Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-based Series 6-6 Version 2 EDUCATION AND INFORMATION

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 November 2016 put Evidence-based Series (EBS) 6-6 Version 2 in the Education and Information Section. This means that the recommendation will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized 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

PEBC Report Citation (Vancouver Style): Members of the Hematology Cancer Disease Site Group. Optimal therapy for patients diagnosed with multiple myeloma and the role of high-dose chemotherapy and stem cell support. Kouroukis T, Rumble B, reviewers. Toronto (ON): Cancer Care Ontario; 2012 Jan 10 [Endorsed 2011 May 24. Ed &

Education and Information

Info 2016 Nov]. Program in Evidence-based Care Evidence-Based Series No.: 6-6 Version 2 Education and Information 2015.

Journal Citation (Vancouver Style): Imrie K, Esmail R, Meyer RM; Members of the Hematology Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative. The role of high-dose chemotherapy and stem-cell transplantation in patients with multiple myeloma: a practice guideline of the Cancer Care Ontario Practice Guidelines Initiative. *Ann Intern Med* 2002;136(8):619-29.

Education and Information

Table of Contents

Overview
Guideline Report History ii
Guideline Review Summary iii

Summary (October 2003)
Guideline Questions v
Target Population v
Recommendations v
Update vi
Methods vi
Key Evidence vi
Update vii
Contact Information vii
Preamble, Copyright, & Disclaimer viii

FULL REPORT (October 2003)
Questions 1
Choice of Topic and Rationale 1
Methods 2
Results 3
Ongoing Trials 22
DSG Consensus Process 23
External Review 24
Policy Implications 27
Practice Guideline 27
Journal Reference 28
Acknowledgements 28
References 29
EBS 6-6 Document Assessment Review Tool 36

Education and Information

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

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 Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Dec 2000	1992 to 1997	Full Report	Peer reviewed publication web publication	Search updated in 1998, 1999 and 2000
Update Oct 2003	2000 to2003	New data added to original Full Report	Updated web publication	Original recommendations modified
Version 2 May 2011	2003 to 2010	New data found in Document Assessment and Review Tool	Updated web publication	2003 recommendations ENDORSED

Education and Information

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

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.

Education and Information

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.

Education and Information

program in evidence-based care
a cancer care ontario program

programme de soins fondé sur des preuves
un programme de action cancer ontario

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

Education and Information

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

Education and Information

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/m^2 and total body radiation with melphalan 200 mg/m^2 as a single modality, survival at 45 months was superior in the group assigned to receive melphalan 200 mg/m^2 (65.8% vs. 45.5%; p=0.05). In addition, patients assigned to receive melphalan 200 mg/m^2 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.

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/
for all additional Practice Guidelines Initiative reports.

Education and Information

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:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

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

Copyright

This guideline is copyrighted by Cancer Care Ontario; the guideline and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

Education and Information

program in evidence-based care
a cancer care ontario program

programme de soins fondé sur des preuves
un programme de action cancer ontario

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 6-6 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

FULL REPORT

I. 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?

Problem/Scenario

A 58 year old man presents with fatigue, back pain, and weight loss and is diagnosed with multiple myeloma with multiple lytic bone lesions. He is in good general health with normal renal function. He has two living siblings.

II. CHOICE OF TOPIC AND RATIONALE

Multiple myeloma is an aggressive cancer with a median survival time of three years (1). Median survival varies from one year to over five years, depending on the stage of disease. Conventional chemotherapy with oral melphalan and prednisone or multi-agent intravenous chemotherapy can provide effective palliation, but is not curative (2).

Peripheral blood stem cell and bone marrow transplantation have established roles in a number of hematologic malignancies including Hodgkin's disease and non-Hodgkin's lymphoma (3). Case series reports have described encouraging results when patients with myeloma are treated with allogeneic (alloBMT) or autologous bone marrow transplantation (ABMT) (4). These data suggest that transplantation may have an important role in treating patients with myeloma. Stronger evidence evaluating transplantation, including a recently published randomized trial, is emerging (5,6).

Education and Information

It was the impression of members of the Hematology Disease Site Group (DSG) that there are widely disparate practices regarding the use of transplantation for multiple myeloma in different parts of the province. This impression was reinforced by differing availability of transplantation throughout the province. The variability in practice together with emerging evidence of higher quality made the assessment of this topic a priority for the Hematology DSG.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-Based Care, using the methods of the Practice Guidelines Development Cycle[1]. Evidence was selected and reviewed by one member of the PGI's Hematology DSG and methodologists.

The practice guideline report is a convenient and up-to-date source of the best available evidence on multiple myeloma, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey for the original practice guideline dated August 10, 1999. The survey consisted of items asking for ratings on the quality of the draft practice guideline and whether the draft recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of 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 PGCC in October 2000.

Guideline History

This practice guideline report was originally completed on December 22, 2000 and published in *Annals of Internal Medicine*, Vol. 136, No. 8, 2002. The guideline was reviewed in May 2000, December 2000, July 2001, April 2002 and most recently in June 2003.

Literature Search Strategy

MEDLINE, CANCERLIT and the Cochrane Library databases were searched from 1992 to December 1997. This search was updated in October 1998, June 1999, and April 2000. "Multiple myeloma" (MeSH and text word) was combined with "bone marrow transplantation" (MeSH and text word) and drug therapy (MeSH). These terms were then combined with the search terms for the following study designs: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials, controlled clinical trials and comparative studies. In addition, Pubmed, the Physician Data Query (PDQ) database (http://cnetdb.nci.nih.gov/trialsrch.shtml), relevant conference proceedings (American Society of Hematology, 1997, 1998, 1999 and American Society of Clinical Oncology, 1999), article bibliographies and personal files were reviewed. To address the issue of optimal chemotherapy, an additional search was performed of the same databases using "multiple myeloma" (MeSH) combined with "randomized controlled trials" (MeSH) and the text word "random:" in the title.

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):505-12.

For education and information

Update

The original literature search has been updated using MEDLINE (Ovid) (through March 2003), Medline® In-Process & Other Non-Indexed Citations (formerly known as PreMedline) (PREM) (March 13, 2003), CANCERLIT (Ovid) (through October 2002), the Cochrane Library (2003, Issue 1), the proceedings of the annual meetings of the American Society of Clinical Oncology (2000 to 2002) and the American Society of Hematology (2001 and 2002), and the abstracts of the VIIIth International Myeloma Workshop. The PDQ (http://www.cancer.gov/search/clinical_trials/) (January 8 and 9, 2003), National Institutes of Health *Clinical Trials.gov* (http://clinicaltrials.gov/) (January 21, 2003), United Kingdom Coordinating Committee on Cancer Research Register (http://www.ctu.mrc.ac.uk/ukcccr/register_new.htm) (January 21, 2003), and European Organization for Research and Treatment of Cancer (http://www.eortc.be/) (January 21, 2003) clinical trials databases were also searched to determine the status of the ongoing trials reported in the original practice guideline report and to search for any new ongoing trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) (January 8, 2003) and the National Guidelines Clearinghouse (http://www.guideline.gov/body_home_nf.asp?view=home) (January 8, 2003) were searched for existing evidence-based practice guidelines. Personal files were also reviewed; in May 2003, the fully published results (23u) of the Medical Research Council (MRC) Myeloma VII trial (4u, 5u) trial became available, so we included the trial in the June 2003 update.

Inclusion Criteria

Articles were selected based on the following criteria:

1. Randomized controlled trials (RCTs) of patients with multiple myeloma that reported on the outcomes of survival and/or quality of life.
2. Non-randomized trials were included if they had appropriate contemporaneous control groups and reported on the outcomes of survival and/or quality of life.

Study results were used to estimate both the potential efficacy and appropriate timing of autologous and allogeneic transplantation. Meta-analyses, systematic reviews and economic analyses were also included. Because of insufficient data addressing the specifics of the transplant manoeuvre and which patients would be most likely to benefit from transplantation, a second literature search was performed to include data from single-arm studies.

Update

As of the June 2003 guideline update, only RCT data will be included except for the questions addressing the relative efficacy of autologous and allogeneic transplantation and pre-transplant chemotherapy. In addition, updated data for nonrandomized trials already included in the guideline will be reported.

Synthesizing the Evidence

As the nine randomized controlled trials on transplantation addressed different questions, statistical pooling of data was not attempted.

Update

The DSG recognizes that the pooling of data comparing standard-dose therapy with high-dose therapy and autologous transplantation may be feasible. The DSG will review whether conducting a published data meta-analysis is appropriate when the results of recently reported abstract publications are reported in article form.

IV. RESULTS

Literature Search Results

Sixty-nine papers met the criteria for inclusion (Table 1). Four meta-analyses, one comparing multi-agent chemotherapy to melphalan and prednisone (2), the second individual patient

Education and Information

data meta-analysis of 27 trials that compared combination chemotherapy versus melphalan and prednisone (7), and two evaluating the role of interferon were identified (8,9). Thirty randomized controlled trials comparing multi-agent chemotherapy to melphalan and prednisone were identified (10-43). Twenty-seven of these were included in the individual patient data meta-analysis (7). Three economic analyses were also found (47,63,64). Nine additional randomized controlled trials were identified (5,44,51-56,65). Two RCTs (5,44), one of which was an abstract (44), compared ABMT versus conventional chemotherapy and addressed the question of who should be transplanted. Six RCTs addressed the question of specifics of the manoeuvre (51-56), five of which were in abstract form (51-55). Of these six, one compared bone marrow to peripheral blood as a source of stem cells (51), one compared CD34+ selected versus unselected autologous peripheral blood progenitor cells (52), one assessed the role of total body irradiation (53), two trials compared single versus double autologous transplants (54,55), and one trial addressed the role of interferon following transplantation therapy (56). One RCT compared bone marrow versus peripheral blood stem cell transplantation published in abstract form (65). Nineteen non-randomized comparative studies were found: three studies on autologous transplantation versus conventional chemotherapy (6,45,46), three studies on the relative place of allogeneic and autologous transplantation (48-50), four studies on age of patients and transplantation (57-60), one of which is published in abstract form (60), one study of melphalan and stem cell support (66) and one comparing early versus delayed autologous transplantation published in abstract form (67), and seven studies (68-74) addressing the issue of age or renal function in autologous transplantation, five of which are published in abstract form (69,70,72-74). Four single-arm studies were found: two addressed the effect of prior chemotherapy on the yield of stem cell collection (61,62) and the other two, published in abstract form (75,76), addressed the upper age limit for transplantation.

Table 1. Evidence included in the practice guideline report.

Question	Papers identified (reference)*
(a) What is optimal conventional chemotherapy?	4 Meta-analyses (2,7,8,9) , 30 RCTs (10-43) Update: 2 RCTs (15u, 17u), one (17u) updating an RCT in the original guideline
(b) Transplantation versus chemotherapy	2 RCT (5,44), 3 NRC (6,45,46), 1 Economic analysis (47) Update: 4 RCTs in 8 reports (3 articles and 5 abstracts) (18u, 19u, 23u, 1u-5u); 1 cohort study (article) (26u) updating an NRC in the original guideline
(c) Relative efficacy of autologous & allogeneic transplantation	3 NRC (48-50) Update: 1 NRC (article) (24u)
(d) Specifics of the manoeuvre	6 RCT (51-56), 4 NRC (57-60), 2 SAS (61,62), 2 Economic analyses (63,64) Update: 8 RCTs in 13 reports (4 articles and 9 abstracts) (19u-22u; 6u-14u, 16u); 1 NRC (article) (25u)
(e) When should it be done?	1 RCT (65), 2 NRC (66,67) Update: no reports identified.
(f) Who should be transplanted?	2 RCT (5,44), 7 NRC (68-74), 2 SAS (74,75) Update: no reports identified.

Note: RCT, Randomized controlled trial; NRC, Non-randomized comparison; SAS, Single-arm study
* Some references in the Update section are multiple reportings of the same trial.

In each section below, we describe the studies, summarize the results and provide an interpretative summary.

Update

From the updating process, 26 relevant reports were identified and included 22 reports of results from randomized trials (16 published in abstract form (1u-15u,16u) and seven published in article form (17u-23u)), two retrospective cohort comparisons published in article form (24u,25u),

Education and Information

and one cohort study (26u). The cohort study was included because it updated results from a non-randomized comparison reported in the original guideline. The article by Attal and Harousseau (19u), considered a full report but is published in a non-peer-reviewed journal, contains results of four randomized trials included in this guideline. Also included are studies that were originally identified as ongoing trials but now have available data (1u,4u,5u,8u,9u,13u-16u,18u,19u,22u,23u) All included studies are categorized by study question and are referenced in Table 1. The present version of the guideline consolidates the original and update tables in each section, seen in previous updates of this guideline, into one table for that section.

Quality Assessment
Update

Of the RCTs located in the June 2003 guideline update (14u-19u,23u), one trial (23u) indicated that a minimization algorithm was used for randomization, but no other trials reported information on the randomization method or procedure. No trials provided any, or adequate, information on allocation concealment or any information on blinding. Seven trials (15u,17u,19u) indicate that patient characteristics were similar or listed the similar characteristics between randomized groups, two trials (18u,23u) provided the baseline characteristics without indicating whether the groups were similar, one trial (16u, abstract) only provided information on median age and gender, and one trial (14u, abstract) did not provide information on patient characteristics between groups. Use of a power calculation was stated in two trials (18u,23u), but the studies may not have been sufficiently powered for the analysis of those outcomes. Five trials (14u,17u,18u, 19u[IFM9401 trial],23u) provided enough information to indicate that an intention-to-treat analysis was used, but only two trials (17u,19u[IFM9401]) indicated that all randomized patients were analyzed for at least one outcome. Information on withdrawals, patient exclusions, and protocol adherence was more extensively reported in some trials (17u,18u,23u); three trials that provided minimal (e.g., reasons for inevaluable patients for one outcome) or no information were in abstract form (14u-16u). One report of four trials (19u) provided some information (e.g., eligibility for randomization or patients who received allocated therapy). One trial (23u) was funded in part by a pharmaceutical company, three trials (14u,17u,18u) had funding from non-pharmaceutical agencies, and five trials (15u,16u,19u) did not report funding information. Of all those trials, five (14u,17u,19u) were updated reports of trials reported in the original guideline.

(a) What is the optimal chemotherapy for patients with multiple myeloma?

To properly compare transplantation to conventional chemotherapy, we have attempted to define the optimal conventional chemotherapy. Melphalan plus prednisone has been standard therapy for myeloma for over 25 years (1). Patients treated with this regimen have a median survival time of about three years. In an effort to improve outcome, more aggressive multi-drug regimens have been developed. These regimens generally consist of a combination of one or more alkylating agents (usually melphalan, BCNU, or cyclophosphamide) in combination with vincristine, and an anthracycline. Evidence from one individual patient data meta-analysis of 27 trials, one meta-analysis of 18 trials, an overview on interferon, and one meta-analysis on the role of maintenance treatment with interferon are discussed below.

Chemotherapy meta-analyses

An individual patient data meta-analysis of 27 trials comparing combination chemotherapy versus melphalan and prednisone was recently published by the Myeloma Trialists' Collaborative Group (7). Individual patient data were supplied from 20 of the trials (4930 patients) (10,11,15,16, 20,24-42), including one unpublished trial (IMMSG M-80). Published data were abstracted from reports of seven of the trials (1703 patients) (12-14,17-19,23). Data could not be obtained from three trials (553 patients) (20,21,40). Overall, there was no significant difference in survival between patients allocated to combination chemotherapy versus melphalan and prednisone. The

Education and Information

proportional reduction in the annual odds of death was 1.5% in favour of combination chemotherapy (95% CI, -8% to 5%; p=0.6). This translated into an odds ratio (OR) of 0.99 (95% Confidence Interval (CI), 0.93 to 1.05-reviewer's calculations). There was also no difference between the results of trials with individual patient data (OR=0.98; 95% CI, 0.92 to 1.04) and those for which published data were used (OR=1.03; 95% CI, 0.83 to 1.25, χ^2 for interaction=0.2; p=0.7). The test for heterogeneity was not significant (27 trials, χ^2=31.9 with 26 degrees of freedom; p=0.2). The response rates were significantly higher with combination chemotherapy than with melphalan and prednisone (60.0% versus [vs.] 53.2%; p<0.00001).

A literature-based meta-analysis of 18 trials comparing melphalan and prednisone to combination chemotherapy was published by Gregory et al (2). That meta-analysis found that more aggressive multi-drug combination chemotherapy results in similar survival to melphalan and prednisone (OR=1.04; 95% CI, 0.90 to 1.19; p=0.61).

Interferon meta-analyses

In an overview of 24 randomized trials published in abstract form (8), interferon increased recurrence-free survival by six months. The improvement in three-year survival was modest (4%). However, this slight clinical benefit must be weighed against cost (both financial and quality of life).

In a meta-analysis by Trippoli et al (9), survival was measured by a unique measure called the 'mean lifetime survival'. Its method of analysis and interpretation is available in the paper (8). Using this survival endpoint, there was no significant improvement in survival between treated patients and controls (IFN=3.9 years vs. Control=3.4 years; p=0.095).

Interpretive summary

No compelling evidence exists to indicate that a specific chemotherapy regimen is associated with a survival advantage in patients with myeloma. It is unlikely that melphalan plus prednisone is superior to multi-agent chemotherapy, particularly for patients with poor prognosis disease. For the purpose of assessing trials of transplantation, we consider multi-agent chemotherapy and melphalan and prednisone to be equivalent and that either regimen is an appropriate control group for randomized trials. There is no significant improvement in survival with the use of interferon.

Update

Chemotherapy trials

This topic was evaluated in the June 2003 update. Poenisch et al (15u) report in abstract form the results of the East German Study Group for Hematology/Oncology trial where 136 patients with myeloma in stage II in progression or stage III were randomized to bendamustine plus prednisone (BP) or melphalan plus prednisone (MP). No differences in probability of survival at 60 months post-diagnosis (BP, 28%, vs. MP, 23%, p=0.72) or response rates (75% vs. 68%, p=not provided; n=131) were detected between groups, but complete remissions were higher in the BP arm (32% vs. 11%, p<0.003).

