Evidence-based Series 6-6 Version 2

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

Optimal Therapy for Patients Diagnosed with Multiple Myeloma and the Role of High-Dose Chemotherapy and Stem Cell Support

Members of the Hematology Disease Site Group

An assessment conducted in October 2015 deferred the review of Evidence-based Series 6-6 Version 2, which means that the document remains CURRENT until it is assessed again next year. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Evidence-based Series (EBS) 6-6 Version 2, the resulting review report, consists of the following 4 parts:
1. Guideline Overview
2. Summary
3. Full Report
4. Document Assessment and Review Tool

and is available on the CCO Website on the PEBC Hematology Cancer DSG page.

Release Date: January 10, 2012

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822   Fax: 905-526-6775   E-mail: ccopgi@mcmaster.ca

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Evidence-based Series 6-6 Version 2

Optimal Therapy for Patients Diagnosed with Multiple Myeloma and the Role of High-Dose Chemotherapy and Stem Cell Support

Guideline Review Summary

Review Date: May 24, 2011

The 2003 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW
Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care, Cancer Care Ontario, in 2000 and its first update released in Oct 2003. In May 2011 the PEBC guideline update strategy was applied and the new updated document released in January 2012. The Summary and the Full Report in this version are the same as in the October 2003 version.

Update Strategy

Using the Document Assessment and Review Tool at the end of this report, the PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS
Questions Considered
1. What is the optimal chemotherapy for patients with multiple myeloma?
2. In terms of survival, is peripheral blood stem cell or autologous bone marrow transplantation better than conventional chemotherapy?
3. What is the relative efficacy of autologous and allogeneic transplantation?
4. What specifics of the transplant manoeuvre can be recommended?
5. When should transplantation be performed?
6. Who should (should not) be transplanted?

Literature Search and New Evidence
The new search (2003 to September 2010) yielded 37 relevant new publications. Brief results of these publications are shown in the Document Assessment and Review Tool (Appendix 1) at the end of this report.

Impact on Guidelines and Its Recommendations
The newly identified evidence supports the existing recommendations. Hence, the Hematology DSG ENDORSED the 2003 guideline and recommendations on optimal therapy for patients diagnosed with multiple myeloma and the role of high-dose chemotherapy and stem cell support.

It was noted that the new search yielded a substantial amount of new evidence that informs the questions of optimal induction therapy prior to transplantation that may warrant further discussion/revision of the document.
Optimal Therapy for Patients Diagnosed with Multiple Myeloma and The Role of High-Dose Chemotherapy and Stem Cell Support
Practice Guideline Report #6-6

K. Imrie, J. Makarski, R. Esmail, R. Meyer,
and members of the Hematology Disease Site Group

Please see the EBS 3-8-2 Guideline Review Summary
and the Document Assessment and Review Tool
for the summary of updated evidence published between 2003 and 2010.

Report Date: October 2003

SUMMARY

Guideline Questions
a) What is the optimal chemotherapy for patients with multiple myeloma?
b) In terms of survival, is peripheral blood stem cell or autologous bone marrow transplantation better than conventional chemotherapy?
c) What is the relative efficacy of autologous and allogeneic transplantation?
d) What specifics of the transplant manoeuvre can be recommended?
e) When should transplantation be performed?
f) Who should (should not) be transplanted?

Target Population
These recommendations apply to adult patients with advanced-stage multiple myeloma and good performance status.

Recommendations
• Update
  • *Autologous* transplantation is recommended for patients with advanced-stage myeloma and good performance status. The evidence is strongest for patients under 65 years of age without significant renal dysfunction following hydration and remission-induction chemotherapy. Physicians must use their clinical judgement in recommending transplantation to patients over 65 years of age or those with renal impairment.
  • There is insufficient evidence to recommend *allogeneic* transplantation as routine therapy for multiple myeloma. Patients who are potentially eligible for transplantation should be referred for transplant assessment early after diagnosis and should not be given extensive exposure to alkylating agents such as melphalan prior to the collection of stem cells. High-dose
glucocorticoid-based regimens such as vincristine, doxorubicin (Adriamycin), dexamethasone (VAD) are preferable for such patients.

- Harvesting of autologous peripheral blood stem cells or bone marrow should be performed early in the patient’s treatment course. The best available data demonstrate that transplantation is most advantageous when performed as part of the initial therapy.
- No conclusions can be reached about the role of interferon alpha following transplantation at this time.

**Update**

- For patients undergoing autologous stem cell transplantation as part of standard therapy, it is recommended that the transplantation regimen include melphalan 200 mg/m$^2$ without total body radiation.
- There is insufficient evidence to recommend a treatment plan that includes two transplants performed in succession (tandem transplantation) outside of a clinical trial.

