp,kf,kw.
18 waldenstrom macroglobulinemia/
19 waldenstro?m: macroglobulin?emia:.mp,kw.
20 WM.mp,kf,kw.
21 or/11-20
22 10 and 21
23 comment.pt.
24 letter.pt.
25 editorial.pt.
26 or/23-25
27 22 not 26
28 limit 27 to human
29 limit 28 to english language

**Appendix 2. Intervention details of included studies.**

| Trial | Patient population | Intervention |
|---|---|---|
| **RELAPSED/REFRACTORY MYELOMA** | | |
| Phase III Randomized Controlled Trials | | |
| Richardson 2004 (3) (APEX) | Relapsed MM (1-3 prior regimens) | B 1.3 mg/m$^2$ d1,4,8,11 q 3wk for 8 cycles followed by 1.3 mg/m$^2$ on d1,8,15,22 q 5wk for 3 cycles<br>vs.<br>D 40 mg po d1-4, 9-12, 17-20 q 5wk for 4 cycles followed by 40 mg po d1-4 q 28 days for 5 cycles |
| Phase II Extension Study Trials | | |
| Jagannath 2004 (4) (CREST) | MM in relapse after or refractory to first-line therapy, including stem cell transplant | B: 1.0 vs. 1.3 mg/m$^2$ d1,4,8,11 of a 21d cycle for up to 8 cycles.<br><br>Separate extension study available if deemed beneficial. Patients with PD after 2 cycles or SD after 4 cycles could receive dexamethasone 20 mg po the day of and the day after each B dose. |
| Richardson 2003 (6) (SUMMIT) | Relapsed MM and refractory to salvage chemotherapy | B 1.3 mg/m$^2$ d1,4,8,11 of a 21d cycle for up to 8 cycles.<br><br>Separate extension study for additional treatment for those still receiving benefit. Patients with PD after 2 cycles or SD after 4 cycles could receive dexamethasone 20 mg po the day of and the day after each B dose. |
| Combination Therapy & Dose Escalation | | |
| Berenson 2004 (10) abs | Previously treated refractory/relapsed MM | B 0.7 mg/m$^2$ d1,4,8,11 +<br>M po (0.025, 0.05, 0.1, 0.15, 0.25 mg/kg) d1-4 q 4wk to max 8 cycles to 3-patient cohorts.<br><br>In absence of dose-limiting toxicity, B increased to 1.0 mg/m$^2$ and M given in doses above to subsequent cohorts. |
| Hollmig 2004 (11) abs | High-risk, advanced MM | B 1.0 or 1.3 mg/m$^2$ d-4,-1 +<br>M 100-250 mg/m$^2$ d-4,-1 or d-1 + ASCT |
| Zangari 2004 (12) abs | Refractory MM after transplant and salvage treatment<br><br>To date accrual done to B 1.3 + T 150 mg | B 1.0 mg/m$^2$ d1,4,8,11 +<br>T 50,100,150, 200 mg/d (10 pts per cohort) d21 second cycle<br><br>B increased to 1.3 mg/m$^2$ plus T as above in absence of grade 3 neurotoxicity. |
| Orlowski 2003 (13) abs | Refractory MM | B 0.9-1.5 mg/m$^2$ d1,4,8,11 of a 21d cycle plus pd 30 mg/m$^2$ on d 4 |

**NEWLY DIAGNOSED MYELOMA**

| | | |
|---|---|---|
| Phase II Monotherapy | | |
| Richardson 2004 (7) abs | Previously untreated, symptomatic myeloma | First-line B 1.3 mg/m$^2$ d 1,4,8,11 of 21d cycle.<br><br>D not permitted |
| Combination Therapy & Dose Escalation | | |
| Wang 2004 (14) abs | Newly diagnosed myeloma | B (1.0, 1.3, 1.5, 1.7, 1.9 mg/m$^2$) d1,4,8,11 +<br>T (100-200 mg/d) +<br>D (20 mg/m$^2$ d 1-4, 9-12, 17-20).<br>Every 4wk for 2-3 cycles. |
| Combination Therapy before ASCT | | |
| Jagannath 2004 (8) abs | Newly diagnosed myeloma patients. ASCT at physician discretion. | B 1.3 mg/m$^2$ twice weekly for 2 of 3 wk for a max 6 cycles. D 40 mg po if less than PR after 2 cycles or less than CR after 4 cycles, given day of and after B. |
| Barlogie 2004 (9) abs | Newly diagnosed myeloma | B,T,D plus PACE x 2 cycles + PBSC collection followed with M 200 mg/m$^2$ / ASCT.<br>Consolidation with B,T,D plus PACE. B,T,D maintenance. |