Data to October 31, 1998 for surviving patients from an RCT included in the individual patient meta-analysis in the original guideline report (38) were updated in a subsequent full report (17u); median survival was 32 versus 25 months and partial response was 45% versus 31.5% for the combination chemotherapy and melphalan plus prednisone groups, respectively (no p values between groups provided).

Interpretive Summary

The original interpretation remains current.

(b) In terms of survival, is peripheral blood stem cell or autologous bone marrow transplantation (ABMT) better than conventional chemotherapy?

Education and Information

Randomized controlled trials

The IFN 90 randomized trial published by Attal et al (5) compared conventional chemotherapy (n=100) with ABMT (n=100) in 200 previously untreated patients less than 65 years of age with clinical stage II and III myeloma. Those with another malignancy, poor cardiac, hepatic, or respiratory function, or psychiatric disease were excluded. Poor performance status and renal dysfunction were not reasons for exclusion at study entry, but did preclude transplantation if these did not improve after the fourth cycle of chemotherapy. Randomization occurred prior to any therapy. Conventional therapy consisted of 12 months of multi-agent chemotherapy with VMCP/BVAP (vincristine, melphalan, cyclophosphamide, and prednisone/ vincristine, carmustine, doxorubicin and prednisone) with interferon alpha three million units/m^2 three times weekly starting at cycle nine of chemotherapy and continuing until relapse. Patients randomized to transplantation received four to six cycles of VMCP/BVAP chemotherapy. Patients with a good performance status, serum creatinine of less than 150 µmol/L and an adequate bone marrow harvest collected after the fourth cycle of chemotherapy received a preparation regimen of melphalan 140 mg/kg and total body irradiation consisting of a total of 800 cGy in daily fractions over four days followed by re-infusion of autologous bone marrow. Interferon alpha three million units three times weekly was administered following hematologic recovery. The data were analysed according to an intention-to-treat model. Quality of life data were not presented.

Seventy-four of the 100 patients assigned to transplantation completed therapy. Reasons for non-completion were insufficient bone marrow harvest (n=10), poor performance status (n=6), abnormal renal function (n=5), and premature death (n=5). Overall survival, median survival and response-to-treatment were all significantly better with ABMT (Table 2). A multivariate analysis showed that event-free survival correlated significantly with the pre-treatment β-2 microglobulin ($p<0.001$) level and with treatment assignment ($p=0.01$). Survival correlated only with the pre-treatment β-2 microglobulin level ($p<0.001$). In patients under the age of 60 years, survival was correlated with both treatment assignment and β-2 microglobulin level. In patients over the age of 60, this correlation was not found.

In a randomized controlled trial published in abstract form (44), with a median follow-up of 56 months, median event-free survival and overall median survival were not significantly different for patients aged 55-65 with multiple myeloma who received high-dose therapy and autologous blood stem cell transplantation versus conventional treatment (VMCP regimen) (Table 2).

Non-randomized comparisons (NRCs)

Three non-randomized studies (6,45,46) were identified which compared ABMT or peripheral blood stem cell transplant with controls or conventional therapy. All three found that survival was superior for patients who received autologous bone marrow or peripheral blood stem cell transplantation compared with controls (Table 2).

Table 2. Comparison of peripheral blood stem cell or marrow transplantation-results from RCTs and NRCs.

Study	Treatment # patients	Control # patients	Response-to-Treatment*	Median event-free survival*	Overall survival (OS)*
Randomized Controlled Trials: Original Guideline					
Attal (5) full paper	ABMT n=100	Conventional chemotherapy (VMCP/BVAP) with interferon alpha n=100	81% vs. 57%** p<0.001	At five years 28% vs. 10% p=0.01	52% vs. 12% at five years p=0.03
Fermand (44) abstract	ABSC and high-dose therapy	Conventional treatment (VMCP) n=96	NR	At 56 mo, 24.3 mo vs. 18.7 mo	Median OS:55.3 mo vs. 50.4 mo p=0.98

For evaluation purposes only

	n=94			p=0.07	
Study	**Treatment # patients**	**Control # patients**	**Response-to-Treatment***	**Median event-free survival***	**Overall survival (OS)***
Randomized Controlled Trials: UPDATE					
Segeren (18u) full paper	IDM+cyclo +TBI+stem cell rescue n=132	IDM n=129	95% vs. 88%** p=NR; 29% vs. 13%, p=0.002 (CR only)	22 vs. 21 mo (p=0.28)	Median OS: 47 vs. 50 mo (p=0.41)
Attal (19u) full paper	ABMT n=100	Conventional chemotherapy (VMCP/BVAP) with interferon alpha n=100	38% vs. 14% p<0.001 (CR+VGPR)	28 mo vs. 18 mo	Median OS: 57 mo vs. 44 mo

Study	**Treatment # patients**	**Control # patients**	**Response-to-Treatment***	**Median event-free survival***	**Overall survival (OS)***
				Median progression-free survival*	**Median overall survival***
Blade (3u) Abstract	HDT/SCT n=81	Conventional chemotherapy (BVMCP/VBAD) n=83	30% vs. 11% p=0.002 (CR)	42.5 mo vs. 34.3 mo p=0.39 (median follow-up of 42 mo)	67.4 mo vs. 66.9 mo p=0.40
Child (23u) Full report	C-VAMP+ HDmel/ PBSC n=201	ABCM n=200	CR: 44% vs. 8% (p<0.001) PR: 42% vs. 40% (p=0.72)	31.6 mo vs. 19.6 mo; p<0.001	54.1 mo vs. 42.3 mo p=0.04
Non-Randomized Comparisons: Original guideline					
				Median event-free survival*	**Overall survival***
Barlogie (6) full paper	ABMT n=123	matched patients received conventional therapy (n=116)	85% vs. 52% (partial response) p=0.0001	NR	62+mo vs. 48 mo p=0.01 61% vs. 39% at five years
Lenhoff (45) full paper	ABSC n=274	Historical control group n=274	41% CR 48% PR vs. NR	median survival not reached vs. 44 mo p<0.01	NR
Musto (46) abstract	PBST n=29	matched control group n=40	34% vs. 5% p<0.01	DFS 33 mo vs. 11 mo p<0.02	49 mo vs. 25 mo p<0.03

Note: ABCM=adriamycin, carmustine, cyclophosphamide (cyclo), and melphalan; ABMT,autologous bone marrow transplantation; ABSC,autologous blood stem cell transplantation; BVAP, vincristine, carmustine, doxorubicin and prednisone; CR,complete response; C-VAMP+HDmel/PBSC=cyclo, vincristine, adriamycin, and methyl-prednisolone followed by high-dose melphalan (mel) with peripheral blood stem cell support; DFS, disease-free survival; EFS=event-free survival; HDT/SCT=high-dose therapy/stem cell rescue (mel 140mg/m2 and total body irradiaton (TBI) of 12 Gy or mel 200 mg/m^2 followed by peripheral blood stem cell infusion); IDM+cyclo+TBI+stem cell rescue=mel 140 mg/m^2 divided in two doses of 70 mg/m^2 (IDM) + cyclo 120 mg/kg and TBI with stem cell rescue; mo=months; PR, partial response; NR, not reported; PBST, peripheral blood stem cell transplantation; vs., versus; VCMP, vincristine, mel, cyclo, and prednisone; VGPR=very good partial response indicating a 90% decrease in serum paraprotein; UPDATE=trials found during updating process.

*Data reported as treatment versus control.

**Complete and partial response.

Publication and Information

Economic analysis

A cost-effectiveness analysis using survival data reported in five large published randomized controlled trials on induction treatment evaluated the incremental cost-effectiveness ratio [the ratio of incremental cost and incremental effectiveness (where incremental cost is the lifetime cost difference between treated patients and controls, and incremental effectiveness is the lifetime survival difference between the two patient groups)] (47). The mean lifetime duration of survival was 3.47 years for melphalan at conventional doses without interferon, 3.74 years for melphalan at conventional doses with interferon and 7.28 years for ABMT. Survival was significantly better for patients undergoing ABMT versus melphalan treatment (Relative risk reduction=54%, 95% Confidence Interval, 46% to 59%; $p<0.05$). Survival after combined melphalan and interferon treatment was not significantly different from melphalan alone ($p>0.05$). The marginal cost-effectiveness ratio of autologous transplantation was approximately an additional $26 000 per life year gained compared with conventional treatment with melphalan.

Economic analyses based on trials that collect data on cost as part of their primary data collection are less susceptible to methodological errors. This economic analysis collected and pooled data from information available in the published literature. Based on the critical appraisal done by the Guidelines Initiative, we have determined it to be methodologically rigorous (77). Therefore, the impact of ABMT compared with conventional treatment with melphalan can be considered to be favourable in terms of cost-effectiveness ratio.

Interpretive summary

Based on the results from the two RCTs (5,44), ABMT results in prolonged progression-free survival and overall survival compared with conventional chemotherapy for newly diagnosed patients under the age of 65 with advanced stage myeloma. However, a subset analysis conducted on data from Attal's randomized controlled trial showed that the survival benefit was confined to patients < 60 years of age. The second randomized controlled trial (44) did not show a benefit for high-dose therapy and ABMT in older patients, however longer follow-up is needed. The impact of autologous transplantation on quality of life remains unclear. The DSG recognized that the conclusion to recommend autologous transplantation was based on one RCT. The results of the second RCT, presented in abstract form, required that this conclusion be reconsidered. The DSG concluded that assessment of more mature results of the Fermand study, presented in full article form for more comprehensive evaluation, are needed before modifying the current recommendation.

Update

Five abstracts (1u-5u) and three full reports (18u,19u,23u) of four RCTs comparing transplantation with standard-dose chemotherapy were identified (Table 2). One full report of a cohort study (26u) was identified; this study updates data of a previously published non-randomized comparison included in the original guideline.

Randomized controlled trials

Child et al conducted the MRC Myeloma VII randomized trial comparing C-VAMP plus high-dose melphalan and peripheral blood stem cell support (intensive treatment) with ABCM (standard treatment); interferon-alpha maintenance therapy was planned in both groups. Two abstracts (4u,5u) and one full paper (23u) report data from this trial; only data from the full report (23u) will be presented. Four hundred and seven previously untreated patients less than 65 years of age were randomized; the stage of myeloma was not provided. Fifty patients in the intensive treatment group did not receive high-dose melphalan and transplantation, some because of early disease progression; before the transplantation, eight patients in that group received total body irradiation plus melphalan in lieu of high-dose melphalan. Thirty-four patients in the standard treatment arm received an autograft or allograft. Four hundred and one patients were included in the intention-to-treat analysis. The study was powered for 10% absolute increase in survival, which was not

Publication Information

reached: absolute improvement was 9% (94 deaths [intensive] vs. 122 deaths [standard]). The median progression-free survival (n=395) and the median overall survival were significantly longer in the intensive treatment group (Table 2). No data were provided on whether age was a prognostic factor, and the authors did not analyze outcomes in age subgroups.

Blade et al (3u) reported in abstract form the results of a randomized trial conducted by the Spanish Cooperative Group, PETHEMA, comparing high-dose therapy and autologous transplantation with conventional chemotherapy. Previously untreated patients with stage II or III myeloma and an ECOG performance status of less than 3 initially received four courses of alternating BVMCP/VBAD. The median age of the enrolled patients was 56 years. Responding patients were then randomized to receive eight additional courses of that chemotherapy, or to a transplantation strategy consisting of either melphalan 140 mg/m^2 and total body radiation (12 Gy) or melphalan 200 mg/m^2. Maintenance therapy consisting of interferon alpha and dexamethasone was administered in both arms. From the initial cohort of 216 patients, 185 responded to initial chemotherapy and 164 were randomized (83 to the chemotherapy arm and 81 to autologous transplantation). Results are shown in Table 2; no differences in median progression-free or overall survival were detected.

Attal and Harousseau (19u) updated the results from the IFM 90 trial reported in the original guideline (5). Patients allocated to ABMT had significantly better response rates than those allocated to conventional chemotherapy (Table 2). Seven-year event-free and overall survival rates for treatment versus control were 16% versus 8% and 43% versus 25%, respectively. Median event-free and median overall survivals were also provided (Table 2). Event-free (p=0.01) and overall (p=0.03) survivals were significantly better with ABMT, but it is not clear whether the p values correspond to the median survival or the seven-year analyses or both.

Segeren et al (1u,2u,18u) randomized 268 previously untreated, stage II or III patients to melphalan without stem cell support or a "myeloablative" strategy (cyclophosphamide, melphalan, total body radiation and autologous stem cell transplantation) in a HOVON group trial (Table 2). Median age of enrolled patients (n=379) was 55 years. By intention-to-treat analysis (n=261), no differences in median overall or median event-free survival were detected between groups, but the myeloablative group had significantly better complete response (Table 2) (18u). The analysis may not have been sufficiently powered to detect a difference in event-free survival because only one of two factors used in the power calculation was met.

Cohort study

Barlogie et al (26u) provided updated results of their previously published non-randomized trial; however, no comparison group was included in the updated report. Of 231 patients (median age 51 years and 53% stage III), 195 received at least one autologous transplantation and 151 in sustained partial remission or complete remission received a second autologous transplantation, while 14 received an allotransplantation after the autotransplantation. In all 231 patients, median overall survival was 68 months, and median time to relapse/progression was 52 months. Complete and partial remission was 83%.

Interpretive Summary

In the two RCTs published in full paper form comparing ASCT to conventional therapy (19u, 23u), survival was superior with transplantation. Two RCTs in abstract form (44, 3u) did not demonstrate a survival benefit, and one study (18u) was not felt to contribute to the analysis as it compared high-dose therapy plus stem cell support with high-dose therapy alone.

(c) What is the relative efficacy of autologous and allogeneic transplantation?

Randomized trials comparing autologous and allogeneic transplantation have not been published. Three non-randomized comparisons have been found (Table 3).

Education and Information

Non-randomized comparisons

One retrospective study with a matched case-control design compared the outcome of allogeneic and autologous transplants reported to the European Bone Marrow Transplant Registry (EBMTR) (48). Among cases reported to the Registry, 189 allogeneic sibling donor transplants were matched for gender and extent of prior chemotherapy with an equal number of autologous stem cell transplants. The allogeneic bone marrow transplants (alloBMT) took place between 1983 and 1994, while the autologous transplants were done between 1986 and 1994. The alloBMT patients were significantly younger than patients who underwent autologous stem cell transplantation (ASCT) (median 43 vs. 49 years; p=0.0001). Several different high-dose therapy regimens and graft-versus-host disease prophylaxis protocols were used. Alpha interferon was given to 96 (51%) ASCT patients but only nine (5%) alloBMT patients. The median survival was significantly longer for ASCT compared with alloBMT (34 months vs. 18 months; p=0.001). The overall survival at 24 months was 70% vs. 47% and at 72 months was 34% vs. 30% (estimated from curves). Treatment-related mortality for alloBMT was 41% compared with 13% for ASCT (p=0.0001) while the relapse rate was higher for ASCT (70% vs. 50% at 48 months; p=0.04). Treatment-related mortality with ASCT improved over the period observed (35% in 1986-89 and 7% in 1992-94), while there was no significant improvement in treatment-related mortality for alloBMT (40% from 1983-87 and 38% 1992-94).

Varterasian et al compared the outcome of 24 consecutive ASCTs performed for myeloma with 24 alloBMTs performed during the same time period in the same institutions (49). The reasons for assignment to ASCT or alloBMT were not detailed. The alloBMT patients were younger and had a shorter interval from diagnosis to transplantation. Six deaths in the allogeneic transplant group versus two deaths in the autologous transplant group occurred within 90 days of transplant. There was no difference in event-free survival (16.7 months vs. 31 months; p=0.854) or median overall survival (33.5 months vs. 38.6 months; p=0.7637). At 46 months, the overall survival was 32% vs. 44% between the two groups (estimated from curves), despite more favourable baseline characteristics in the alloBMT patients.

Couban et al compared the outcome of 40 consecutive patients undergoing autologous blood or marrow transplantation with 22 consecutive patients undergoing alloBMT in the same institution (50). The reasons for assignment to autologous or allogeneic transplantation were not detailed. There were no significant differences in baseline characteristics between the two groups. Survival was significantly longer for those undergoing autologous transplantation.

Table 3. Comparison of autologous and allogeneic transplantation from NRCs.

Study	Autologous (PBST/ASCT) # patients	Allogeneic (alloABMT) # patients	Median survival*	Overall Survival*
Bjorkstrand (48) full paper	189	189	34 months vs. 18 months p=0.001	At 72 months, 34% vs. 30%** p=0.001
Varterasian (49) full paper	24	24	33.5 months vs. 38.6 months p=0.7637	At 46 months, 32% vs. 44%** p=0.7637
Couban (50) full paper	40	22	48+ months vs. 7 months p<0.0002	At 3 years, 74% ± 11% vs. 32% ± 10% p=NR

Note: PBSC, peripheral blood stem cell transplantation; NR, not reported
*Data reported as autologous versus allogeneic.
**Estimated from the survival curves.

Education and Information Division

Interpretive summary

On the basis of the limited evidence available, overall survival following autologous transplantation is comparable to the overall survival following allogeneic transplantation and may in fact be longer. In view of the greater toxicity of allogeneic transplantation, it is reasonable to recommend autologous transplantation. Allogeneic transplantation is not recommended outside a clinical trial.