**Methods**

Entries to MEDLINE (1992 through March 2003), PREM (March 13, 2003), CANCERLIT (1992 through October 2002), and Cochrane Library (2003, Issue 1) databases, abstracts published in the proceedings of the annual meetings of the American Society of Hematology (1997-2002) and the American Society of Clinical Oncology (1999-2002), and the abstracts of the VIIIth International Myeloma Workshop (2001) were systematically searched for evidence relevant to this practice guideline report. The Canadian Medical Association Infobase (January 8, 2003) and the National Guidelines Clearinghouse (January 8, 2003) were also searched for existing evidence-based clinical practice guidelines.

Evidence was selected and reviewed by one member of the Practice Guidelines Initiative Hematology Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Hematology Cancer Disease Site Group, which is comprised of hematologists, medical oncologists, radiation oncologists, methodologists, and two patient representatives.

External review by Ontario practitioners was obtained through a mailed survey for the original practice guideline dated August 10, 1999. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information. This guideline was subsequently updated and reviewed by the Practice Guidelines Coordinating Committee in October 2000.

**Key Evidence**

- An individual patient data meta-analysis of data from 27 randomized trials did not find a significant difference in survival between multi-agent chemotherapy and melphalan plus prednisone (Odds ratio (OR)=0.99; 95% Confidence Interval (CI), 0.93 to 1.05; p=0.6).

- One randomized controlled trial (RCT) found autologous bone marrow transplantation prolonged survival in newly diagnosed patients under the age of 65 with advanced stage disease compared with conventional chemotherapy with interferon alpha (five-year survival, 52% vs. 12%; p=0.03).

- In terms of the specifics of the manoeuvre, an RCT in abstract form comparing bone marrow to peripheral blood stem cell infusion found that neutrophil engraftment was faster for patients receiving peripheral blood stem cells (9.7 days vs. 12.2 days; p<0.001); however, toxic death rates, response rates and two-year survival were not significantly different; an RCT in abstract form that compared high-dose melphalan plus total body irradiation versus high-dose
melphalan did not find a difference in terms of response and two-year event-free survival, but toxicity was significantly greater for patients receiving the total body regimen; two RCTs in abstract form of single versus double bone marrow transplantation did not find a significant difference in progression-free survival or overall survival between the two groups: An RCT on interferon following transplantation found that there was a non-significant trend towards longer median progression-free survival in the patients given interferon (46 months vs. 27 months; p=0.11); however, there was no difference in overall survival.

- One randomized controlled trial on early versus late transplantation found the median survival was 64.6 months for early transplant, and 64 months for late transplantation (p=0.92). The quality of life measure, TWISTT (time-without symptoms, treatment and treatment toxicity) was 27.8 months (95% CI, 23.8 to 31.8) in the early transplant group versus 22.3 months (95% CI, 16.0 to 28.6) in the late transplant group.

- Three non-randomized comparisons of autologous and allogeneic transplantation found autologous transplantation to be less toxic and associated with at least equivalent survival.

**Update**

- In an updated report of the randomized trial comparing combination therapy with melphalan 140 mg/m² and total body radiation with melphalan 200 mg/m² as a single modality, survival at 45 months was superior in the group assigned to receive melphalan 200 mg/m² (65.8% vs. 45.5%; p=0.05). In addition, patients assigned to receive melphalan 200 mg/m² experienced less severe mucositis, required fewer transfusions, and had shorter durations of hospitalization and intravenous antibiotics administration.

- In addition to the single RCT comparing high-dose therapy and stem cell transplantation with conventional chemotherapy identified in the original document, three more RCTs have been published. Two of the four studies reported a survival benefit for patients randomized to receive high-dose therapy and autologous stem cell transplantation.

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For further information about this practice guideline report, please contact Dr. Ralph Meyer, Co-Chair, Hematology Disease Site Group, Juravinski Cancer Centre, 699 Concession Street, Hamilton, Ontario L8V 5C2; TEL 905-575-7820; FAX 905-575-6340 or Dr. K. Imrie, Co-Chair, Hematology Disease Site Group, Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5; TEL (416) 480-4757; FAX (416) 480-6002.

The Practice Guidelines Initiative is sponsored by: Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care

Visit [https://www.cancercare.on.ca/](https://www.cancercare.on.ca/) for all additional Practice Guidelines Initiative reports.
PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

Reference:

For the most current versions of the guideline reports and information about the PEBC, please visit the CCO website at: http://www.cancercare.on.ca
For more information, contact our office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775
E-mail: ccopgi@mcmaster.ca

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