**LYMPHOMA**

| | | |
|---|---|---|
| O'Connor 2005 (18) | Relapsed, refractory, or untreated indolent NHL and mantle cell lymphoma; One patient was untreated. | B 1.5 mg/m$^2$ d1,4,8,11 q 21d.<br><br>No max amount set in protocol. |
| Goy 2002 (19) abs | Relapsed/refractory lymphoma | B 1.5 mg/m$^2$ d1,4,8,11 q 21d. Max 6 cycles. |
| Strauss 2004 (20) abs | Relapsed/refractory lymphoma subset | B 1.3 mg/m$^2$ twice weekly q 21d up to 8 cycles. |
| Dunleavy 2004 (21) abs | Relapsed/refractory aggressive B-cell lymphoma (activated B-cell DLBCL) | B 1.3 mg/m$^2$ d1,4,8,11 q 21d<br><br>If patients require chemo or do not achieve CR, then: B dose cohorts 0.5,1.0,1.5,1.7 mg/m$^2$ d1,4 with dose-adjusted EPOCH q 21d. |
| Belch 2004 (22) abs | Mantle cell lymphoma; advanced stage previously untreated or ≤2 prior chemo regimens | B 1.3 mg/m$^2$ d1,4,8,11 q 21d.<br><br>Max 4 cycles if nr. If PR/CR, receive for two more cycles. |

Notes: ASCT=autologous stem cell transplantation; B=bortezomib; chemo=chemotherapy; CR=complete response; d=day; D=dexamethasone; DLBCL=diffuse large B-cell lymphoma; EPOCH=etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone; M=melphalan; MM=multiple myeloma; NHL=non-Hodgkin's lymphoma; nr=no response; PACE=four-day infusion of cisplatin 10mg/m$^2$, cyclophosphamide 400 mg/m$^2$, and etoposide 40 mg/m$^2$; PBSC=peripheral blood stem cell; pd=pegylated doxorubicin; PD=progressive disease; po=pulsed oral; PR=partial response; pts=patients; q=every; SD=stable disease; T=thalidomide; wk=week.

**Appendix 3. List of ongoing trials.**

| Protocol ID(s) | Title and details of trial |
|---|---|
| Multiple myeloma | |
| M34101-040 | An International, Non-Comparative, Open-Label Study of PS-341 Administered to Patients with Multiple Myeloma Who Experienced Relapsed or Progressive Disease After Receiving at Least Four Previous Regimens or Experienced Progressive Disease After Receiving Dexamethasone in Millennium Protocol M34101-039. Target enrolment: 600 (12 months). Source: personal files (KI). |
| M34103-058 | Repeat-Dose Pharmacokinetics and Pharmacodynamics of Bortezomib in Patients with Relapsed Multiple Myeloma. Design: Bortezomib 1.3 or 1.0 mg/m$^2$ administered as 3- to 5-second IV push on days 1, 4, 8, and 11 of a 21-day cycle. Phase I trial. Target enrolment: 40. Source: personal files (KI). |
| 6329/CALGB-10301 | Phase II Study of Bortezomib (PS-341) and Pegylated Liposomal Doxorubicin as Initial Therapy for Adult Patients with Symptomatic Multiple Myeloma. Target enrolment: 55. Source: personal files (KI). |
| E2A02 | Phase II Study of PS-341 for Patients with High-Risk, Newly Diagnosed Multiple Myeloma. Design: Induction Bortezomib 1.3 mg/m$^2$ days 1, 4, 8 and 11 every 21 days x 8 cycles. Maintenance Bortezomib 1.3 mg/m$^2$ days 1 and 15 every 28 days until progressive disease or toxicity. Reinduction Bortezomib 1.3 mg/m$^2$ days 1, 4, 8 and 11 every 21days. Target enrolment: 44. Source: personal files (KI). |
| i056-341-03 | Phase I study of VELCADE (bortezomib) with DT-PACE for induction and stem cell collection of newly diagnosed multiple myeloma patients. Design: DVT-PACE cycles repeated every 5 weeks x 2 dose escalation VELCADE 0.7, 1, 1.3 mg/m2 days 1,4,8 of each cycle. Target enrolment: 24. Source: personal files (KI). |
| i064-341-03 | A Phase I/II Trial of Arsenic Trioxide (ATO) and Bortezomib Combination Therapy in Patients with Relapsed or Refractory Multiple Myeloma. Design: Dose escalation Bortezomib mg/m$^2$ + ATO mg/m2 days 1, 4, 8, + 11 every 3 weeks - Dose Level (DL) 1: .7/.125; DL2: 1/.125; DL3: 1.3/.125; DL4: .7/.25; DL5: 1/.25; DL6: 1.3/.25. Target enrolment: 28. Source: personal files (KI). |
| i067-341-03 | A phase II open-label trial of VELCADE in VELCADE naive patients with multiple myeloma who have undergone high dose melphalan therapy followed by autologous peripheral blood stem cell transplantation and failed to achieve a complete response. Design: VELCADE 1.3mg/m$^2$ days 1, 4, 8, 11 every 21 days x 4 cycles. Responders - option 4 more cycles. Target enrolment: 68. Source: personal files (KI). |
| i34101-009 | A Prospective, Open-Label, Safety and Efficacy Study of Combination Treatment with PS-341 and Melphalan in Patients with Relapsed or Refractory Multiple Myeloma. Design: Cohorts 1-5: PS-341 0.7 mg/m$^2$ days 1,4,8,11 every 28 days & dose escalation melphalan 0.025, 0.05, 0.1, 0, 0.15, 0.25 mg/kg days 1-4 every 28d. Cohorts 6-8: PS-341 1.0 mg/m$^2$ days 1,4,8,11 every 28 days & dose escalation melphalan 0.025, 0.1, 0.25 mg/kg days 1-4 every 28 days. Target enrolment: 50. Source: personal files (KI). |
| i34101-014 | Phase I Exploratory Study of Combination PS-341 and Thalidomide in Refractory Multiple Myeloma. Design: 2 dosing groups:<br>Group I: PS-341 1.0mg/m$^2$ d1,4,8,11 every 21 days with 4 cohorts treated with escalating doses of thalidomide 50, 100, 150, 200 mg/d.<br>Group 2 (if no MTD): PS-341 1.3 mg/m$^2$ d1,4,8,11 every 21 days with 4 cohorts treated with escalating doses of thalidomide. Target enrolment: 87. Source: personal files (KI). |
| i34102-017 | A Phase II Trial of PS-341 Alone and in Combination with Dexamethasone in Previously Untreated Multiple Myeloma Patients. Design: Velcade 1.3mg/m$^2$ days 1,4,8,11 every 21 days. Patients with less than PR and with PD receive PS-341 + Dexamethasone 40 mg x 2 days with each dose of PS-341. Target enrolment: 42. Source: personal files (KI). |