Update

The European Group for Blood and Marrow Transplantation (24u) reported the results of a retrospective cohort comparison evaluating myeloma patients who underwent allogeneic transplantation during different periods of time. As reported in our original guideline, that Group has previously conducted a similar retrospective analysis (48), which demonstrated superior overall survival in patients receiving an autologous as compared with an allogeneic transplant. The present study included a comparison of patients undergoing allogeneic bone marrow transplantation between 1983 and 1993 (group 1; 334 patients), or 1994 and 1998 (group 2; 223 patients), and a group receiving a transplantation with allogeneic peripheral blood stem cells between 1994 and 1998 (group 3; 133 patients). In comparison with group 1, patients in group 2 experienced less treatment-related mortality at six months (38% vs. 21%) and two years (46% vs 30%) and had a superior median overall survival ($p < 0.0001$). A comparison of groups 2 and 3 patients failed to detect differences in treatment-related mortality, median overall survival, or rate of relapse from a complete remission. Outcomes of a group undergoing autologous transplantation were not included in the analysis.

Interpretive Summary

This analysis suggests that outcomes with allogeneic transplantation have improved over time. However, treatment-related mortality continues to be significant problem and no comparisons have demonstrated superior survival in comparison with a group undergoing autologous transplantation.

(d) What specifics of the transplant manoeuvre can be recommended?

Autologous transplantation is a complex procedure with a number of distinct components. We attempted to evaluate the optimal pre-transplant chemotherapy, source of stem cells, role of purging or selection, high-dose therapy regimen, supportive care, single versus double transplants, and post-transplant therapy.

Pre-transplant chemotherapy

Chemotherapy may adversely affect the ability to harvest bone marrow stem cells and therefore might adversely affect engraftment of autologous stem cells (78). This concern has been particularly suggested with respect to therapy with alkylating agents such as melphalan. The impact of prior chemotherapy exposure on the yield of bone marrow harvest has not been addressed in randomized controlled trials. In the randomized controlled trial discussed previously (5), four to six cycles of alkylating-agent-based chemotherapy (BVAP/VMCP) were given prior to bone marrow harvest. Ten percent of eligible patients did not have sufficient marrow collected to permit transplantation. Conclusions cannot be drawn on the effect of chemotherapy on bone marrow harvesting from this study.

Case series

Two case series have addressed the effect of cumulative alkylating agent exposure on the quality of peripheral blood stem cell collection (61,62).

Tricot et al performed a multivariable analysis of factors predicting engraftment in 225 patients undergoing double-autologous transplantation for myeloma (61). Three hundred and sixty-

For Information and Interpretation

four consecutive patients with multiple myeloma were enrolled in the study of autologous transplantation at a single institution. Newly diagnosed patients (45%) and previously treated patients were included. The engraftment kinetics of the 225 patients who underwent transplantation were reported. Peripheral blood stem cells were mobilized using high-dose cyclophosphamide and granulocyte-macrophage colony-stimulating factor (GM-CSF). The target cell dose was $6x10^8$ mononuclear cells/kg. No minimum CD34 positive cell dose was used. Patients with marginal peripheral blood stem cell yield enrolled before July 1993 received both peripheral blood stem cells and bone marrow. High-dose therapy for transplantation consisted of melphalan (200 mg/m^2). The primary end-points of the study were time to engraftment of platelets (>$50x10^9$/L) and granulocytes (>0.5 $x10^9$/L). Time-to-engraftment of both granulocytes and platelets was inversely correlated with extent of alkylating agent exposure (any exposure for granulocytes, and >1 month for platelets).

Prince et al evaluated the impact of extent of melphalan exposure on the ability to harvest peripheral blood stem cells (62). Fifty-four consecutive peripheral blood stem cell collections in 37 patients were reviewed. All patients had multiple myeloma and were 65 years of age or younger. Peripheral blood stem cells were collected after administration of cyclophosphamide (4 g/m^2) and either GM-CSF or sequential interleukin 3 and GM-CSF. Treatment was defined by local policies which changed over time. The primary end points were number of granulocyte macrophage colony forming units (CFU-GM) per collection and proportion of patients with a collection exceeding 10 x 10^4 CFU-GM/kg. The extent of melphalan exposure adversely affected the ability to collect stem cells. Only 32% of patients given more than four courses of melphalan had collections that met or exceeded the threshold value compared with 85% for those who had received zero to four courses (p=0.001).

Interpretive summary

The effect of prior alkylating agent exposure on bone marrow harvesting is not clear. However, alkylating agent exposure adversely affects peripheral blood stem cell yield and engraftment following ASCT. If stem cell transplantation is considered, patients should not be given extensive exposure to melphalan or other alkylating agents prior to stem cell collection. High-dose glucocorticoid-based regimens such as VAD (vincristine, doxorubicin [Adriamycin], dexamethasone) may be preferable for such patients.

Source of stem cells: bone marrow versus peripheral blood

Peripheral blood stem cells (PBSC) are replacing bone marrow as the principal source of stem cells for use in ABMT. The use of peripheral blood stem cells results in faster engraftment of both neutrophils and platelets (79). In myeloma it has been suggested that the use of (PBSC) could improve survival post-transplant because of reduced contamination with malignant cells of the autograft (80).

Randomized controlled trial

One randomized trial comparing bone marrow to peripheral blood as a source of stem cells has been published in abstract form (51). Three hundred and thirty-three patients were randomized to receive peripheral blood stem cells (n=133) or bone marrow (n=89). Neutrophil engraftment was faster for patients receiving peripheral blood (9.7 days vs. 12.2 days; p<0.001), however, toxic death (n=1 vs. n= 3); response rates and two-year survival were not significantly different.

Non-randomized comparisons

The same authors of the randomized controlled trial described above (51) published an earlier non-randomized comparison of bone marrow and PBSC which yielded similar results (57).

An additional comparison of PBSC with bone marrow-derived stem cells for myeloma was conducted on 63 patients with multiple myeloma (58). Twenty-six patients received autologous bone marrow transplantation and 37 received peripheral blood stem cell transplantation. This study found

Education and Information

a significant acceleration of engraftment (19 days vs. 33 days; p=0.0015) for PBSC as compared with autologous transplantation without improvement in transplant-related mortality or survival.

A retrospective analysis of 123 patients who received transplants of either bone marrow or peripheral blood stem cells performed for multiple myeloma or breast cancer was performed (59).

Patients undergoing peripheral blood stem cell transplantation had faster engraftment, the requirement for transfusions of red blood cells and platelets was reduced, and the number of days needed in the hospital was significantly lower. There was no difference in the frequency of infectious complications between the two groups, but the number of days with fever and with antibiotic treatment were significantly lower in the peripheral blood stem cell transplantation patients.

Economic analyses

Two studies assessing economic endpoints have addressed this topic. Duncan et al performed a cost-minimization analysis to compare PBSC transplantation with ABMT (63) and Powles et al included costing data in a non-randomized comparison that assessed tolerance in interferon post-transplant as its primary outcome parameter (64). Both analyses demonstrated that PBSC transplantation had economic advantages when compared with ABMT.

Interpretive summary

These findings are compatible with data from other diseases which suggest that while engraftment is accelerated with peripheral blood stem cells, no difference in relapse rate is observed. Bone marrow or PBSC are acceptable sources of stem cells for transplantation in myeloma. Outcomes that assess clinical efficiency, other than patient survival, should guide the choice of treatment. Based on the limited data suggesting more rapid engraftment and an economic advantage with PBSC, with no apparent loss of efficacy, the DSG favoured the use of PBSCs as the source of stem cells.

Update

Attal and Harousseau (19u) provide updated results of the IFM 9401 trial reported in the original guideline (51). Four hundred and three previously untreated patients less than 60 years of age were initially randomized at diagnosis to single or double autologous transplantation and then randomized three months after diagnosis to bone marrow (n=163) or PBSC (n=180); all patients in the second randomization (n=343) were analyzed for at least most of the outcomes. When bone marrow was compared with PBSC, no differences in response rate (data not provided), six-year event-free survival (21% vs. 26%; p=not significant), or six-year overall survival (37% vs. 50%; p=0.07) were detected.

Interpretive summary

There remains relatively scant data directly comparing peripheral blood with bone marrow as a source of stem cells for transplantation. The available data is consistent with that in other diseases: there appears to be no difference in long-term outcome, but engraftment with PBSC appears to be more rapid. For that reason, PBSC remains the preferred source of stem cells for hematopoietic reconstitution following high-dose therapy.

Role of Purging or Selection

The relationship between reinfusion of malignant cells in the autograft and disease relapse is unclear. Numerous different methods have been used to attempt to eliminate malignant contamination. Limited data exist on the clinical benefit of such therapy.

Randomized controlled trial

Stewart et al reported preliminary results of a randomized trial of CD34 selection. This trial compared CD34+ selected (n=93) versus unselected (n=97) autologous peripheral blood progenitor

Education and Information

cells (52). After a median follow-up of 37.2 months, 33 patients (36%) in the selected arm and 34 patients (35%) in the unselected arm had died (p=0.784). A median overall survival in the selected arm was reached at 50 months and is not reached in the unselected one.

Interpretive summary

Insufficient data exist to recommend purging or selection outside a randomized controlled trial.

Update

Two articles (20u,21u) in which the results of a previously included abstract publication (52) are updated, and three new abstracts (6u,7u,9u) addressing the role of cell purging and selection were found.

Preliminary results demonstrating that a process to select CD34 positive cells could reduce the number of myeloma cells contained within autologous harvests were reported in abstract form (52) and described in the original version of this guideline. The results of that trial have now been reported in two articles. In the first article, Vescio et al (20u) confirm that this processing procedure reduces myeloma cell contamination of the harvested product. Stewart et al (21u) again report this finding in the final analysis of this study in which clinical outcomes of all 190 patients are also described. Although tumour cell contamination was reduced with the selection process, when the group receiving selected stem cells was compared with those receiving unselected stem cells, no differences were detected in median disease-free survival (100 vs. 104 months; p=0.82) or overall survival (50 months vs. not reached; p=0.78) (21u).

Goldschmidt et al (6u) have reported results of a randomized comparison of autologous transplantation using CD34 positive selected stem cells or unselected stem cells in 127 patients with stage II-III myeloma. No differences in response rate, event-free or overall survival were detected. More frequent serious infections were observed in the CD34 selected arm (12 vs. 1; p value not indicated).

Fermand et al (7u,9u) reported results of a randomized comparison of autologous transplantation using CD34 positive selected stem cells or unselected stem cells in 230 patients; the trial included a factorial design comparing single with tandem transplantation. In that preliminary analysis in which results are reported in abstract form, no differences in the frequency of relapse (data not reported) or death (22 vs. 27; p not provided) were detected between patients receiving unselected or selected stem cells (7u). More frequent serious infections were observed in patients receiving CD34 positive selected stem cells (data not provided) (7u).

Interpretive Summary

While contamination of the stem cell harvest with myeloma cells can be reduced with use of a CD34 positive selection process, these three trials all failed to detect benefits in clinically relevant outcomes. In addition, the use of selected stem cells may be associated with more frequent infections. Purging or selection of harvested stem cells is not recommended outside the setting of a clinical trial.

High-dose therapy preparative regimen and supportive care

One randomized controlled trial and one non-randomized comparison, both in abstract form, have assessed the role of total body irradiation (TBI).

Randomized controlled trial

Two hundred and thirty-one patients were randomized to receive either high-dose melphalan 140 mg/m^2 plus total body irradiation (n=113) versus high-dose melphalan 200 mg/m^2 (n=108) as a conditioning regimen for peripheral blood progenitor cell autologous transplantation in patients with newly diagnosed multiple myeloma (53). There was no difference in response rate and 2-year

Education and Information

survival rate between the two groups, but the TBI containing regimen was more toxic (median duration of neutropenia 8 days vs.10 days; p<0.001, median duration of thrombocytopenia 4 days vs. 6 days; p<0.001, median number of red blood cell transfusions 1.7 vs. 3, p=0.001, mean number of platelet transfusions 1.9 vs. 3.8; p<0.001, median duration of IV antibiotics 8 days vs. 11 days; p<0.001).

Non-randomized comparison

Analysis of data on 1905 patients submitted to the European Group for Blood and Marrow Transplantation (EBMT), was reported by Bjorkstrand et al (60). The analysis of pretreatment variables reported that transplants performed with preparatory regimens that included TBI were associated with inferior survival.

Interpretive summary

In Section IV b), the IFN 90 randomized controlled trial was described in detail (5). This study found survival to be superior when transplantation was combined with a high-dose therapy regimen consisting of high-dose melphalan and total body irradiation. Outcomes in the preliminary abstracts reported above appear to be no worse when total body irradiation is omitted from the high-dose therapy regimen and toxicity is improved. In the absence of additional data, it is reasonable to recommend a single transplant using high-dose melphalan (200mg/m^2) alone or melphalan (140mg/m^2) with total body irradiation as standard therapy outside a clinical trial.

Update

Moreau et al (8u, 22u) and Attal and Harousseau (19u) provide the final results of the Intergroupe Francophone du Myélome 9502 trial initially described in the original guideline (53); data from the more recent full report (22u) will be presented here. Newly diagnosed patients, less than 65 years of age, initially received three cycles of VAD, with responding patients then receiving a fourth cycle of that treatment followed by high-dose therapy and autologous transplantation. The transplantation procedure included the harvesting of peripheral blood stem cells and randomization to receive combined modality therapy consisting of melphalan 140 mg/m^2 and total body radiation, or melphalan 200 mg/m^2 as a single modality. A comparison of the outcomes of the 142 patients receiving melphalan as a single modality with the 140 patients receiving combined modality therapy failed to detect a difference in response rate (55% vs. 43%; p=0.06) or median event-free survival (20.5 vs. 21 months; p=0.6). Overall survival at 45 months was superior in patients receiving melphalan as a single modality (65.8% vs. 45.5%; p=0.05). Patients assigned to receive melphalan 200 mg/m^2 experienced less severe mucositis, required fewer transfusions, and had shorter durations of hospitalization and intravenous antibiotics administration (p<0.001 for all comparisons).

Schneider et al (16u) randomized 56 of 116 enrolled patients in stage II or III myeloma to high dose melphalan (200 mg/m^2) (n=30, median age 55 years) or a combination regimen of idarubicin (42 mg/m^2), melphalan (200 mg/m^2), and cyclophosphamide (120 mg/kg) (n=26, median age 57 years) followed with autologous stem cell transplantation. No differences in complete or partial remission after three months or overall survival (no statistical analysis provided) were detected between the groups.

Interpretive Summary

The final analysis of the IFM 9502 trial confirms superior survival and reduced toxicities in patients receiving melphalan 200 mg/m^2 in comparison with a regimen that includes total body radiation. For this reason, the Hematology DSG concluded that melphalan 200 mg/m^2 is the recommended high-dose regimen.

Education and Information

Single versus double transplants

Two randomized controlled trials and one non-randomized comparison have compared single versus double transplants (Table 4).

Randomized controlled trials

Two randomized controlled trials of a single autologous bone marrow versus tandem (double) autologous bone marrow transplantation have been presented in abstract form (54,55). Both studies found that event-free and overall survival were not significantly different between the two groups. However, in one study (55) there was a trend for a longer relapse-free and event-free survival for patients assigned to receive a double transplant. This difference was statistically significant (p=0.03) when the analysis was restricted to patients who actually completed double transplants.

Non-randomized comparison

Two hundred and seventy-eight patients were included in a double transplant program versus 1252 patients received a single transplant in the study by Bjorkstrand et al (60). Progression-free survival was significantly better in the patients treated in a double transplant program versus those who received a single transplant (data not reported). There was also a trend for improved overall survival in the double transplant group.

Table 4. Comparison of single versus double transplantations from RCTs and one NRC.

Study	Single Transplant # patients	Double Transplant # patients	Complete Response Rate*	Event-Free survival*	Overall Survival*
Randomized Controlled Trials: Original Guideline					
Attal (54) Abstract	200	202	39% vs. 49% p=0.06	At 3 years, 31% vs. 39% p=ns	At 3 years, 58% vs. 66% p=ns
Tosi (55) abstract	98	94	27% vs. 35% p=ns	Trend towards longer event-free survival in double transplant group p=ns	At 2 years, 90% vs. 90% p=ns
Randomized Controlled Trials: UPDATE					
Fermand (7u) abstract	n=94	n=99	42% vs. 37% (p=ns) (CR+minimal residual disease)	NR; 41 vs. 43 events (p=ns)	NR; 27 vs. 22 deaths (p=ns)
Attal (19u)§ Full report	167: n=79 (BM)/ n=88 (PBSC)	177: n=85 (BM)/ n=92 (PBSC)	43%/50% vs. 50%/61% (p<0.05)† (CR+VGPR)	At 5 years‡, 19%/20% vs. 27%/35% (p<0.01)†	At 5-years‡, 35%/40% vs. 43%/60% (p<0.05)†
Cavo (14u) abstract	n=110	n=110	21% vs. 24% (p=NR) (cr)	median: 25 vs. 34 months (p=0.05)	median: 56 vs. 60 months; (p=ns)

Education and Information

Non-Randomized Comparison: Original Guideline					
Bjorkstrand (60) abstract	1252	278	NR	PFS p=significant	trend towards improved survival in double transplant group

Note: BM=bone marrow; CR=complete response; cr=complete remission; ns, not significant; NR, not reported; PBSC=peripheral blood stem cell; PFS, progression-free survival; UPDATE=trials found during updating process; VGPR=very good partial response defined as greater than 90% reduction of M component on electrophoresis; ; vs., versus.
*Data reported as single versus double transplant.
§Updated data of Attal (54).
†Analyzed across all four groups.
‡At 5 years after second randomization.

Interpretive summary

Based on the intent-to-treat analysis of the two randomized controlled trials, there is no clear benefit for double versus single transplantation. A survival benefit was only seen when analysis was restricted to those who completed therapy. Double transplantation should be performed only in the setting of a clinical trial.

Update

Five abstracts and one full report reporting the results of three randomized trials comparing single with double (tandem) transplantation were found (9u-14u,19u).

Fermand et al (7u, 9u) have reported results of a randomized trial that included a factorial design; the trial evaluated the role of stem cell selection (see above) and single as compared with double transplantation. Among the 193 patients randomized to receive single or double transplantation, no differences were observed in total events or deaths (Table 4) (7u).

Attal et al have reported updated results of the IFM 94 02 randomized trial comparing single and double autologous transplantation that was included in the original version of this guideline (54); updated data were reported in three abstracts (10u-12u), but data from the published report (19u) are presented. This trial randomized 403 previously untreated patients who were less than 60 years of age. The trial was factorial in design, with patients randomized first to single or double transplantation and then, if eligible for a transplant (n=344), randomized second to bone marrow or PBSC transplantation. Patients randomized to receive a single transplantation received melphalan (140 mg/m^2) and total body irradiation for the high-dose regimen. Those randomized to the double transplant arm were given high-dose melphalan alone (140 mg/m^2) with the first transplantation and received melphalan (140 mg/m^2) and total body irradiation with the second. An interim analysis was presented. At a median follow-up of five years post-diagnosis, a significant difference across the groups was detected for response (complete plus very good partial response) and five-year event-free and overall survivals (Table 4) (19u).

Cavo et al (13u, 14u) reported updated interim analyses of the Bologna 96 randomized trial in the original guideline (55) comparing single versus double autologous peripheral blood stem cell transplantation in previously untreated patients; results from the more mature analysis (14u; n=220) will be presented here. At a median follow-up of five years, no difference in median overall survival was detected between groups, but median event-free survival was longer in the double transplant group (Table 4). Complete remission was reported in each group (Table 4).

Interpretive Summary

The benefits of double transplantation remain unclear. The Attal study (19u) is large, but the fact that for the single transplant arm the investigators used a high-dose regimen now considered inferior (melphalan, 140 mg/m^2, and total body irradiation) limits the study's interpretability. In

Evaluation Report Information

addition, two smaller studies published in abstract form did not report a survival benefit. Definitive conclusions regarding the role of double transplantation will need to await more mature results from those studies. Because of the relatively complex design of a number of these trials, the full published form of these studies may need to be examined before firm recommendations regarding the role of double transplantation can be made.

Post-transplant therapy

Interferon alpha has been used following conventional or high-dose therapy in an effort to delay recurrence. An overview of randomized trials of interferon use with conventional therapy as well as the use of interferon in maintenance therapy has been discussed in Section IV (a) (8,9). There has been interest in the use of interferon following ABMT, as an immunomodulatory effect may be more prominent in a minimal residual disease state. Interferon administration after transplantation is a commonly described practice (1). In the randomized study comparing transplantation with conventional dose chemotherapy (5) interferon alpha, three million units/m^2 was given three times weekly to both the transplant and conventional therapy groups until disease progression. It is not possible to factor out the contribution to this component of that entire treatment manoeuvre in order to comment upon the importance of interferon**.** The major justification of using interferon after ABMT comes from two studies which are described below.

Randomized controlled trial

One randomized trial of interferon administration following transplantation has been reported (56). Eighty-four patients with myeloma were randomized to receive either three million units of interferon alpha three times weekly until progression or no maintenance therapy. There was a trend towards longer median progression-free survival in the patients given interferon (46 months vs. 27 months; p=0.11). Overall survival was not different in the two groups.

Non-randomized comparison

The analysis of 1905 patients from the European Group for Blood Marrow Transplantation registry found that post-transplant alpha-interferon (IFN) maintenance treatment was associated with prolonged survival previously discussed in Section IV (c) (60).

Interpretive summary

The evidence on the benefit of interferon is conflicting. One preliminary report of a cohort comparison suggests a survival benefit (60), while a small randomized trial shows no benefit (56). For this reason, the DSG was unable to reach consensus and a recommendation about using interferon was therefore not included.

Update

Bjorkstrand et al (25u) have updated, in article form, results of a cohort comparison assessing the role of post-transplant use of interferon alpha in patients whose data have been entered into the European Group for Blood and Marrow Transplantation database. An earlier analysis (60) had been published in abstract form and was included in the initial version of this guideline. The updated analysis includes 473 patients who did and 419 patients who did not receive interferon alpha; a Cox analysis was used to attempt to balance prognostic factors. Treatment with interferon alpha was associated with longer median progression-free survival (29 vs. 20 months; p=0.006) and overall survival (78 vs. 47 months; p=0.007).

Interpretive summary

The new evidence supports the hypothesis that maintenance therapy with interferon alpha may improve outcomes in myeloma patients who undergo autologous transplantation. However, these data result from a non-randomized comparison, and the trial design is subject to biases,

Education and Information

including imbalances of prognostic factors between the treatment groups. There is no change in the overall interpretation of evidence assessing this topic.

(e) When should transplantation be performed?

In the IFN 90 study patients were considered for transplantation prior to any therapy (5). Bone marrow was obtained early after diagnosis and transplantation took place at a median of 5.5 months after diagnosis of myeloma. It is unclear whether transplantation has to be performed this early in the course of the disease to be of benefit.

Randomized controlled trial

One randomized trial compared early (n=91) and late (n=94) autologous transplantation in patients who have had stem cells collected shortly after diagnosis (65). Patients under age 56 with symptomatic advanced stage myeloma were enrolled and had PBSC collection performed. Patients with an adequate collection and adequate organ function were randomized to early or delayed transplantation. Patients assigned to the early transplant arm received three to four courses of vincristine, doxorubicin (Adriamycin), methylprednisolone (VAMP) followed by high-dose therapy and transplantation using a high-dose regimen of lomustine, VP-16, cyclophosphamide, melphalan and total body irradiation. Patients assigned to late transplantation received monthly courses of vincristine, melphalan, cyclophosphamide and prednisone (VMCP) until a plateau phase was reached. At progression, patients who received VMCP underwent transplantation. All patients in remission in either arm received interferon alpha. Two hundred and two patients were enrolled and 185 patients were randomized. Median overall survival was similar in both arms (64.6 months in the early transplant group vs. 64 months in the late transplant group; p=0.92). Median event-free survival was superior for early transplant group compared with the late transplant group (39 months, 95% CI 29 to 48 vs. 13 months, 95% CI 9.4 to 17.6; p=not reported). Time-without-symptoms, treatment and treatment toxicity (TWISTT) was 27.8 months (95% CI, 23.8 to 31.8) for the early transplant group vs. 22.3 months (95% CI, 16.0 to 28.6) for the late transplant group. Eighty-nine of 91 (98%) patients assigned to early transplant underwent transplantation while 73 of 94 (78%) patients in the late high-dose therapy arm were transplanted.

Non-randomized comparison

A non-randomized study reported on 64 patients who had stem cells harvested within 12 months of diagnosis but were not transplanted until relapse or refractory disease developed (66). The authors found that the median survival from diagnosis in patients who received delayed transplant was 51 months with a median survival of 19.3 months post-transplant. A second non-randomized controlled trial has suggested that delaying transplantation until patients have shown evidence of progressive disease may result in loss of efficacy for this procedure (67).

Interpretive summary

While delaying transplantation until progression in patients who have stem cells collected at diagnosis does not adversely affect survival, it does decrease time without symptoms and delays the need for treatment. It also increases time without treatment toxicity. Furthermore, delay is not reasonable unless stem cells have been collected prior to extensive alkylator therapy. The DSG emphasize the need for early harvest and consideration of patient preference. Furthermore, the DSG felt that unless extenuating circumstances exist, there are advantages to early treatment related to symptom control.

(f) Who should (should not) be transplanted?

Age

The maximum age for ABMT in any disease remains controversial. Transplantation is commonly performed in patients up to the age of 65 years. It is reasonable to expect that older

Education and Information

patients may risk greater transplant-related mortality and therefore derive less survival benefit from transplantation. However, some centres have routinely offered this procedure to older (69-73,75,76). Two randomized controlled trials and six non-randomized comparisons are described below.

Randomized controlled trials

The Attal study enrolled patients up to the age of 65 years (5). The authors did not report age to be an adverse prognostic factor, but 42% of patients over age 60 did not complete the transplant compared to 18% of younger patients (p=0.01). In this study, multivariate analysis found that randomization to the transplant arm was independently associated with improved outcome only for patients under the age of 60.

One randomized trial comparing transplantation to conventional therapy in older patients (age 55-65) has been reported in preliminary form (44). This trial showed outcome to be no better with transplantation than conventional therapy (55.3 months vs. 50.4 months; p=0.98). However follow-up was short and a longer follow-up is required to assess the role of transplantation in this population.

Non-randomized comparisons

One study reported as a full paper compared 71 patients (median age, 64 years) who received dose intensive melphalan with stem cell support with 71 matched pair mates (median age, 64 years) who received oral melphalan and prednisone (68). Median event-free survival was 34 months in the transplant arm and 17.7 months in the melphalan group (p<0.001). Median overall survival was 56+ months vs. 48 months (p<0.01), in those same groups.

Numerous non-randomized studies show that transplantation can be performed in selected patients over age 65 with toxicity and survival similar to younger patients (69-73).

Interpretive summary

Transplantation can be safely performed in older patients, however the survival benefit has only been documented for patients under age 60. Physicians must use clinical judgement when recommending transplantation to patients over the age of 60 years.

Update

Randomized controlled trials

The MRC trial (23u) compared high-dose therapy and autologous stem cell transplantation with standard therapy in patients with previously untreated myeloma younger than age 65 years. The trial reported a survival benefit for the high-dose therapy arm when compared with the standard treatment arm. Although age was included as a minimization factor in a Cox model analysis, the authors did not indicate whether it was a significant prognostic factor for survival.

Interpretive summary

The Attal (5) and MRC trials (23u) both enrolled patients up to age 65 years and both demonstrated an overall survival benefit for the high-dose therapy arms. The Attal trial did not report a benefit for older patients on subgroup analysis, and the Fermand trial (44) trial, which included only patients over age 55, was negative.

Renal function

The randomized controlled trial published by Attal et al (5) included patients with renal dysfunction; however, transplantation was only performed if the serum creatinine fell to less than 150 μmol/L after initial chemotherapy and before transplantation. While some centres have transplanted patients with severe renal dysfunction, it is reasonable to expect that transplant-related mortality may be higher for such patients and survival may not be prolonged to the same extent as for patients with intact renal function.

Education and Information

Non-randomized comparison

Mehta et al (74) compared the outcome of 42 patients with renal failure (creatinine ≥200 μg/L) to 84 pair-matched controls with normal renal function. The study found that although morbidity was higher, treatment-related mortality and three-year survival rates were no different (44%, 95% CI 15 to 74 vs. 59%, 95% CI 43 to 76; p=0.15).

Interpretive summary

While autologous transplantation can be performed in patients with significant renal dysfunction, it remains unclear whether such patients benefit from the transplant procedure. For this reason, transplantation cannot be routinely recommended for patients with significant renal dysfunction until randomized controlled trials demonstrate a survival benefit for these patients. Renal function may improve with chemotherapy. In the Attal study (5), patients were only excluded if serum creatinine levels were abnormal after four to six cycles of initial chemotherapy.

Dosing/Scheduling Considerations

In the trial by Attal et al (5), the following regimen schedule was used:

- Four to six cycles of vincristine, melphalan, cyclophosphamide, prednisone, carmustine, and doxorubicin (VCMP/BVAP).
- After fourth cycle of chemotherapy, a preparative regimen of total body irradiation 200 cGy per day x 4 days (day -7 to day -4) and melphalan 140 mg/kg (day -2) followed by re-infusion of autologous bone marrow.
- Interferon alpha three million units/m^2 three times weekly was administered following hematologic recovery

Update

Issues regarding the details of therapy have been discussed in previous sections.

V. ONGOING TRIALS

Members of the Hematology DSG are aware of the following ongoing trials. The progress of these open trials will be monitored and the reported results will be reviewed when available:

1. Southern England Collaborative Trials Group randomized trial of high-dose versus intermediate-dose melphalan after initial vincristine, doxorubicin, dexamethasone (VAD) or vincristine, doxorubicin, methylprednisolone (VAMP) chemotherapy in newly diagnosed stage II or III myeloma patients.
2. Français du Myélome and the Groupe Myélome-autogreffe are conducting a meta-analysis of individual patient data comparing high-dose chemotherapy supported by ASCT with conventional chemotherapy as treatment for newly diagnosed multiple myeloma patients.
3. Cooperative clinical study of the German Multiple Myeloma Study Group (DSMM) and the East German Study Group for Hematology/Oncology comparing bendamustine plus prednisone with standard therapy.

The following trials are now closed and will be reported in future updates when data become available:

1. National Cancer Institute (NCI) high-priority clinical trial that randomized patients to autologous stem cell transplantation versus vincristine, BCNU, melphalan, cyclophosphamide, prednisone (VBMCP) chemotherapy with further randomization to interferon alpha or observation.

Education and Information

2. Leukemia Cooperative Group randomized trial testing the effect of bone marrow transplantation or conventional chemotherapy with or without alpha interferon for aggressive myeloma.
3. Australasian BMT Co-operative Study Group's randomized trial comparing melphalan with or without amifostine prior to autologous stem cell transplantation (ASCT) in multiple myeloma patients.

VI. DISEASE SITE GROUP CONSENSUS PROCESS

The Hematology DSG was asked to develop a broad guideline on the management of patients with multiple myeloma. The DSG considered the potential of developing a more comprehensive guideline and concluded that the complexity and importance of the high-dose therapy transplant topic warranted a specific guideline; the possibility remains for subsequently merging this guideline into a document dealing with a wider range of issues in myeloma.

On appraising the published literature regarding transplant therapy, there were two major issues that yielded considerable debate. The first issue related to the quality and volume of data assessing the transplant question. Specifically, debate centered on the strength of the recommendation for transplantation given that the supporting data were limited to only one well-conducted positive randomized trial (5). After careful consideration, there was unanimous agreement that patients ought to be informed about the results of this study and this was reflected in the wording of the recommendations. There was further discussion about whether there was sufficient evidence to not only offer, but to "recommend" this treatment as the preferred therapeutic option. While the DSG felt that patients should have a choice, they felt that that the current evidence is sufficient to warrant the "recommend" terminology.

The second point of debate dealt with the role of interferon. Some members of the group felt that as interferon was part of the treatment maneuver in the Attal study (5), and was reported by Cunningham et al (56) to result in superior time-to-disease progression, the use of interferon should be included in transplant treatment strategies. Other members felt that in the absence of data demonstrating a survival advantage, the toxicity of this agent precludes routine use. The DSG was unable to reach consensus and a recommendation about using interferon was therefore not included.

The DSG members considered whether a firm recommendation should be made regarding the timing of transplantation. Members felt that the best available evidence found a survival benefit when transplantation was used as part of the initial therapy (5). In a randomized trial of early versus delayed transplantation in patients in whom stem cells had been collected at diagnosis, delaying transplant did not shorten survival although there was a suggestion that quality of life was adversely affected; however the 95% confidence intervals overlapped. For this reason, the DSG members did not feel that a strong recommendation could be made regarding the timing of transplantation, although there was consensus that if a delayed transplant is contemplated, stem cells should be collected soon after diagnosis.

The initial draft recommendations were circulated for practitioner feedback in May 1999 and received wide support. The initial Practice Guideline was approved by the Practice Guidelines Coordinating Committee in October 1999. Since the release of the initial guideline, new data emerged in abstract form that included assessment of the role of total-body irradiation (TBI) (53,60) and a further randomized trial evaluating autologous transplantation in patients over age 55 years (44).

The DSG concluded that the study comparing melphalan 140 mg/m^2 plus TBI with melphalan 200 mg/m^2 required modification of the previous recommendation regarding the details of the high-dose therapy regimen (bullet five) (53). The reworded recommendation now permits either option (see bullet five). There was considerable discussion regarding the results of the report by Fermand et al (44). This trial, published in abstract form, compared a transplant strategy with standard dose treatment in patients 55 years and greater and failed to detect a survival benefit. The DSG

Education and Information

considered whether these data should lead to a rewording of the overall recommendation regarding "offering" versus "recommending" high-dose therapy and transplantation and/or whether an age restriction should be suggested. The DSG concluded that while the Fermand trial was large and appeared to be well conducted, insufficient information was provided in the abstract to change the initial recommendations. However, the wording of the new recommendation (bullet one) highlights the indication by age. The DSG acknowledges that the final results of the Fermand trial and other ongoing studies may influence the nature and wording of the recommendations in the future.

The DSG did not consider these new data and the resulting modifications sufficiently different from the initial guideline to warrant another cycle of practitioner feedback. This revised guideline was circulated to the Practice Guidelines Coordinating Committee.

Update

The Hematology DSG's evaluation of new evidence resulted in extensive discussions of two topics: the role of autologous stem cell transplantation in comparison with standard-dose therapy and the nature of the high-dose therapy regimen.

The publication of the MRC trial (23u) has strengthened the evidence in favor of high-dose therapy and autologous transplantation over standard dose therapy for newly diagnosed patients with myeloma. While a meta-analysis will be required to better define the magnitude of benefit, the DSG concluded that high-dose therapy should continue to be recommended for patients with myeloma and that the text of the recommendation should be amended to indicate that the evidence is strongest in patients under the age of 65 years.

Given the updated evidence regarding high-dose therapy preparative regimens, the DSG unanimously concluded that melphalan 200 mg/m^2 as a single modality should be the recommended regimen for patients undergoing autologous transplantation outside a clinical trial setting. In comparison with melphalan 140 mg/m^2 and total body radiation, melphalan given as 200 mg/m^2 was associated with superior survival and less toxicity, and was less resource intensive (22u).

The DSG discussed whether the publication of the Attal study (19u) should lead to a change in the recommendation regarding double (tandem) autologous transplantation. The DSG concluded that the survival benefit reported in that trial was potentially important, but noted that other trials did not report a benefit. The DSG also noted that the high-dose therapy regimen used in the single transplant arm in that trial no longer represents the standard of care, as it has been shown to be inferior to melphalan (200 mg/m^2) alone. The DSG members concluded that the recommendations should not be changed until new data are available from those studies. The DSG concluded that new evidence regarding the role of post-transplantation interferon maintenance did not warrant a change in the recommendations.