| Protocol ID(s) | Title and details of trial |
|---|---|
| i34102-023 | Pilot study of PS-341 prior to mobilization of hematopoietic progenitors and as maintenance therapy post-high dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) in patients with multiple myeloma. Phase II trial. Design: PS-341 1.3mg/$m^2$ days 1,4,8,11 every 21 days x 2 cycles. Stem cell mobilization. Post-SCT maintenance PS-341 1.3mg/$m^2$ days 1, 8, 15, 22 every 35 days x 6 cycles. Target enrolment: 40. Source: personal files (KI). |
| i34102-025 | Phase II study to assess the safety, efficacy, and tolerability of combination therapy with VELCADE (PS), Adriamycin, and dexamethasone (PAD) as primary therapy for patients with multiple myeloma. Design: Level I: PS-341 1.3mg/$m^2$ days 1,4,8,11 + Dexamethasone (D) 40 mg orally days 1-4. Level II: PS 1.3mg/m2 days 1,4,8,11, D 40 mg orally days 1-4, Adriamycin 4.5mg/$m^2$ days 1-4 continuous infusion. Level III: PS 1.3mg/$m^2$ days 1,4,8,11, D 40mg orally days 1-4, Adriamycin 9.0mg/$m^2$ days 1-4 continuous infusion. Target enrolment: 41. Source: personal files (KI). |
| i34102-035 | A Multicenter Open-Label Phase II Study of VELCADE Combined with High-Dose Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma. Design: Velcade 1.3mg/$m^2$ days 1,4,9,12 every 21 days x 4 cycles and Dexamethasone 40 mg orally days 1-4 and days 9-12 in cycles 1&2 and days 1-4 in cycles 3&4. Target enrolment: 50. Source: personal files (KI). |
| i34103-038 | An Open-Label Phase I Study of the Safety and Efficacy of Bortezomib in Combination With CC-5013 (Revimid) In the Treatment of Subjects With Relapsed and Relapsed/Refractory Multiple Myeloma. Design: Velcade mg/m2 days 1,4,8,11 + Revimid mg/$m^2$ days 1-14 every 21 day cycle - Dose Level (DL) 1: 1/5; DL2: 1.3/5; DL3: 1/10; DL4: 1.3/10; DL5 1/15; DL6 1.3/15; DL7 1/20; DL8 1.3/20. Target enrolment: 58. Source: personal files (KI). |
| i34103-039 | Phase II Trial of VELCADE (bortezomib) in Patients with Previously Untreated Multiple Myeloma. Design: PS-341 1.3mg/$m^2$ days 1,4,8,11 every 21 days x 2 cycles. Max 8 cycles (6 months). Target enrolment: 44. Source: personal files (KI). |
| i34103-043 | Total Therapy III: A Phase II Study Incorporating Bone Marrow Microenvironment (ME) - Co-Targeting Bortezomib into Tandem Melphalan-Based Autotransplants with DT PACE for Induction/Consolidation and Thalidomide + Dexamethasone for Maintenance. Design: Induction Velcade, Dexamethasone, Thalidomide (VDT)-PACE x 2 cycles with 6 cohorts of V 1.0 mg/$m^2$ for days 1,4 or days 1,4,8 or days 1,4,8,11 every cycle. TD until SCT with Melphalan 200 x2. Consolidation VDT-PACE x2 cycles with TD between. Target enrolment: 300. Source: personal files (KI). |
| i34103-045 | Phase II trial of weekly bortezomib (VELCADE) in the treatment of patients with relapsed or refractory multiple myeloma. Design: Bortezomib 1.6mg/$m^2$ IV bolus on days 1, 8, 15, and 22 of each 5-week cycle, maximum 8 cycles. Stable disease or disease progression after 2 courses (10 weeks) receive 1.3 mg/$m^2$ days 1,4,8 & 11 every 21days. Target enrolment: 40. Source: personal files (KI). |
| i34103-047 | Bortezomib in Combination with High-Dose Dexamethasone and Continuous Low-Dose Oral Cyclophosphamide for Primary Refractory or Relapsed Multiple Myeloma - A Phase II Study of the Deutsche Studiengruppe Multiples Myelom (DSMM). Design: Velcade 1.3mg/$m^2$ days 1,4,8,11 every 21days x 8 cycles then days 1,8,15,22 every 35 days x 3 cycles; D 20mg day of and after V; CTX 50 mg every day. Target enrolment: 50. Source: personal files (KI). |
| VEL-03-076 | A National, Multi-Center, Open-Label Study of VELCADE Plus Melphalan and Prednisone (V-MP) in Elderly Untreated Multiple Myeloma Patients. Design: Phase I - escalating dose Velcade 1.0, 1.3 mg/m2 days 1, 4, 8, 11, Melphalan 9 mg/$m^2$ and Prednisone 60 mg/$m^2$ days 1-4. Phase II - Velcade at MTD day 1, 4, 8, 11, 22, 25, 29 and 32 every 42 day (6 week) cycle x 4 followed by days 1, 8, 15 and 22 every 35 days (5 week). Target enrolment: 60. Source: personal files (KI). |

| Protocol ID(s) | Title and details of trial |
|---|---|
| VEL-03-080 | Phase I/II study to determine the MTD of intravenous melphalan when used in combination with Bortezomib and to assess the safety, efficacy and tolerability of combination therapy with Bortezomib plus intravenous melphalan in patients with relapsed MM. Design: Velcade 1.3 mg/m$^2$ iv days 1,4,8,11 every 28 days and dose escalation melphalan 10,15,20,25 mg/m$^2$ iv day 2 every 28 days, maximum of eight cycles. Dexamethasone 20 mg on the day of and after bortezomib for PD after 2 cycles or SD after 4 cycles. Target enrolment: 40. Source: personal files (KI). |
| VEL-04-113 | An Open-Label Phase I Study of the Safety and Efficacy of Bortezomib in Combination with Cyclophosphamide and Predisone in the Treatment of Patients with Relapsed and Relapsed/Refractory Multiple Myeloma. Design: This is an open-label, dose-finding study intended to identify an MTD of the combination of bortezomib with cyclophosphamide and prednisone. Five dose levels are planned. Target enrolment: 25. Source: personal files (KI). |
| Lymphoma | |
| VEL-03-075 | A Pilot Study of Low Dose Melphalan and Bortezomib for Treatment of Acute Myelogenous Leukemia and High-Risk Myelodysplastic Syndromes. Target enrolment: 24. Source: personal files (KI). |
| 6126 | A Phase I Trial of PS-341 and Fludarabine for Relapsed and Refractory Indolent Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia. Histologies: Lymphoma (FL, MCL, MZL), CLL, WM. Design: Dose escalation PS-341 0.7, 1, 1.3 mg/m$^2$ days 1, 4, 8 and 11 plus fludarabine 25 mg/m$^2$ days 1-3 every 21 days. Target enrolment: 18. Source: personal files (KI). |
| CALGB-50206 | A Phase II Study Of PS-341 (Bortezomib) In Patients With Relapsed Or Refractory Hodgkin's Lymphoma. Target enrolment not provided. Source: personal files (KI). |
| M34101-061 | A Phase II Study of VELCADE with Rituximab in Subjects with Relapsed or Refractory Indolent B-cell Lymphoma. Target enrolment not provided. Source: personal files (KI). |
| 5748 | PS-341 and PS-341 + Epoch Chemotherapy and Molecular Profiling in Relapsed or Refractory Diffuse Large B-Cell Lymphomas. Design: Part A: PS-341 1.3 mg/m$^2$ days 1, 4, 8, 11 every 21 days x max. 1 year. Part B (Patients require immediate medical response or fail to achieve a CR on Arm A): dose escalation PS-341 0.5, 1, 1.5, 1.7 mg/m$^2$ days 1, 4 + EPOCH - Repeat cycles every 21 days x 6 max. cycles. Target enrolment: 30. Source: personal files (KI). |
| i34102-019 | A phase 2 study of PS-341 (Velcade) in chemotherapy-refractory diffuse large B-cell lymphoma (DLBCL). Design: PS-341 1.3mg/m$^2$ days 1,4,8,11 every 21 days, max. 8 cycles. Target enrolment: 40. Source: personal files (KI). |
| i34101-005 | Combined PS-341 with cyclophosphamide and prednisolone in relapsed/refractory indolent lymphoma. Design: Dose escalation PS-341 1.0, 1.3, 1.5 mg/m$^2$ days 1,4,8 and 11 every 21 days, Cyclophosphamide 750 mg/m2 on day 1 every 21 days, + prednisolone 40 mg/m$^2$ Days 1-5 every 21 days, max. 8 cycles. Phase I trial. Target enrolment: 50. Source: personal files (KI). |
| 2795 | A Phase II Study of PS-341 in Low Grade Lymphoproliferative Disorders. Histologies: Lymphoma, Low Grade Lymphoproliferative Disorders. Design: Bortezomib 1.5mg/m$^2$ days 1, 4, 8 and 11 every 3 weeks. Target accrual: 70. Source: personal files (KI). |
| NCIC-150 | A Phase II Study of PS-341 in Patients with Untreated or Relapsed Mantle Cell Lymphoma. Design: PS-341 1.3 mg/m$^2$ days 1, 4, 8 and 11 every 21 days. Target enrolment: 30. Source: personal files (KI). |
| M34103-053 | A Phase II Study of VELCADE in Patients with Relapsed or Refractory Mantle Cell Lymphoma. Target enrolment: 152. Source: personal files (KI). |
| i34103-049 | Phase I/II Trial of VELCADE + CHOP-Rituximab in Patients with Previously Untreated Diffuse Large B-Cell or Mantle Cell Non-Hodgkin's Lymphoma (NHL). Design: Standard CHOP, Rituxan 375 mg day 1, + dose escalation VELCADE 0.7, 1, 1.3 mg/m$^2$ day 1+4 every 21 days. Target enrolment: 78. Source: personal files (KI). |