VII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

This section describes the external review activities undertaken for the original guideline report. For a description of external review activities of the new information presented in the updated sections of this report, please refer to Update below.

Draft Recommendations

Based on the evidence described in the original guideline report, the Hematology DSG drafted the following recommendations in December 1998:

Target Population

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

Education and Information

Draft Recommendations

- Autologous transplantation is recommended for patients with advanced-stage myeloma and good performance status. The evidence is strongest for patients under 60 years of age without significant renal dysfunction. Physicians must use their clinical judgement in recommending transplantation to patients over 60 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, Adriamycin, dexamethasone (VAD) may be preferable for such patients.
- Harvesting of autologous peripheral blood stem or bone marrow should be performed early in the patient's treatment course. The best available data demonstrate that transplantation is advantageous when performed as part of the initial therapy.
- There are insufficient comparative data regarding the specifics of transplant process to allow for definitive recommendations. In the absence of such data, the use of a single transplant with high-dose melphalan and total body irradiation as high-dose therapy is suggested for patients who undergo transplantation outside of the setting of a clinical trial.
- No conclusions can be reached about the role of interferon alpha following transplantation at this time.

Practitioner Feedback

Based on the evidence contained in the original guideline report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 221 practitioners in Ontario (94 hematologists, 93 medical oncologists, and 24 radiation oncologists). The survey consisted of items evaluating the methods, results, and interpretative summary used to inform the draft recommendations outlined and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (postcard) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Hematology DSG.

Results

1. Return Rate: 71%
2. Quality of data synthesis: 91% agreed or strongly agreed that the summary of the evidence was acceptable
3. Agreement with the draft recommendations: 87%
4. Approval of the recommendations as a practice guideline: 81%

Summary of Main findings

Forty-three percent (39/90) of the respondents provided written comments. The main points were:

1. Nine respondents felt that one randomized trial was insufficient evidence to "recommend" stem cell transplantation as the preferred option. These respondents felt that the publication of the guideline should be delayed until further evidence is available or that transplantation should be "offered" rather than "recommended".

Education and Information

2. There were two comments that renal function at presentation should not dictate transplant eligibility, as function may improve with initial chemotherapy.
3. There were three comments on total body irradiation (TBI) as part of the high-dose therapy regimen. Respondents indicated that it should be omitted or administered differently from the Attal et al study (5).
4. Four respondents indicated concern regarding resource availability.
5. There were two comments indicating a potential future role of allogeneic transplantation. Both respondents acknowledged the toxicity and comments short survival in published reports of allogeneic transplantation.

Modifications/Actions

1. Members of the DSG acknowledged that the first recommendation is based on a single randomized trial. The DSG felt that the trial was well done and showed statistically significant differences in the important clinical outcomes. None of the nine respondents indicated weaknesses in the trial, but rather a need for further evidence. In "recommending" the treatment, the DSG realize that patient preferences should be considered. However, the group felt that rather than just being "an option", the strength of the report makes this the "preferred option".
2. Members of the DSG felt this was an appropriate comment and have inserted the following phrase in the first recommendation: "following hydration and initial chemotherapy". The following statement was also added under the renal function in section (f): "Renal function may improve with chemotherapy. In the Attal study, patients were only excluded if serum creatinine levels were abnormal *after* 4-6 cycles of initial chemotherapy."
3. Members of the DSG felt that while no RCTs compared high-dose therapy regimens, the only published trial showing a survival benefit for transplantation used melphalan and TBI. For this reason melphalan and TBI should be recommended as standard practice outside of a clinical trial. As a further follow-up to this, based on preliminary data (53,60), the fifth bullet of the recommendations was modified (see Section VI).There were three comments on total body irradiation (TBI) as part of the high-dose therapy regimen. Respondents indicated that it should be omitted or administered differently from the Attal et al study (5).
4. The issue of resource impact lies outside the scope of evidence-based guidelines.
5. The review of the European Bone Marrow Transplant Registry study (44) found substantially shorter survival in patients undergoing allogeneic transplantation. Members of the DSG felt that ongoing clinical trials of improved allogeneic transplantation technology should be encouraged.

Approved Practice Guideline Recommendations

These practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Hematology DSG and the Practice Guidelines Coordinating Committee.

- Autologous transplantation is recommended for patients with advanced-stage myeloma and good performance status. The evidence is strongest for patients under 55 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 55 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 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 stem cells. High-dose glucocorticoid-based

Education Information

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 of transplantation is most advantageous when performed as part of the initial therapy.
- There are insufficient comparative data regarding the specifics of the transplant process to allow for definitive recommendations. In the absence of such data, the use of a single transplant with high-dose melphalan (200 mg/m^2) alone or melphalan (140mg/m^2) with total body irradiation is suggested for patients who undergo transplantation outside of the setting of a clinical trial.
- No conclusions can be reached about the role of interferon alpha following transplantation at this time.

Update

The recommendations regarding autologous transplantation and high-dose regimens have been modified to reflect the updated evidence. The changes in recommendations were not sent for external review because they did not substantially deviate from the original recommendations. The new recommendations are as follows:

- 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 judgment in recommending transplantation to patients over 65 years of age or those with renal impairment.
- 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.

VIII. POLICY IMPLICATIONS

In Ontario, myeloma treatment is provided by hematologists, medical oncologists and a number of internists in community practice as well as in larger cancer centres. For this reason there is potential for a wide variation in practice. In order to ensure that all patients have access to ideal therapy, the dissemination of this guideline is very important.

Myeloma is currently an indication for transplantation in all transplant centres in Ontario. It is the perception of the Hematology DSG that rates of referral to the transplant centres vary substantially across the province. Adoption of this practice guideline is likely to increase the pressure on transplant centres, but to differing degrees for each centre.

IX. PRACTICE GUIDELINE

This practice guideline reflects the most current information and integrates the new evidence with evidence from the original guideline report.

Target Population

This recommendation applies to 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

Education and Information

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.

X. JOURNAL REFERENCE

Imrie K, Esmail R, Meyer RM; Members of the Hematology Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative. The role of high-dose chemotherapy and stem-cell transplantation in patients with multiple myeloma: a practice guideline of the Cancer Care Ontario Practice Guidelines Initiative. *Ann Intern Med* 2002;136(8):619-29.

XI. ACKNOWLEDGEMENTS

The Hematology DSG would like to thank Drs K. Imrie and R. Meyer and Ms. R. Esmail for taking the lead in drafting this practice guideline report and Drs K. Imrie and R. Meyer, Ms. J. Makarski, and Ms. A. Stevens for revising this practice guideline report.

For a complete list of the Hematology Disease Site Group members, please visit the PEBC https://www.cancercare.on.ca/toolbox/qualityguidelines/pebc/

Education and Information

REFERENCES

1. Bataille R, Harousseau JL. Multiple myeloma. *N Engl J Med* 1997;336:1657-64.
2. Gregory WM, Richards MA, Malpas JS. Combination chemotherapy versus melphalan & prednisolone in the treatment of multiple myeloma: An overview of published trials. *J Clin Oncol* 1992;10:334-42.
3. Armitage JO. Bone marrow transplantation. *N Engl J Med* 1994;330:827-38.
4. Mahendra P, Hood IM, Johnson D, Ethell M, Jestice HK, Scott MA, et al. Autografting for multiple myeloma: a 5 year experience at a single institution. *Bone Marrow Transplant* 1995;16:759-63.
5. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med* 1996;335:91-7.
6. Barlogie B, Jagannath S, Vesole DH, Naucke S, Cheson B, Mattox S, et al. Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. *Blood* 1997;89:789-93.
7. Myeloma Trialists' Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6633 patients from 27 randomized trials. *J Clin Oncol* 1998;16:3832-42.
8. Wheatley K, for the Myeloma Trialists' Collaborative Group (MTCG). The role of interferon (IFN) as therapy for multiple myeloma: an overview of 24 randomized trials with over 4000 patients [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 1998;17:8a. Abstract 28.
9. Trippoli S, Becagli P, Messori A, Tendi E. Maintenance treatment with interferon in multiple myeloma. A survival meta-analysis. *Clin Drug Invest* 1997;14:392-9.
10. Abramson N, Lurie P, Mietlowski WL, Schilling A, Bennett JM, Horton J. Phase III study of intermittent carmustine (BCNU), cyclophosphamide, and prednisone versus intermittent melphalan and prednisone in myeloma. *Cancer Treat Rep* 1982;66:1273-7.
11. Cohen HJ, Silberman HR, Tornyos K, Bartolucci AA. Comparison of two long-term chemotherapy regimens, with or without agents to modify skeletal repair, in multiple myeloma. *Blood* 1984;63:639-48.
12. Harley JB, Pajak TF, McIntrye OR, Kochwa S. Improved survival of increased-risk myeloma patients on combined triple-alkylating-agent therapy: A study of the CALGB. *Blood* 1979;54:13-22.
13. McIntyre OR, Pajak T, Leone L, Kyle R, Corwell GG, Harley J, et al. Nitrosoureas in the treatment of multiple myeloma. In: Prestayko AN, Crooke St, Baker LH, Careter SK, Schein PS, eds. *Nitrosoureas: Current status and new developments.* New York, NY: Academic Press; 1981:313-24
14. Bergsagel DE, Bailey AJ, Langley GR, MacDonald RN, White DF, Miller AB. The chemotherapy of plasma-cell myeloma and the incidence of acute leukemia. *N Engl J Med* 1979;301:743-8.
15. Pavlovsky S, Corrado C, Santarelli MT, Saslavsky J, Cavagnaro F, Paulau M, et al. An update of two randomized trials in previously untreated multiple myeloma comparing melphalan and prednisone versus three- and five-drug combinations: An Argentine group for the treatment of acute leukemia study. *J Clin Oncol* 1988;6:769-75.
16. Cavagnaro F, Lein JM, Pavlosky S, Becherini JO, Pileggi JE, Micheo EQ, et al. Comparison of two combination chemotherapy regimens for multiple myeloma: methyl-CCNU, cyclophosphamide, and prednisone versus melphalan and prednisone. *Cancer Treat Rep* 1980;64:73-9.
17. Tribalto M, Amadori S, Cantonetti M, Franchi A, Papa G, Pileri A, et al. Treatment of multiple myeloma: A randomized study of three different regimens. *Leuk Res* 1985;9:1043-9.
18. Alexanian R, Dreicer R. Chemotherapy for multiple myeloma. *Cancer* 1984;53:583-8.

Education and Information

19. Cooper MR, McIntrye OR, Propert KJ, Kochwa S, Anderson K, Coleman M, et al. Single, sequential, and multiple alkylating agent therapy for multiple myeloma: A CALGB study. *J Clin Oncol* 1986;4:1331-9.
20. Salmon SE, Haut A, Bonnett JD, Amare M, Weick JK, Durie BG, et al. Alternating combination chemotherapy and levamisole improves survival in multiple myeloma: A Southwest Oncology Group Study. *J Clin Oncol* 1983;1:453-61.
21. Western Cancer Study Group. Sequential therapy compared with combination therapy in multiple myeloma. *Arch Intern Med* 1975;135:163-71.
22. Alexanian R, Bonnett J, Gehan E, Haut A, Hewlett J, Lane M, et al. Combination chemotherapy for multiple myeloma. *Cancer* 1972;30:382-9.
23. Hansen OP, Clausen NAT, Drivsholm A, Laursen B. Phase III study of intermittent 5-drug regimen (VBCMP) versus intermittent 3-drug regimen (VMP) versus intermittent melphalan and prednisone (MP) in myelomatosis. *Scand J Haematol* 1985;35:518-24.
24. Palva IP, Ahrenberg P, Ala-Harja K, Almqvist A, Apajalahti J, Hallman H, et al. Treatment of multiple myeloma with an intensive 5-drug combination or intermittent melphalan and prednisone; a randomised multicentre trial. Finnish Leukaemia Group. *Eur J Haematol* 1987;38:50-4.
25. Osterborg A, Ahre A, Bjokholm M, Bjoreman M, Brenning G, Gahrton G, et al. Alternating combination chemotherapy (VMCP/VBAP) is not superior to melphalan/prednisone in the treatment of multiple myeloma patients stage III-A randomized study from MGCS. *Eur J Haematol* 1989;43:54-62.
26. Kildahl-Andersen O, Bjark P, Bondevik A, Bull O, Burgess G, Dehli O, et al. Multiple myeloma in central and northern Norway 1981-1982: A follow-up study of a randomized clinical trial of 5-drug combination therapy versus standard therapy. *Eur J Haematol* 1988;41:47-51.
27. Kildahl-Andersen O, Bjark P, Bondevik A, Bull O, Dehli O, Kvambe V, et al. Multiple myeloma in central Norway 1981-1982: A randomized clinical trial of 5-drug combination therapy versus standard therapy. *Scand J Haematol* 1986;37:243-8.
28. Peest D, Deicher H, Coldewey R, Schmoll HJ, Schedel I. Induction and maintenance therapy in multiple myeloma: A multicenter trial of MP versus VCMP. *Eur J Cancer Clin Oncol* 1988;24:1061-7.
29. Hjorth M, Hellquist L, Holmberg E, Magnusson B, Rodjer, Westin J. Initial treatment in multiple myeloma: No advantage of multidrug chemotherapy over melphalan-prednisone. The Myeloma Group of Western Sweden *Br J Haematol* 1990;74:185-91.
30. Boccadoro M, Marmont F, Tribalto M, Avvisati G, Andriani A, Barbui T, et al. Multiple myeloma: VMCP/VBAP alternating combination chemotherapy is not superior to melphalan and prednisone even in high-risk patients. *J Clin Oncol* 1991;9:444-8.
31. Oken MM, Tsiatis A, Abramson N, Glick J. Evaluation of intensive (VBMCP) vs standard (MP) therapy for multiple myeloma [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 1987;6:203. Abstract 802.
32. MacLennan IC, Cusick J. Objective evaluation of the role of vincristine in the induction and maintenance therapy for myelomatosis. Medical Research Council Working Party on Leukemia in Adults. *Br J Cancer* 1985;52:153-8.
33. Pavlovsky S, Saslavsky J, Tezanos Pinto M, Palmer L, Curuchet M, Lein JM, et al. A randomized trial of melphalan and prednisone versus melphalan, prednisone, cyclophosphamide, MeCCNU, and vincristine in untreated multiple myeloma. *J Clin Oncol* 1984;2:836-40.
34. Durie BGM, Dixon DO, Carter S, Stephens R, Rivkin S, Bonnet J, et al. Improved survival duration with combination chemotherapy induction for multiple myeloma: A Southwest Oncology Group Study. *J Clin Oncol* 1986;4:1227-37.

Evaluation and Information

35. Riccardi A, Merlini G, Montecucco C, Danova M, Ucci G, Cassano E, et al. Peptichemio, vincristine and prednisone versus melphalan and prednisone as induction therapy in multiple myeloma. *Eur J Cancer Clin Oncol* 1986;22:787-91.
36. Peest D, Coldeway R, Deicher H. Overall vs tumour-related survival in multiple myeloma. *Eur J Cancer* 1991;27:672.
37. MacLennan IC, Chapman C, Dunn J, Kelly K. Combined chemotherapy with ABCM versus melphalan for treatment of myelomatosis. Medical Research Council Working Party on Leukemia in Adults. *Lancet* 1992;339:200-5.
38. Blade J, San Miguel JF, Alcala A, Maldonado J, Sanz MA, Garcia-Conde J. Alternating combination VCMP/VBAP chemotherapy versus melphalan/prednisone in the treatment of multiple myeloma: A randomized multicentric study of 487 patients. *J Clin Oncol* 1993;11:1165-71.
39. Oken MM, Harrington DP, Abramson N, Kyle RA, Knospe W, Glick JH. Comparison of melphalan and prednisone with vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of multiple myeloma: results of Eastern Cooperative Oncology Study E2479. *Cancer* 1997;79:1561-7.
40. Riccardi A, Ucci G, Luoni R, Brugnatelli S, Mora O, Spanedda R, et al. Treatment of multiple myeloma according to the extension of the disease: A prospective randomised study comparing a less with a more aggressive cytostatic policy. *Br J Cancer* 1994;70:1203-10.
41. Rossi JF, Bouabdullah R, Fuzibet JG, Lepeu G, Martin C, Gris JC, et al. Result of randomized study comparing melphalan-prednisone (MP) to alternating MP and hydroxyurea-VAD (vincristine, Adriamycin, dexamethasone, HVAD) in 148 patients with multiple myeloma (MM) [abstract]. *Blood* 1995;86:187a. Abstract 735.
42. Keldsen N, Bjerrum OW, Dahl IMS, Drivsholm A, Ellegaard J,Gadeberg O, et al. Multiple myeloma treated with mitoxantrone in combination with vincristine and prednisolone (NOP regimen) versus melphalan and prednisolone: a phase III study. *Eur J Haematol* 1993;51:80-5.
43. Peest D, Deicher H, Coldeway R, Leo R, Bartl R, Bartels H, et al. A comparison of polychemotherapy and melphalan/prednisone for primary remission induction, and interferon-alpha for maintenance treatment, in multiple myeloma. A prospective trial of the German Myeloma Treatment Group. *Eur J Cancer* 1995;31A:146-51.
44. Fermand JP, Ravaud P, Katsahian S, Divine M, Leblond V, Belanger C, et al. High dose therapy (HDT) and autologous blood stem cell (ABSC) transplantation versus conventional treatment in multiple myeloma (MM): Results of a randomized trial in 190 patients 55 to 65 years of age [abstract]. *Blood* 1999;94 (Suppl1):396a. Abstract 1754.
45. Lenhoff S, Hjorth M, Holmberg E, Turesson I, Westin J, Nielsen JL, et al. Impact on survival of high-dose therapy with autologous stem cell support in patients younger than 60 years with newly diagnosed multiple myeloma: a population-based study. *Blood* 2000;95:7-11.
46. Musto P, Arena GD, Falcone A, Bodenizza, Greco MM, Matera R, et al. Intensive chemotherapy followed by single or multiple peripheral blood stem cell transplant (PBSCT) improves the prognosis of patients affected by multiple myeloma (MM) with high proliferative activity [abstract]. *Blood* 1999;94:576a. Abstract 2570.
47. Trippoli S, Messori A, Becagli P, Alterini R, Tendi E. Treatments for newly diagnosed multiple myeloma: analysis of survival data and cost-effectiveness evaluation. *Oncology Report* 1998 5:1475-82.
48. Bjorkstrand B, Ljungman P, Svensson H, Hermans J, Alegre A, Apperley J, et al. Allogeneic bone marrow transplantation versus autologous stem cell transplantation in multiple myeloma: A retrospective case-matched study from the European Group for Blood and Marrow Transplantation. *Blood* 1996;88:4711-8.
49. Varterasian M, Janakiraman N, Karanes C, Abella E, Uberti J, Dragovic J, et al. Transplantation in patients with multiple myeloma: A multicenter comparative analysis of peripheral blood stem cells and allogeneic transplant. *Am J Clin Oncol* 1997;20:462-6.