| Protocol ID(s) | Title and details of trial |
|---|---|
| i34101-008 | A Phase II, Open Label Trial of the Proteasome Inhibitor PS-341 in Hodgkin's Disease and Non-Hodgkin's Lymphoma. Design: PS-341 1.3 mg/$m^2$ days 1,4,8 and 11 every 21 day cycle, max. 8 cycles. Target enrolment: 50. Source: personal files (KI). |
| Waldenström's macroglobulinemia | |
| i34102-022 | Phase II Study of VELCADE (bortezomib, PS-341) in Patients with Relapsed or Refractory Waldenstrom's Macroglobulinemia. Design: VELCADE 1.3 mg/$m^2$ days 1, 4, 8, 11 every 21 days; up to 8 cycles. Target enrolment: 27. Source: personal files (KI). |
| NCIC-152/5858 | A Phase II Study of PS-341 in Patients with Untreated or Relapsed Waldenstrom's Macroglobulinemia. Design: PS-341 1.5 mg/m² days 1, 4, 8, 11 of a 21-day cycle. Target enrolment: 25. Source: personal files (KI). |
| Hematologic malignancies | |
| 1860 | A Phase I and Pharmacologic Study of the Proteasome Inhibitor PS-341 in Combination with Paclitaxel and Carboplatin in Patients with Advanced Malignancies. Histologies: Solid Tumors + Hematology Malignancies. Design: Stage A - Dose escalation PS-341 mg/m² days 1, 4, 8, 11, 15, 18, 22, 25 + Paclitaxel day 1 + 22 - Dose Levels 1-6:.7/150, .7/175, .9/175, 1.2/175, 1.5/175, 1.7/175, repeat every 6 weeks x 6 courses. Stage B, MTD of PS-341 days 1, 4, 8, 11, 15, 18, 22, 25 + MTD Paclitaxel. Target enrolment: 54. Source: personal files (KI). |

Note: PS-341=bortezomib; IV=intravenous; PACE=cisplatin, doxorubicin, cyclophosphamide, etoposide; DT or TD=dexamethasone, thalidomide; DVT=dexamethasone, bortezomib, thalidomide; MTD=maximum tolerated dose; PR=partial remission; PD=progressive disease; max=maximum; CTX=cyclophosphamide; SD=stable disease; FL=follicular lymphoma; MCL=mantle cell lymphoma; MZL=marginal zone lymphoma; CLL=chronic lymphocytic leukemia; WM=Waldenström's macroglobulinemia; EPOCH=etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone.

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**Evidence-based Series #6-18: Section 3**

# Bortezomib in Multiple Myeloma and Lymphoma: Guideline Development and External Review - Methods and Results

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

A Quality Initiative of the
Program in Evidence-based Care, Cancer Care Ontario
Developed by the Hematology Disease Site Group

**Report Date: April 3, 2006**

## THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

### The Evidence-based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline*. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.

- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

## DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

### Development and Internal Review

This evidence-based series was developed by the Hematology DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on bortezomib in multiple myeloma and lymphoma, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

### External Review by Ontario Clinicians

Section 2 reports the results of the systematic review of bortezomib for patients with multiple myeloma and lymphoma. On the basis of that evidence and the interpretation by members of the DSG, draft recommendations were developed and circulated to Ontario practitioners for feedback. Section 3 details the results from the practitioner feedback, changes made to the draft report, and the final recommendations that were submitted to the PEBC Report Approval Panel (RAP) for review and final approval. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the PGCC.

| Box 1: DRAFT RECOMMENDATIONS (approved for external review Nov 15, 2005) |
|---|
| *Target Population*<br>• This evidence-based series applies to adult patients with myeloma, Waldenstrom's macroglobulinemia, or lymphoma of any type, stage, histology, or performance status. |
| *Recommendations*<br>• For patients with myeloma refractory to or relapsing within one year of the conclusion of initial or subsequent treatment(s) who are candidates for further chemotherapy, bortezomib is recommended as the preferred treatment option.<br>• Bortezomib is 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.<br>• For patients with myeloma relapsing at least one year after conclusion of alkylating agent-based chemotherapy who are candidates for further chemotherapy, further treatment with alkylating agent-based chemotherapy is recommended.<br>• There is insufficient evidence to support the use of bortezomib in patients with non-Hodgkin's lymphoma or Waldenstrom's macroglobulinemia. |
| *Qualifying Statements*<br>• 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.<br>• The Hematology DSG recommends the same dose of bortezomib used in the RCT (1); |

bortezomib 1.3 mg/m$^2$, 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 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). In patients with progressive myeloma 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 offer those patients an objective response.
- 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.

***Methods***

The above recommendations were submitted with the systematic review (Section 2) to a sample of 161 hematologists, medical oncologists, and radiation oncologists in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on November 15, 2005, and reminder cards and complete repeat mailings sent thereafter.

***Results***

The response rate for the survey was 78 responses out of 161 questionnaires mailed (48%). Of the 78 respondents, 46 (59%) indicated they cared for patients for whom the guideline is relevant and completed the survey.

Overall, respondents showed strong support for the guideline (selected response data is presented in Table 2). For questions that addressed issues such as the rationale for the guideline, the quality of the guideline, and the clarity of the recommendations, a substantial majority of respondents (range 93% to 100%) expressed modest to “strong” support (1 or 2) for the report (Scale 1 to 5, 1 = “strongly agree,” 3 = “neither agree or disagree,” 5 = “strongly disagree”).

With respect to the appropriateness of the recommendations, an overwhelming majority of respondents, 41-43 of 46 (91-93%) agreed with the draft recommendations and their appropriateness for the specified target population. A strong majority (78%) also felt that the recommendations were not excessively rigid and could be applied to individual patients.

A strong majority responded positively for all but four of the 23 questions. The four items with lower rates of positive responses were related to the feasibility of implementing the recommendations or to economic issues. When asked about the need to reorganize practice to accommodate these guidelines (Q13), 37% of respondents felt there would be a need to reorganize practice, 20% were ambivalent, and 43% did not feel there would be a need.

Similarly, when asked if they felt that implementing the draft recommendations would be technically challenging (Q14), 21% agreed, 37% were ambivalent, and 42% disagreed.