Evaluation and Information

50. Couban S, Stewart AK, Loach D, Panzarella T, Meharchand J. Autologous and allogeneic transplantation for multiple myeloma at a single centre. *Bone Marrow Transplant* 1997;19:783-9.
51. Harousseau JL, Attal M, Payen C. Facon T, Michaux JL, Guilhot F, et al. Bone marrow (BM) versus peripheral blood versus CD34+ progenitors as the source of stem cell for autologous transplantation in multiple myeloma [abstract]. *Blood* 1998;92:443a. Abstract 1832.
52. Stewart AK, Schiller G, Vescio R, Ballester O, Noga S, Rugo H, et al. CD34 selection does not prolong disease free or overall survival in myeloma patients undergoing autologous stem cell transplant: results of a phase III study [abstract]. *Blood* 1999;94:714a. Abstract 3151.
53. Harrousseau JL, Facon T, Moreau P, Michallet M, Guilhot F, Hulin C, et al. Comparison of high-dose melphalan 140 mg/m^2 plus total body irradiation and high-dose melphalan 200mg/m^2 as conditioning regimen for peripheral blood progenitor cell autotransplantation in patients with newly diagnosed multiple myeloma. Preliminary results of the IFM 9502 randomized trial [abstract]. *Blood* 1999;94:713a. Abstract 3150.
54. Attal M, Harousseau JL, Facon T, Michaux JL, Guilhot F, Fruchard C, et al. Single versus double transplant in myeloma: a randomized trial of the "inter group francais du myelome" (IFM) [abstract]. *Blood* 1999;94:714a. Abstract 3152.
55. Tosi P, Cavo M, Zamagni E, Ronconi S, Benni M, Tura S, et al. A multicentric randomized clinical trial comparing single versus double autologous peripheral blood stem cell transplantation for patients with newly diagnosed multiple myeloma: results of an interim analysis [abstract]. *Blood* 1999;94:715a. Abstract 3155.
56. Cunningham D, Powles R, Malpas JS, Raje N, Milan S, Viner C, et al. A randomized trial of maintenance interferon following high-dose chemotherapy in multiple myeloma: long-term follow-up results. *Br J Haematol* 1998;102:495-502.
57. Harousseau JL, Attal M, Divine M, Milpied N, Marit G, Leblond V, et al. Comparison of autologous bone marrow transplantation and peripheral blood stem cell transplantation after first remission induction treatment in multiple myeloma. *Bone Marrow Transplant* 1995;15:963-9.
58. Raje N, Powles R, Horton C, Millar B, Shepherd V, Middleton G, et al. Comparison of marrow vs. blood-derived stem cells for autografting in previously untreated multiple myeloma. *Br J Cancer* 1997;75:1684-9.
59. Larsson K, Bjorkstrand B, Ljungman P. Faster engraftment but no reduction in infectious complications after peripheral blood stem cell transplantation compared to autologous bone marrow transplantation. *Supp Care in Cancer* 1998;6:378-83.
60. Bjorkstrand BT, Svensson H, Goldschmidt, Ljungman PT, Apperley J, Remes K, et al. 5489 autotransplants in multiple myeloma-a registry study from the European group for blood and marrow transplantation (EBMT) [abstract]. *Blood* 1999;94:714a. Abstract 3154.
61. Tricot G, Jagannath S, Vesole D, Nelson J, Tindle S, Miller L, et al. Peripheral blood stem cell transplants for multiple myeloma: identification of favourable variables for rapid engraftment in 225 patients. *Blood* 1995;85:588-96.
62. Prince HM, Imrie K, Sutherland DR, Keating A, Meharchand J, Crump RM, et al. Peripheral blood progenitor cell collections in multiple myeloma: Predictors and management of inadequate collections. *Brit J Haematol* 1996;93:142-5.
63. Duncan N, Hewetson M, Powles R, Raje N, Mehta J. An economic evaluation of peripheral blood stem cell transplantation as an alternative to autologous bone marrow transplantation in multiple myeloma. *Bone Marrow Transplantation* 1996;18:1175-9.
64. Powles R, Raje N, Horton C, Mehta J, Singhal S, Hickish T, et al. Comparison of interferon tolerance after autologous bone marrow or peripheral blood stem cell transplants for myeloma patients who have responded to induction therapy. *Leukemia & Lymphoma* 1996;21:421-7.
65. Fermand JP, Ravaud P, Chevret S, Divine M, Leblond V, Belanger C, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: Up-front or

Evaluation and Information

rescue treatment? Results of a multicenter sequential randomized clinical trial. *Blood* 1998;92:3131-6.
66. Gertz MA, Lacy MQ, Gastineau DA, Inwards DJ, Tefferi A, Chen M, et al. Delayed stem cell transplantation for the management of relapsed or refractory multiple myeloma [abstract]. *Blood* 1999;94:577a. Abstract 2573.
67. Alexanian R, Dimopoulos M, Smith T, Delasalle K, Barlogie B, Champlin R. Limited value of myeloablative therapy for late multiple myeloma. *Blood* 1994;83:512-6.
68. Palumbo A, Triolo S, Argentino C, Bringhen S, Dominietto A, Rus C, et al. Dose-intensive melphalan with stem cell support (MEL100) is superior to standard treatment in elderly myeloma patients. *Blood* 1999;94:1248-53.
69. Lenhoff S, Turesson I, Hjorth M. Holmberg E, Westin J. Intensive therapy in newly diagnosed multiple myeloma patients below 60 years. A prospective, controlled, population based study [abstract]. *Blood* 1998;92:727a. Abstract 2985.
70. Mainwaring PN, Horton C, Powles R, Treleaven J. Role of autologous transplantation in patients with multiple myeloma (MM) aged 65 years and over [abstract]. *Blood* 1998;92:662a. Abstract 2731.
71. Siegel DS, Desikan KR, Mehta J, Singhal S, Fassas A, Munshi N, et al. Age is not a prognostic variable with autotransplants for multiple myeloma. *Blood* 1999;93:51-4.
72. Sirohi B, Powles R, Treleaven J, Mainwaring P, Kulkarni S, Bhagwati N, et al. High-dose chemotherapy and autologous transplantation in myeloma patients aged 65 years and over: a case -control comparison with younger patients [abstract]. *Blood* 1999;94;578a. Abstract 2578.
73. Badros A, Zangari M, Desikan R, Anaissie E, Munshi N, Chatta G, et al. Feasibility and efficacy of melphalan-based high-dose therapy (MEL-HDT) with autologous peripheral blood stem cell support for patients with multiple myeloma (MM) aged >=70 years [abstract]. *Blood* 1999;94;578a. Abstract 2579.
74. Mehta J, Ayers D, Mattox S, Singh J, Singhal S, Siegel D, et al. High-dose melphalan and autotransplantation in myeloma with renal impairment: A matched-pair comparison with patients without renal failure [abstract]. *Blood* 1997;90:419a. Abstract 1863.
75. Vesole DH, Jagannath S, Tricot G, Vaught L, Bartogie B. High-Dose intensive therapy with autologous transplantation (AT) in multiple myeloma (MM) patients over age 60 [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 1994;13:410. Abstract 1400.
76. Siegel DS, Jagannath S, Desikan KR, Tricot G, Bracy D, Maddox S, et al. Feasibility of high-dose chemotherapy with peripheral blood stem cell support for multiple myeloma patients over the age 70 [abstract]. *Blood* 1996;88:130a. Abstract 508.
77. Greenhalgh T. Papers that tell you what things cost (economic analyses). In: How to read a paper: The basics of evidence based medicine. London, BMJ Publishing; 1997: Chapter 10.
78. Haas R, Mohle R, Fruhauf S, Goldschmidt H, Witt B, Flentje M, et al. Patient characteristics associated with successful mobilizing and autografting of peripheral blood progenitor cells in malignant lymphoma. *Blood* 1994;83:3787-94.
79. Hartmann O, Le Corroller GA, Blaise D, Michon J, Philip I, Norol F, et al. Peripheral blood stem cell and bone marrow transplantation for solid tumors and lymphomas hematologic recovery and costs. *Ann Intern Med* 1997;126:600-7.
80. Henry JM, Sykes PJ, Brisco MJ, To LB, Juttner CA, Morley AA. Comparison of myeloma cell contamination of bone marrow and peripheral blood stem cell harvests. *Brit J Haematol* 1996;92:614-9.

Education and Information

Update

This section includes all references obtained from the review and updating activities.

1u. Segeren CM, Sonneveld P, van der Hold B, Vellenga E, Croockewit AJ, GE Verhoef, et al. Intensive versus double intensive therapy in previously untreated multiple myeloma: a prospective randomized phase III study in 450 patients. VIIIth International Myeloma Workshop, Banff, Canada, 2001. Abstract S17.

2u. Segeren CM, Sonneveld P, Van der Holt B, Vellenga E, Croockewit SJ, Verhoef EG, et al. Myeloablative treatment following intensified chemotherapy in untreated multiple myeloma: a prospective, randomized phase III study [abstract]. *Blood* 2001;98:815a. Abstract 3388.

3u. Blade J, Sureda A, Ribera JM, Diaz-Mediavilla J, Palomera L, Fernandez-Calvo J, et al. High-dose therapy autotransplantation/intensification vs continued conventional chemotherapy in multiple myeloma patients responding to initial treatment chemotherapy. Results of a prospective randomized trial from the Spanish Cooperative Group PETHEMA [abstract]. *Blood* 2001;98:815a. Abstract 3386.

4u. Child JA, Selby PJ, Morgan GJ, Davies FE, Rawstron AC, Owen RG, et al. Standard ABCM chemotherapy versus intensive therapy incorporating high dose melphalan with supporting stem cell autograft early analysis of the Medical Research Council (MRC) Myeloma VII trial. VIIIth International Myeloma Workshop, Banff, Canada, 2001. Abstract S38.

5u. Morgan GJ, Davies FE, Hawkins K, Brown J, Bell SE, Drayson MT, et al. The MRC Myeloma VII Trial of standard versus intensive treatment in patients <65 years of age with multiple myeloma [abstract]. *Blood* 2002;100: 178a. Abstract 668.

6u. Goldschmidt H, Bouko Y, Bourhis JH, Greinix H, Salles G, Derigs G, et al. CD34+ selected PBPCT results in an increased infective risk without prolongation of event free survival in newly diagnosed myeloma: a randomized study from the EBMT [abstract]. *Blood* 2000;96:558a. Abstract 2396.

7u. Fermand JP, Marolleau JP, Alberti C, Divine M, Leblond V, Macro M, et al. In single versus tandem high dose therapy (HDT) supported with autologous blood stem cell (ABSC) transplantation using unselected or CD34 enriched ABSC: preliminary results of a two by two designed randomized trial in 230 young patients with multiple myeloma (MM) [abstract]. *Blood* 2001;98:815a. Abstract 3387.

8u. Moreau P, Facon T, Hulin C, Attal M, Michallet M, Maloisel F, et al. Superiority of 200 mg/m2 melphalan (HDM200) over 8 Gy total body irradiation plus 140 mg/m2 melphalan (TBI + HDM140) as conditioning regimens for peripheral blood stem cell (PBSC) transplantation in patients with newly diagnosed multiple myeloma (MM). Final analysis of the IFM9502 randomized trial. VIIIth International Myeloma Workshop, Banff, Canada, 2001. Abstract P43.

9u. Fermand JP, Marolleau JP, Alberti C, Divine M, Leblond V, Macro M, et al. Single versus tandem high dose therapy (HDT) supported with autologous blood stem cell (ABSC) transplantation using unselected or CD-34 enriched ABSC: preliminary results of a two by two designed randomized trial in 230 young patients with multiple myeloma (MM). VIIIth International Myeloma Workshop, Banff, Canada, 2001. Abstract P61.

10u. Attal MM, Harousseau JL, Facon TT, Michaux JL, Guilhot FF, Fruchard CC, et al. Single versus double transplantation in myeloma: a prospective randomized trial of the Inter Groupe Francophone du Myelome (IFM) [abstract]. *Blood* 2000;96:557a. Abstract 2393.

11u. Attal M, Harousseau JL, Facon T. Single versus double transplant in myeloma: a randomized trial of the “Inter Groupe Français Du Myélome” (IFM). VIIIth International Myeloma Workshop, Banff, Canada, 2001. Abstract S15.

12u. Attal M, Harousseau J-L, Facon R, Guilhot F, Doyen C, Fuzibet J-G, et al. Double autologous transplantation improves survival of multiple myeloma patients: final analysis of a prospective randomized study of the “Intergroupe Francophone du Myelome” (IFM 94) [abstract]. *Blood* 2002;100:5a. Abstract 7.

Education and Information

13u. Cavo M, Tosi P, Zamagni E, Ronconi S, Cellini C, Cangini D, et al. The “Bologna 96” clinical trial of single vs. double PBSC transplantation for previously untreated MM: results of an interim analysis. VIIIth International Myeloma Workshop, Banff, Canada, 2001. Abstract S16.
14u. Cavo M, Tosi P, Zamagni E, Cellini C, Ronconi S, De Vivo A, et al. The “Bologna 96” clinical trial of single vs. double autotransplants for previously untreated multiple myeloma patients [abstract]. *Blood* 2002;100(11 part 1 of 2):179a. Abstract 669.
15u. Poenisch W, Mitrou PS, Merkle K, Herold M, Assmann M, Wilhelm G, et al. Bendamustine/prednisone versus melphalan/prednisone in the primary treatment of multiple myeloma: a randomized trial of the East German Study Group for Hematology/Oncology (OSHO). VIIIth International Myeloma Workshop, Banff, Canada, 2001. Abstract P139.
16u. Schneider P, Kropff M, Berdel WE, Heyll A, Haas R, for the Westgerman Myeloma Study Group. Randomized trial comparing an intensified therapy (HD-IMC) with a standard high dose therapy (HD-M) for multiple myeloma. VIIIth International Myeloma Workshop, Banff, Canada, 2001. Abstract P46.
17u. Blade J, San Miguel JF, Fontanillas M, Esteve J, Maldonado J, Alcala A, et al. Increased conventional chemotherapy does not improve survival in multiple myeloma: long-term results of two PETHEMA trials including 914 patients. *Hematol J* 2001;2:272-8.
18u. Segeren CM, Sonneveld P, van der Holt B, Vellenga E, Croockewit AJ, Verhoef GE, et al. Overall and event-free survival are not improved by the use of myeloablative therapy following intensified chemotherapy in previously untreated patients with multiple myeloma: a prospective randomized phase 3 study. *Blood* 2003;101:2144-51.
19u. Attal M, Harousseau J-L. Randomized trial experience of the Intergroupe Francophone du Myélome. *Semin Hematol* 2001;38:226-30.
20u. Vescio R, Schiller G, Stewart AK, Ballester O, Noga S, Rugo H, et al. Multicenter phase III trial to evaluate CD34+ selected versus unselected autologous peripheral blood progenitor cell transplantation in multiple myeloma. *Blood* 1999;93:1858-68.
21u. Stewart AK, Vescio R, Schiller G, Ballester O, Noga S, Rugo H, et al. Purging of autologous peripheral-blood stem cells using CD34 selection does not improve overall or progression-free survival after high-dose chemotherapy for multiple myeloma: results of a multicenter randomized controlled trial. *J Clin Oncol* 2001;19:3771-9.
22u. Moreau P, Facon T, Attal M, Hulin C, Michallet M, Maloisel F, et al. Comparison of 200 mg/m^2 melphalan and 8 Gy total body irradiation plus 140 mg/m2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. *Blood* 2002;99:731-5.
23u. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al, for the Medical Research Council Adult Leukemia Working Party. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med* 2003;348:1875-83.
24u. Gahrton G, Svensson H, Cavo M, Apperley J, Bacigalupo A, Bjorkstrand B, et al. Progress in allogeneic bone marrow and peripheral blood stem cell transplantation for multiple myeloma: a comparison between transplants performed 1983-93 and 1994-98 at European Group for Blood and Marrow Transplantation centres. *Brit J Haematol* 2001;113:209-16.
25u. Bjorkstrand B, Svensson H, Goldschmidt H, Ljungman P, Apperley J, Mandelli F, et al. Alpha-interferon maintenance treatment is associated with improved survival after high-dose treatment and autologous stem cell transplantation in patients with multiple myeloma: a retrospective registry study from the European Group for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant* 2001;5:511-5.
26u. Barlogie B, Jagannath S, Desikan KR, Mattox S, Vesole D, Siegel D, et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. *Blood* 1999;93:55-65.