With respect to costs (Q15), only 33% of respondents disagreed with the statement that the recommendations are too expensive to apply, with 35% being ambivalent and 33% feeling it was economically feasible. When asked if they felt the recommendations would result in more resource efficient practice (Q19), only 30% of respondents agreed, while a significant proportion responded with ambivalence (43%) or disagreed (11%).

**Table 2. Responses to selected items on the practitioner feedback survey.**

| Item | Number (%) | | |
|---|---|---|---|
| | **Strongly agree or agree** | **Neither agree nor disagree** | **Strongly disagree or disagree** |
| Q2: The rationale for developing a guideline, as stated in the "Introduction" section of the report, is clear. | 45 (97) | | 1 (2) |
| Q3: There is a need for a guideline on this topic. | 46 (100) | | |
| Q4: The literature search is relevant and complete. | 43 (94) | 2 (4) | 1 (2) |
| Q6: The results of the trials described in the report are interpreted according to my understanding of the data. | 45 (98) | | 1 (2) |
| Q7: The draft recommendations in the report are clear. | 46 (100) | | |
| Q8: I agree with the draft recommendations as stated. | 43 (93) | 2 (4) | 1 (2) |
| Q13: To apply the draft recommendations will require reorganization of services/care in my practice setting. | 17 (37) | 9 (20) | 20 (44) |
| Q14: To apply the draft recommendations will be technically challenging. | 10 (21) | 17 (37) | 19 (42) |
| Q15: The draft recommendations are too expensive to apply. | 15 (33) | 16 (35) | 15 (33) |
| Q19: When applied, the draft recommendations will result in better use of resources than current usual practice. | 14 (31) | 20 (43) | 5 (11) |
| Q21: This report should be approved as a practice guideline. | 42 (94) | 2 (4) | 1 (2) |
| | **Very likely or likely** | **Unsure** | **Not at all likely or unlikely** |
| Q22: If this report were to become a practice guideline, how likely would you be to make use of it in your own practice? | 6 (13) | 6 (13) | 33 (73) |

***Summary of Written Comments and DSG Responses***

The DSG reviewed and addressed the written feedback as follows:

(a) Scope of Guideline

- One individual felt that there should be separate reports for bortezomib in myeloma and for bortezomib in other diseases.

The systematic review of the literature was designed to retrieve studies of bortezomib in patients with myeloma, Waldenstrom's macroglobulinemia, or lymphoma, as the DSG was aware that this agent had been studied in each of these diseases. Given the similarity in dosing of this agent for each indication, presenting the data in a single document was felt appropriate, with the data presented separately for each indication. The DSG will update this guideline report as new evidence is made available; this update may include the development of separate reports for specific disease populations.

(b) Recommendations and Qualifying Statements

- Two individuals felt the scope of the recommendations should be expanded and that bortezomib should be recommended for use in patients with mantle-cell lymphoma.

The DSG is aware of emerging evidence regarding the efficacy of bortezomib in this population. At the present time, the DSG feels that there is insufficient evidence to support the use of bortezomib in patients with mantle-cell lymphoma.

- Two individuals were not clear why the recommended usage of bortezomib is limited to patients with relapse more than one year after autologous stem cell transplant (ASCT). One felt that bortezomib is appropriate for patients relapsing within a year (noting that the APEX/SUMMIT reports show remissions in non-responders, and after-reports demonstrate efficacy in high-risk and aggressive disease). The other would like to see better justification either way (acknowledging that treatment comparisons for relapse within a year are not available).

The DSG regards these disagreements as misinterpretations of the recommendations. The first recommendation states that bortezomib is the preferred treatment option in patients who relapse *within one year* of treatment. For patients relapsing more than one year after ASCT, bortezomib is recommended as *an option* (in addition to thalidomide, alkylating agents, or repeat ASCT). The DSG acknowledges there may be the need to further clarify the recommendations to prevent any confusion on the issue.

- One individual felt the clause “outside of clinical trial” should be added to the recommendations for non-Hodgkin’s lymphoma or Waldenstrom’s macroglobulinemia.

The DSG agreed that the addition of this clause would make the recommendations clearer.

- One individual acknowledged there was no direct comparison between thalidomide and bortezomib and was not sure when to recommend which.

The systematic review did not identify any trials directly comparing bortezomib with thalidomide in this patient population. In the absence of such data, the DSG is unable to provide more specific advice on the relative role of the two agents.

- One individual felt the Qualifying Statements should specify a specific duration of treatment for patients who respond to bortezomib.