Evaluation Information

PG 6-6 Document Assessment Review Tool.

cancer care ontario | action cancer ontario program in evidence-based care | programme de soins fondé sur des preuves	***Document Assessment and Review Tool***
Number and title of document under review	PG6-6: Optimal Therapy for Patients Diagnosed with Multiple Myeloma and The Role of High-Dose Chemotherapy and Stem Cell Support
Date of current version	June 2003
Clinical reviewer	Dr. T. Kouroukis
Research coordinator	Bryan Rumble
Date DART initiated	17 September 2010
Date and final results / outcomes	24 May 2011
Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.	
1. Is there still a need for a guideline covering one or more of the topics in this document? Answer Yes or No, and explain if necessary:	1. Yes If No, then the document should be **ARCHIVED**[1] with no further action; **go to 11**. If Yes, then **go to 2**.
2. Are all the current recommendations based on the current questions **definitive**[*] or **sufficient**[§], and have less than **5 years elapsed** since the latest search? Answer Yes or No, and explain if necessary:	2. No Current recommendations are sufficient. However, more than 5 years have elapsed since the last search. If Yes, the document can be **ENDORSED**[2] with no further action; **go to 11**. If No, **go to 3**.
3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:	3. No If Yes, the document should be taken off the website as soon as possible. A **WARNING**[¶] should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, g**o to 4**.
4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:	4. YES • there is a designated research co-ordinator at the PEBC to carry out the literature search If No, a **DEFERRAL**[3] should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go **to 5**.
5a. List below any new, relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered.	
Original Question(s): 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?	
5b. List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence	
Inclusion criteria: Articles were selected based on the following criteria: 1. Randomized controlled trials (RCTs) of patients with multiple myeloma that reported on the outcomes of survival and/or quality of life. 2. Non-randomized trials were included if they had appropriate contemporaneous control groups and reported on the outcomes of survival and/or quality of life. Study results were used to estimate both the potential efficacy and appropriate timing of autologous and allogeneic transplantation. Meta-analyses, systematic reviews and economic analyses were also included. Because of insufficient data addressing the specifics of the transplant manoeuvre and which patients would be most likely to benefit from transplantation, a second literature search was performed to include data from single-arm studies.	

Evaluation Information

5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.

Brief Summary/Discussion of New Evidence:

Search date	Database	Number of hits	Number ordered for full text review	Number retained
Sept 17, 2010	MEDLINE	955	37	30
Sept 29, 2010	Cochrane dB of SRs	39	1 protocol	0
Sept 29, 2010	ASCO 2008-2010	160	4	2
Sept 29, 2010	ASH 2008-2009	1005	7	4
Sept 29, 2010	CMA Infobase	0	-	-
Sept 29, 2010	NGC dB	24	1	1
TOTALS	**-**	**2183**	**49**	**37**

Table 1: Comparison of peripheral blood stem cell or marrow transplantation from RCTs.

Authors, year	Arm 1 (N)	Arm 2 (N)	Arm 3 (N)	Response-to-treatment (%)	Median event-free survival (Months)	Overall survival (%)
Arora M et al, 2004 (1)	G-CSF →autoSCT 35	GM-CSF →autoSCT 37	-	27 vs. 19, p=0.6-	-	-
Fenk R et al, 2005 (2)	HD-IMC →autoSCT 26	HD-M →autoSCT 30	-	30 vs. 10, p=0.1	20 vs. 16, p=0.8	p=ns
Fermand JP et al, 2005 (3)	HDT_1 →autoSCT 94	SDT_1 96	-	36 vs. 20, p=ns	25.3 vs. 18.7, p=0.07	36 vs 36, p=ns
Barlogie B et al, 2006 S9321 (4)	HDT_2 261	SDT_2 255	-	7 vs. 11 p=ns	-	38 vs. 38, p=ns
Barlogie B et al, 2006 (5)	SDT_3+Thal →autoSCT 323	SDT_3-Thal →autoSCT 345	-	62 vs. 43, p<0.001	-	65 vs. 65, p=ns
Moreau P et al, 2006 IFM 99-04 (6)	DXM+mel220 →autoSCT 85	DXM+BE8 +mel220 →autoSCT 81	-	30.6 vs. 34.6, p=0.62	35 vs. 31, p=0.39	46 vs. 51, p=0.9
Bourhis JH et al, 2007 EBMT (7)	CD34+ autoSCT 56	autoSCT 55	-	27 vs. 20, p=0.5	-	51 vs. 45, p=ns
Facon T et al, 2007 IFM 99-06 (8)	MP 196	MPT 125	Mel100+autoSCT 126	2 vs. 13 vs. 18 MP vs. MPT, p=0.0008 MP vs. MEL100, p<0.0001	-	MPT vs. MP, HR=0.56, p=0.002 MPT vs. MEL100, HR=0.6, p=0.009 MP vs. MEL100, p=0.75
Mellqvist UH et al, 2007 NMSG (9)	VAD+autoSCT 156	Cy-Dex+autoSCT 158	-	36 vs. 32, p=ns	29 vs. 29, p=ns	75 vs. 75, p=ns
Cavo M et al, 2009 [abstract]M (10)	VTD →autoSCT 236	TD →autoSCT 238	-	19 vs. 5, p<0.001	-	p=ns
Spencer A et al, 2009 (11)	TA →autoSCT 114	CA →autoSCT 129	-	65 vs. 44, p<0.001	-	86 vs. 75, p=0.004
Lokhorst H et al, 2010 HOVON-50 (12)	VAD →autoSCT 268	TAD →autoSCT 268	-	23 vs. 31, p=0.04	22 vs. 34, p<0.001	p=0.29
McCarthy PL et al, 2010 CALGB 100104 [abstract] (13)	AutoSCT +lenalidomide 210	AutoSCT alone 208	-	-	-	p=0.2
Palumbo A et al, 2010 (14)	MEL200 →autoSCT 149	MEL100 →autoSCT 149	-	15 vs. 8, p=0.07	-	HR=0.74, p=0.13

Note: G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte macrophage colony stimulating factor; HD-IMC, High-dose idarubicin, melphalan,

Education and Information

cyclophosphamide; HD-M, High-dose melphalan; HDT_1, vincristine, doxorubicin, methylprednisolone (VAMP regimen); SDT_1, vincristine, melphalan, cyclophosphamide. prednisone; HDT_2, melphalan plus radiation therapy; SDT_2, vincristine, carmustine, melphalan, cyclophosphamide, prednisone; SDT_3, dexamethasone, cyclophosphamide, etoposide, cisplatin [or] cyclophosphamide, doxorubicin, dexamethasone [or] dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide; DXM, dexamethasone; MEL200, melphalan 200 mg/m^2; BE8, anti-IL6-mAb; MP, melphalan, prednisone; MPT, melphalan, prednisone, thalidomide; MEL100, melphalan 100 mg/m^2; VAD, vincristine, doxorubicin, dexamethasone; Cy-Dex, cyclophosphamide, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone; TD, thalidomide, dexamethasone; TA, thalidomide; CA, prednisone; TAD, thalidomide, doxorubicin, dexamethasone.

Table 2: Comparison of peripheral blood stem cell or marrow transplantation from non-randomized trials.

Authors, year	Group 1 (N)	Group 2 (N)	Response-to-treatment (%)	Median event-free survival (Months)	Overall survival (%)
Kaufmann H et al, 2003 (15)	HDT_1 77	SDT_1 64	NR	PFS: 30. Vs. 21.2, p=0.01	Median: 54.9 vs. 49.4, p=0.048
Corso A et al, 2004 (16)	DCEP →autoSCT 106	HD-CTX →autoSCT 40	7.5 vs. 0, p<0.05	-	-
Murakami H et al, 2004 (17)	AutoPBSCT 60	SDT_2 90	-	-	Median: 76 vs. 28, p<0.0001
Cavo M et al, 2005 (18)	Thal-Dex→ autoPBSCT 100	SDT_2 →autoPBSCT 100	10 vs. 8, p>0.05	-	-
Gahrton G et al, 2007 (19)	alloPBSCT -RIC: 596 -MAC: 401 1179	alloBM -RIC: 52 -MAC: 369 488	PBSCT, RIC: 33.5 PBSCT, MAC: 41.9 BM, RIC: 16.3 BM, MAC: 42.5 MAC, PBSCT vs. BM, p=ns RIC, PBSCT (34) vs. BM (16), p<0.05	-	-
Kumar SK et al, 2008 (20)	Group 1 (N): autoSCT+VAD 116 Group 2 (N): autoSCT+Dex 165	Group 3 (N): autoSCT+Thal-Dex 156 Group 4 (N): autoSCT+Len-Dex 35	VAD: 48.2 DEX: 38.2 Thal-DEX: 30.1 Len-DEX: 35	-	-
Rosinol L et al, 2008 PETHEMA/GEM (21)	Tandem autoSCT 85	autoSCT→RIC alloSCT 25	11 vs. 40, p=0.001	25.8 vs. 26.7, p=0.9	60 vs. 61.8, p=ns
Sabry W et al, 2008 [abstract] (22)	AutoSCT→alloSCT, NMA 73	AutoSCT→alloSCT, Non-NMA 39	-	-	67 vs. 44, p=0.001
Corso A et al, 2009 [abstract] (23)	Group 1: VAD 145 Group 2: VAD+Thal-Dex 67 Group 3: Vel-Dex 57		19 vs. 22 vs. 38, p<0.05 favouring group 3 over group 1 and 2	-	51 vs. 65 vs. 90, favouring group 3 over group 1 and 2
Eom HS et al, 2009 (24)	→autoSCT Bortezomib regimens: Newly diagnosed: 16 Previously treated: 14	→autoSCT VAD 39	-	-	P=0.835
Gupta A et al, 2009 [abstract] (25)	HDT_2 95	SDT_3 149	34.7 vs. 12.8, p<0.001	-	66.6 vs. 20.7, p<0.05
Gay F et al, 2010 (26)	Len/Dex 228	Thal/Dex 183	13.6 vs. 3.3, p<0.001	-	97.3 vs. 97.8, p=ns

Note: HDT_1, melphalan, radiation therapy, alloBMT (N=10); SDT_1, melphalan, prednisone [or] vincristine, melphalan, cyclophosphamides, prednisone [or] VAD (vincristine, doxorubicin, dexamethasone); DCEP, dexamethasone, cyclophosphamide, etoposide, cisplatinum; HD-CTX, VAD, G-CSF, high-dose cyclophosphamide; SDT_2, VAD; Thal-Dex, thalidomide, dexamethasone; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; Len, lenalidomide; NMA, non-myeloablative; HDT_2, melphalan 200 mg/m^2, SDT_3, undefined in abstract.

Table 3: Comparison of single versus double transplantations from RCTs.

Authors, year	Single transplant N	Double transplant N	Complete response rate (%)	Event-free survival (months)	Overall survival (7-year, %)	TRM (%)
Attal M et al, 2003 IFM (27)	autoSCT 199	autoSCT 200	42 vs. 50, p=ns	25 vs. 30, p=0.03	48 vs. 58, p=0.01	4 vs. 6, p=0.4

Education and information

Cavo M et al, 2007 Bologna 96 (28)	autoSCT 163	autoSCT 158	33 vs. 47, p=0.008	23 vs. 35, p=0.001	46 vs. 43, p=0.9	3 vs. 4, p=0.7

Note: SCT, stem cell transplantation

Table 4: Comparison of double versus triple transplantations from RCTs.

Authors, year	Double transplant N	Triple transplant N	Complete response rate (%)	Event-free survival (months)	Overall survival (7-year, %)	TRM (%)
Ludwig H et al, 2008 [abstract] (29)	MEL200 →autoSCT	MEL100 →autoSCT	41 vs. 41, p=ns	-	85 vs. 81, p=ns	NR

Note: MEL200, melphalan 200 mg/m^2.

Table 5: Meta-analyses.

Authors, year	Comparison	Response-to-treatment (%)	Median event-free survival (Months)	Overall survival (%)
Levy V et al, 2005 Meta-analysis (Three trials, IFM 90, MAG 90, MAG 91) (30)	HDL-ASCT (285) vs. SDT (290)	13 vs. 11.9 vs. 5.3, p=ns	-	26 vs. 23, p=ns

Note: HDL-ASCT, high-dose autoSCT; SDT, conventional chemotherapy regimens.

Table 6: Clinical Practice Guidelines, other summative evidence.

Authors, year	Endorsing Entity	Recommendations
Barosi G et al, 2004 (31) Clinical Practice Guideline	SIE, SIES, GITMO	-Those patients aged below 65 years who do not have severe co-morbidities should receive autologous stem cell transplantation, while patients not candidates for autologous stem cell transplantation should receive oral melphalan and prednisone. -Interferon-a should not be associated with conventional chemotherapy, but it can be offered with or without steroids as a maintenance therapy to patients who have reached a plateau phase. -High-dose dexamethasone-containing regimens or high-dose dexamethasone alone are recommended as a first-line therapy when cytoreduction is urgently required (i.e., MM with spinal cord compression or with rapidly progressive renal failure). --MM patients with moderate-to-severe anemia should receive erythropoietin, while patients with bone disease or osteopenia should receive long-term bisphophonates.
Smith A et al, 2005 (32)	UK Myeloma Forum, Nordic Myeloma Study Group, British Committee for Standards in Haematology	**Initial chemotherapy where HDT is not planned – 'conventional therapy'** • VAD or a VAD-type regimen should be used as initial therapy in patients where future HDT is planned (grade B recommendation; level II a evidence). • No firm recommendation can be made on whether oral idarubicin and dexamethasone or high-dose dexamethasone alone are equivalent to VAD. • For older patients in whom HDT is not planned, either melphalan or cyclophosphamide should be used, with or without prednisolone (grade A recommendation; level Ia evidence). • Thalidomide should only be used in newly diagnosed patients in the context of a clinical trial (grade C recommendation; level IV evidence). • In all patients dose modifications may be required because of impaired renal function or cytopenia (grade C recommendation; level IV evidence). **High-dose therapy and transplantation: Autologous stem cell transplantation** • HDT with ASCT should be part of the primary treatment strategy in newly diagnosed patients up to the age of 65 years with adequate performance status and organ function (grade A recommendation; level Ib evidence). • HDT with ASCT may be considered in patients aged >65 years with good performance status (grade B recommendation; level IIa evidence). • Conditioning with melphalan alone, without TBI, is recommended (grade B recommendation; level IIa evidence). The usual dose is 200 mg/m2 but the dose should be reduced in older patients (over 65–70 years) and in renal failure. • Planned double (tandem) ASCT cannot be recommended on the current evidence. However, it is recommended that enough stem cells are collected to support two high-dose procedures (grade C recommendation; level IV evidence). • Currently available methods of purging have not demonstrated clinical benefit and are not, therefore, recommended (grade A recommendation; level Ib evidence). • HDT and ASCT may be considered for patients with severe renal impairment (creatinine clearance/GFR <30 ml/min) but the dose of melphalan should be

Education and Information

		reduced to 140 mg/m2 (grade B recommendation; level IIb evidence) and the procedure should only be carried out in a centre with special expertise (grade C recommendation; level IV evidence). **High-dose therapy and transplantation: Allogeneic stem cell transplantation** **Transplantation with conventional conditioning regimens** • Patients up to the age of 50 years who have achieved at least a partial remission after initial therapy may be considered for HLA-matched sibling allogeneic SCT. The procedure should be performed as part of a clinical trial, where possible (grade B recommendation; level IIb evidence). • DLI should be considered for patients with persistent or progressive disease following transplantation (grade B recommendation; level IIa evidence). • SCT should be carried out in EBMT accredited centres where data are collected prospectively as part of international transplant registries (grade C recommendation; level IV evidence). • RIC allografting may be considered in patients up to the age of 70 years with an HLA-matched sibling (grade B recommendation; level IIb evidence). The procedure would usually follow an initial autograft, should be done early in the disease phase and should always be done as part of a clinical trial (grade C recommendation; level IV evidence). • Matched unrelated donor transplants using RIC may be considered within the context of a clinical trial. Conventional conditioning cannot presently be recommended (grade C recommendation).
Finnish Medical Society, 2007 (33) EBM Guidelines	Finnish Medical Society	**Pharmacological Treatment of Myeloma** • The aim is usually intensive therapy with the support of autologous stem cell transplantations (patients under 70 years). • Cytotoxic drugs (cyclophosphamide, melphalan, vincristine or adriamycin), often combined with corticosteroids • Corticosteroid alone (either dexamethasone or methylprednisolone) • Thalidomide (or lenalidomide) either alone or in combination with other drugs • Bortezomib (proteasome inhibitor) • Interferon in individual cases, usually in order to sustain the achieved treatment response **Stem Cell Transplantation** • Intensive treatment with the support of autologous stem cell transplantation is used increasingly and is often the first-line treatment for patients over 70 years of age (Johnson et al., 1998; DARE-989011, 2000). • Allogeneic stem cell transplantation is also used increasingly, but it is still possible only for few patients.
Anderson KC et al, 2009 (34) Clinical Practice Guideline	NCCN	Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplant. **Primary induction therapy for transplant candidates:** Bortezomib/dexamethasone (category 1) Bortezomib/cyclophosphamide/dexamethasone Bortezomib/doxorubicin/dexamethasone (category 1) Bortezomib/lenalidomide5/dexamethasone (category 2B) Bortezomib/thalidomide/dexamethasone (category 1) Dexamethasone (category 2B) Lenalidomide5/dexamethasone (category 1) Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B) Thalidomide/dexamethasone (category 2B) **Primary induction therapy for non-transplant candidates:** Bortezomib/dexamethasone Dexamethasone (category 2B) Lenalidomide/low-dose dexamethasone (category 1) Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B) Melphalan/prednisone (MP) Melphalan/prednisone/bortezomib (MPB) (category 1) Melphalan/prednisone/lenalidomide (MPL) Melphalan/prednisone/thalidomide (MPT) (category 1) Thalidomide/dexamethasone (category 2B) Vincristine/doxorubicin/dexamethasone (VAD) (category 2B) **Maintenance therapy:** Interferon (category 2B) Lenalidomide Steroids (category 2B) Thalidomide (category 1) ± prednisone (category 2B)
Harousseau JL et al, 2009 (35) Clinical Practice Guideline	ESMO	**Advanced stage or symptomatic myeloma (CRAB) (II or III)** **Elderly patients:** • Oral combination of melphalan (9 mg/m2/day for 4 days) and prednisone (30 mg/m2/day for 4 days) was previously the standard of treatment for patients ineligible for high-dose chemotherapy with stem-cell support [I, A]. Cycles • are repeated every 4–6 weeks until a stable response is achieved.