Qualifying statements pertaining to the treatment regimen are not intended to be recommendations for practice and instead are intended to serve an informational purpose. The data provided for dose administration and other treatment information are taken from protocols used in the major trials evaluated in this report. The DSG will determine if additional information can be provided on the duration of treatment for bortezomib.

(c) Results and Discussion

- One individual stated that it was not clear that retreatment is more effective than Bortezomib in “alkylator sensitive” patients.

The DSG acknowledges that no direct comparison of bortezomib to retreatment with alkylating-agent–based therapy has been published. In the absence of such data, the DSG favours the use of alkylator retreatment in patients known to be sensitive to alkylating agents, as this treatment is effective, non-toxic, more convenient, and much less expensive.

- One individual stated that the use of bortezomib following front-line melphalan, prednisone, or thalidomide, specifically, may lead to increased toxicity.

The systematic review evaluated the toxicity associated with bortezomib use in patients receiving prior therapy. The DSG felt that the toxicity rates were acceptable.

- One individual thought that the observed effectiveness of bortezomib may be a result of the limited availability of the drug for use in patients.

It is generally true that patients enrolled in clinical trials may differ in some important respects from the overall patient population (e.g., they may be healthier or may represent the most severe cases) and that this discrepancy may bias outcomes. Nonetheless, the DSG felt that the principal RCT informing these recommendations (APEX trial) was of appropriate quality and sufficiently generalizable to the target patient population.

- One individual felt the Discussion should address the discrepancy in the APEX study between the reported improvement in progression-free survival < three months, and the 14% improvement at one year.

In the APEX trial, there was statistically significant improvement in survival and progression-free survival in the bortezomib arm. The DSG considered the 14% improvement in survival to be clinically important. The DSG cannot comment on the perception of a difference in magnitude in improvement in the two end points.

(d) Policy Implications

- Six individuals felt that the funding status for bortezomib was a major issue for this guideline. Some felt that the guideline should only be approved if bortezomib receives funding.
- Four individuals stated the drug was too costly. One stated the costs outweighed the benefits, and that toxicity may outweigh benefits as well.

The PEBC guidelines are designed primarily to address clinical concerns, including outcome measures related to efficacy and toxicity. Economic analyses of the impact of agents are not included in this assessment.

(e) Process or Methodological Considerations

- One individual thought that the Hematology DSG should be involved in the regular monitoring of patient data for new agents, in general, to ensure evidence is up-to-date and fine tuned.

The Hematology DSG monitors publications and meeting reports to identify emerging evidence in order to identify topics for evidence-based series reports and periodically reconsiders its priorities.

### *Discussion*

The DSG notes that, generally speaking, feedback for this report was positive for those questions related to the report development process and supportive of the recommendation for bortezomib use (e.g., in patients with multiple myeloma who relapse within one year of treatment). The main areas of reviewer disagreement were related to the funding and implementation of bortezomib in Ontario. A proportion of respondents felt that implementing the recommendations made in this report would be technically challenging, and the cost of the drug coupled with the fact that it is not currently funded in the province, would be a barrier to its widespread use in the province.

In light of feedback provided by external reviewers, the DSG made the following modifications to the report:

- The clause "(including autologous stem cell transplantation)" was added to the first recommendation regarding bortezomib use.
- The clause "outside of clinical trial" was added to the recommendations for non-Hodgkin's or Waldenstrom's macroglobulinemia.
- Additional information on the duration of treatment for bortezomib has been provided in the Qualifying Statements.

### Report Approval Panel

The final evidence-based series report was reviewed and approved by the PEBC Report Approval Panel in March 2006. The Panel consists of two members, including an oncologist, with expertise in clinical and methodology issues. No significant issues were raised by the panel, and the report was approved for distribution.

### Policy Review

A draft of this practice guideline report was submitted to the Drug Quality and Therapeutics Committee - Standing Oncology Subcommittee (DQTC-SOS) during the final stages of preparation by the DSG for practitioner feedback. The draft was submitted during 2005.

As multiple myeloma has a chronic, relapsing natural history, it is likely that bortezomib will be required in the majority of patients at some point in the disease course—most likely as second- or third-line therapy. As the incidence of multiple myeloma is about 700 per year in Ontario, the introduction of bortezomib will have a significant impact on cancer drug funding. On the other hand, its use will be counterbalanced by an additional estimated 1.5 years of extended life in 30-50% of multiple myeloma patients.

The Hematology DSG recommended to the DQTC-SOS that bortezomib be the preferred option for patients with relapsed or refractory myeloma who fail to respond to prior therapy or who progress within one year of therapy. The Hematology DSG also recommended that bortezomib be an option for patients who relapse a year or more following autologous stem cell transplantation.

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