Education and Information

		• Multiagent chemotherapy has not been proved superior and may even be inferior in elderly patients [I, A]. • Recently, two randomized studies have shown that the combination of melphalan–prednisone with thalidomide (100 mg/day) is superior to melphalan–prednisone [I, A]. • Bortezomib in combination with melphalan–prednisone also achieved significantly higher survival rates [I, A]. Another novel agent (lenalidomide) is currently being tested with low-dose dexamethasone in patients >65 years of age. **Younger patients (<65 years)** • For patients in good clinical condition, high-dose therapy with autologous stem-cell transplantation (ASCT) is the standard treatment [II, B]. • Attempts to increase the complete remission rate before autologous transplantation are ongoing. Currently, the induction therapy should be dexamethasone-based in order to avoid stem-cell damage induced by alkylating agents. In randomized studies, combinations of novel agents (thalidomide • or bortezomib) plus dexamethasone are superior to the classical VAD regimen (vincristine, adriamycine and high-dose dexamethasone). • Melphalan 200 mg/m2 i.v. is the preparative regimen before autologous transplantation [II, B]. Peripheral blood progenitor cells should be used as the source of stem cells, rather than bone marrow [III, B]. **Double ASCT:** • Three randomized studies show superiority of double versus single ASCT. However, the French (IFM 94) and Italian study suggests that double ASCT does not benefit patients in complete remission after one ASCT. • Long-term administration of bisphosphonates (oral or i.v.) reduces the incidence of skeletal events and should be proposed for patients with stage III or relapsed disease receiving conventional dose chemotherapy [II, A].

New References Identified (alphabetical order):

1. Arora M, Burns LJ, Barker JN, Miller JS, Defor TE, Olujohungbe AB, et al. Randomized comparison of granulocyte colony-stimulating factor versus granulocyte-macrophage colony-stimulating factor plus intensive chemotherapy for peripheral blood stem cell mobilization and autologous transplantation in multiple myeloma. Biol Blood Marrow Transplant. 2004 Jun;10(6):395-404.
2. Fenk R, Schneider P, Kropff M, Huenerlituerkoglu AN, Steidl U, Aul C, et al. High-dose idarubicin, cyclophosphamide and melphalan as conditioning for autologous stem cell transplantation increases treatment-related mortality in patients with multiple myeloma: results of a randomised study. Br J Haematol. 2005 Aug;130(4):588-94.
3. Fermand JP, Katsahian S, Divine M, Leblond V, Dreyfus F, Macro M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol. 2005 Dec 20;23(36):9227-33.
4. Barlogie B, Kyle RA, Anderson KC, Greipp PR, Lazarus HM, Hurd DD, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. J Clin Oncol. 2006 Feb 20;24(6):929-36.
5. Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med. 2006 Mar 9;354(10):1021-30.
6. Moreau P, Hullin C, Garban F, Yakoub-Agha I, Benboubker L, Attal M, et al. Tandem autologous stem cell transplantation in high-risk de novo multiple myeloma: final results of the prospective and randomized IFM 99-04 protocol. Blood. 2006 Jan 1;107(1):397-403.
7. Bourhis JH, Bouko Y, Koscielny S, Bakkus M, Greinix H, Derigs G, et al. Relapse risk after autologous transplantation in patients with newly diagnosed myeloma is not related with infused tumor cell load and the outcome is not improved by CD34+ cell selection: long term follow-up of an EBMT phase III randomized study. Haematologica. 2007 Aug;92(8):1083-90.
8. Facon T, Mary JY, Hulin C, Benboubker L, Attal M, Pegourie B, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet. 2007 Oct 6;370(9594):1209-18.
9. Mellqvist UH, Lenhoff S, Johnsen HE, Hjorth M, Holmberg E, Juliusson G, et al. Cyclophosphamide plus dexamethasone is an efficient initial treatment before high-dose melphalan and autologous stem cell transplantation in patients with newly diagnosed multiple myeloma - Results of a randomized comparison with vincristine, doxorubicin, and dexamethasone. Cancer. 2008 Jan 1;112(1):129-35.
10. Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, et al. A Phase III Study of Double Autotransplantation Incorporating Bortezomib-Thalidomide-Dexamethasone (VTD) or Thalidomide-Dexamethasone (TD) for Multiple Myeloma: Superior Clinical Outcomes with VTD Compared to TD. ASH Annual Meeting Abstracts. 2009 November 20, 2009;114(22):351-.
11. Spencer A, Prince HM, Roberts AW, Prosser IW, Bradstock KF, Coyle L, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol. 2009 Apr 10;27(11):1788-93.
12. Lokhorst HM, van der Holt B, Zweegman S, Vellenga E, Croockewit S, van Oers MH, et al. A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. Blood. 2010 Feb 11;115(6):1113-20.
13. McCarthy PL, Owzar K, Anderson KC, Hofmeister CC, Hassoun H, Hurd DD, et al. Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB 100104. J Clin Oncol (Meeting Abstracts). 2010 May 20, 2010;28(15_suppl):8017-.
14. Palumbo A, Bringhen S, Bruno B, Falcone AP, Liberati AM, Grasso M, et al. Melphalan 200 mg/m(2) versus melphalan 100 mg/m(2) in newly diagnosed myeloma patients: a prospective, multicenter phase 3 study. Blood. 2010 Mar 11;115(10):1873-9.
15. Kaufmann H, Ackermann J, Greinix H, Nosslinger T, Gisslinger H, Keck A, et al. Beneficial effect of high-dose chemotherapy in multiple myeloma

For Information and Information

patients with unfavorable prognostic features. Ann Oncol. 2003 Nov;14(11):1667-72.
16. Corso A, Barbarano L, Zappasodi P, Cairoli R, Alessandrino EP, Mangiacavalli S, et al. The VAD-DCEP sequence is an effective pre-transplant therapy in untreated multiple myeloma. Haematologica. 2004 Sep;89(9):1124-7.
17. Murakami H, Fujii H, Inaba T, Shimazaki C, Okamoto S, Miwa A, et al. High-dose chemotherapy and autologous peripheral blood stem cell transplantation in high-risk multiple myeloma. Eur J Haematol. 2004 Sep;73(3):169-73.
18. Cavo M, Zamagni E, Tosi P, Tacchetti P, Cellini C, Cangini D, et al. Superiority of thalidomide and dexamethasone over vincristine-doxorubicindexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. Blood. 2005 Jul 1;106(1):35-9.
19. Gahrton G, Iacobelli S, Bandini G, Bjorkstrand B, Corradini P, Crawley C, et al. Peripheral blood or bone marrow cells in reduced-intensity or myeloablative conditioning allogeneic HLA identical sibling donor transplantation for multiple myeloma. Haematologica. 2007 Nov;92(11):1513-8.
20. Kumar SK, Dingli D, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Impact of pretransplant therapy in patients with newly diagnosed myeloma undergoing autologous SCT. Bone Marrow Transplant. 2008 Jun;41(12):1013-9.
21. Rosinol L, Perez-Simon JA, Sureda A, de la Rubia J, de Arriba F, Lahuerta JJ, et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. Blood. 2008 Nov 1;112(9):3591-3.
22. Sabry W, Fontaine A, Le Blanc R, Sauvageau G, Roy D-C, Busque L, et al. Tandem Autologous-Nonmyeloablative (NMA) Allogeneic(Allo) Transplant (Tx) in Newly Diagnosed Multiple Myeloma (MM) Leads to Improved Survival When Compared to Conventional Allogeneic Transplant. ASH Annual Meeting Abstracts. 2008 November 16, 2008;112(11):3299-.
23. Corso A, Mangiacavalli S, Barbarano L, Citro A, Brasca P, Montalbetti L, et al. Evaluation of the Impact of Three Different Pre-Transplant Strategies On the Outcome of Myeloma Patients Candidates to High-Dose Therapy. ASH Annual Meeting Abstracts. 2009 November 20, 2009;114(22):1223-.
24. Eom HS, Min CK, Cho BS, Lee S, Lee JW, Min WS, et al. Retrospective comparison of bortezomib-containing regimens with vincristine-doxorubicin-dexamethasone (VAD) as induction treatment prior to autologous stem cell transplantation for multiple myeloma. Jpn J Clin Oncol. 2009 Jul;39(7):449-55.
25. Gupta A, Kumar L, Dabkara D, Gupta D, Sharma O, Sreeniwas V. Multiple myeloma: Autologous stem cell transplantation versus conventional chemotherapy--A retrospective age and stage matched analysis. J Clin Oncol (Meeting Abstracts). 2009 May 20, 2009;27(15S):7041-.
26. Gay F, Hayman SR, Lacy MQ, Buadi F, Gertz MA, Kumar S, et al. Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma: a comparative analysis of 411 patients. Blood. 2010 Feb 18;115(7):1343-50.
27. Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med. 2003 Dec 25;349(26):2495-502.
28. Cavo M, Tosi P, Zamagni E, Cellini C, Tacchetti P, Patriarca F, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. J Clin Oncol. 2007 Jun 10;25(17):2434-41.
29. Ludwig H, Spicka I, Linkesch W, Greil R, Kasparu H, Gunsilius E, et al. Double Transplantation with Melphalan (200 mg/m2) Compared with Triple Transplantation with Intermediate Dose Melphalan (100 mg/m2) in Patients with Multiple Myeloma. ASH Annual Meeting Abstracts. 2008 November 16, 2008;112(11):3317-.
30. Levy V, Katsahian S, Fermand JP, Mary JY, Chevret S. A meta-analysis on data from 575 patients with multiple myeloma randomly assigned to either high-dose therapy or conventional therapy. Medicine (Baltimore). 2005 Jul;84(4):250-60.
31. Barosi G, Boccadoro M, Cavo M, Corradini P, Marchetti M, Massaia M, et al. Management of multiple myeloma and related-disorders: guidelines from the Italian Society of Hematology (SIE), Italian Society of Experimental Hematology (SIES) and Italian Group for Bone Marrow Transplantation (GITMO). Haematologica. 2004 Jun;89(6):717-41.
32. Smith A, Wisloff F, Samson D. Guidelines on the diagnosis and management of multiple myeloma 2005. Br J Haematol. 2006 Feb;132(4):410-51.
33. Finnish Medical Society Duodecim. Multiple Myeloma (MM). Helsinki: Wiley Interscience, John Wiley & Sons; 2007 [updated May 30, 2007; cited 2010 September 30].
34. Anderson KC, Alsina M, Bensinger W, Biermann JS, Chanan-Khan A, Cohen AD, et al. NCCN clinical practice guidelines in oncology: multiple myeloma. J Natl Compr Canc Netw. 2009 Oct;7(9):908-42.
35. Harousseau JL, Dreyling M. Multiple myeloma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009 May;20 Suppl 4:97-9.

Literature Search Strategy:

Medline

1. multiple myeloma/
2. myeloma.tw.
3. exp bone marrow transplantation/
4. bone marrow transplantation.tw.
5. 1 or 2
6. 3 or 4
7. exp drug therapy/
8. 6 or 7
9. 5 and 8
10. letter.pt.
11. comment.pt.
12. editorial.pt.
13. or/10-12
14. controlled:.sh,tw,pt.
15. clinical trial?.sh,tw,pt.
16. (double-blind method: or single-blind method:).sh,tw.
17. multicent: stud:.sh,tw.
18. multicenter study.pt.
19. placebos/
20. comparative study/

Education and Information

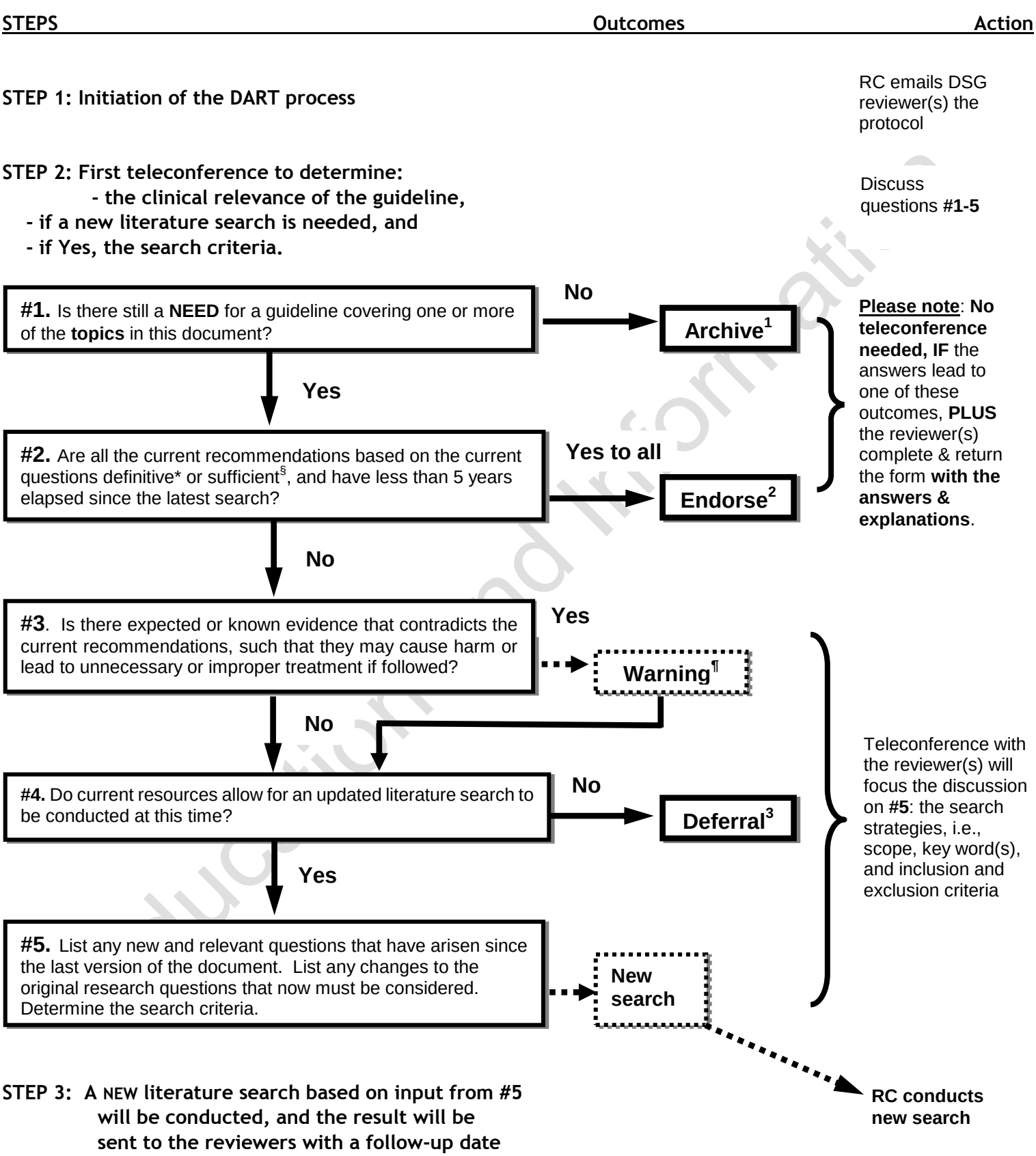
21. or/14-20
22. 9 and 21
23. (medline or medlars).sh,tw. or (embase or cancerlit or scisearch or database).tw.
24. (hand search: or manual search:).tw.
25. (pooling or pooled analy: or mantel haenszel or peto).tw.
26. (der simonian or dersimonian or fixed effect? or random effect?).tw.
27. review?.sh,tw,pt. or overview?.tw.
28. phase iii trial?.tw.
29. or/23-28
30. 9 and 29
31. meta-analysis.sh,pt.
32. (meta-anal: or metaanal: or metanal:).tw.
33. (systemic review? or systematic: overview?).tw.
34. (quantitativ: review? or quantitative: overview?).tw.
35. (methodologic: review? or methodologic: overview?).tw.
36. quantitativ: synthes:.tw.
37. or/31-36
38. exp practice guidelines/
39. exp guidelines/
40. guideline?.tw,pt,sh.
41. (practice guideline or guideline?).tw,sh,pt.
42. consensus.sh,tw,pt.
43. or/38-42
44. exp randomized controlled trials/
45. random:.tw,sh,pt.
46. 44 or 45
47. 9 and 37
48. 9 and 43
49. 9 and 46
50. 22 or 30 or 47 or 48 or 49
51. 50 not 13
52. limit 51 to human
53. limit 52 to yr="2003 -Current"

Go to 6.

6. Are the volume and content of the newly identified evidence such that a new document is necessary to address the topic?	6. No If Yes, then the document should be **ARCHIVED** with no further action; **go to 11**. If No, **go to 7**.
7. On initial review, does the newly identified evidence support the **existing recommendations**? Do the current recommendations **cover all relevant subjects** addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:	7. Yes. The newly identified evidence supports the existing recommendations. However, there is 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. If Yes, the document can be **ENDORSED**. If No, **go to 8**.
8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	8. Not Applicable If Yes, a **WARNING** note will be placed on the web site. If No, **go to 9**.
9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	9. Not applicable If Yes, the document update will be **DEFERRED**, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, **go to 10.**
10. An update should be initiated as soon as possible. List the expected date of completion of the update:	10. Not applicable An **UPDATE**[4] will be posted on the website, indicating an update is in progress.
11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.	
DSG Approval Date:	24 May 2011

Archived Information

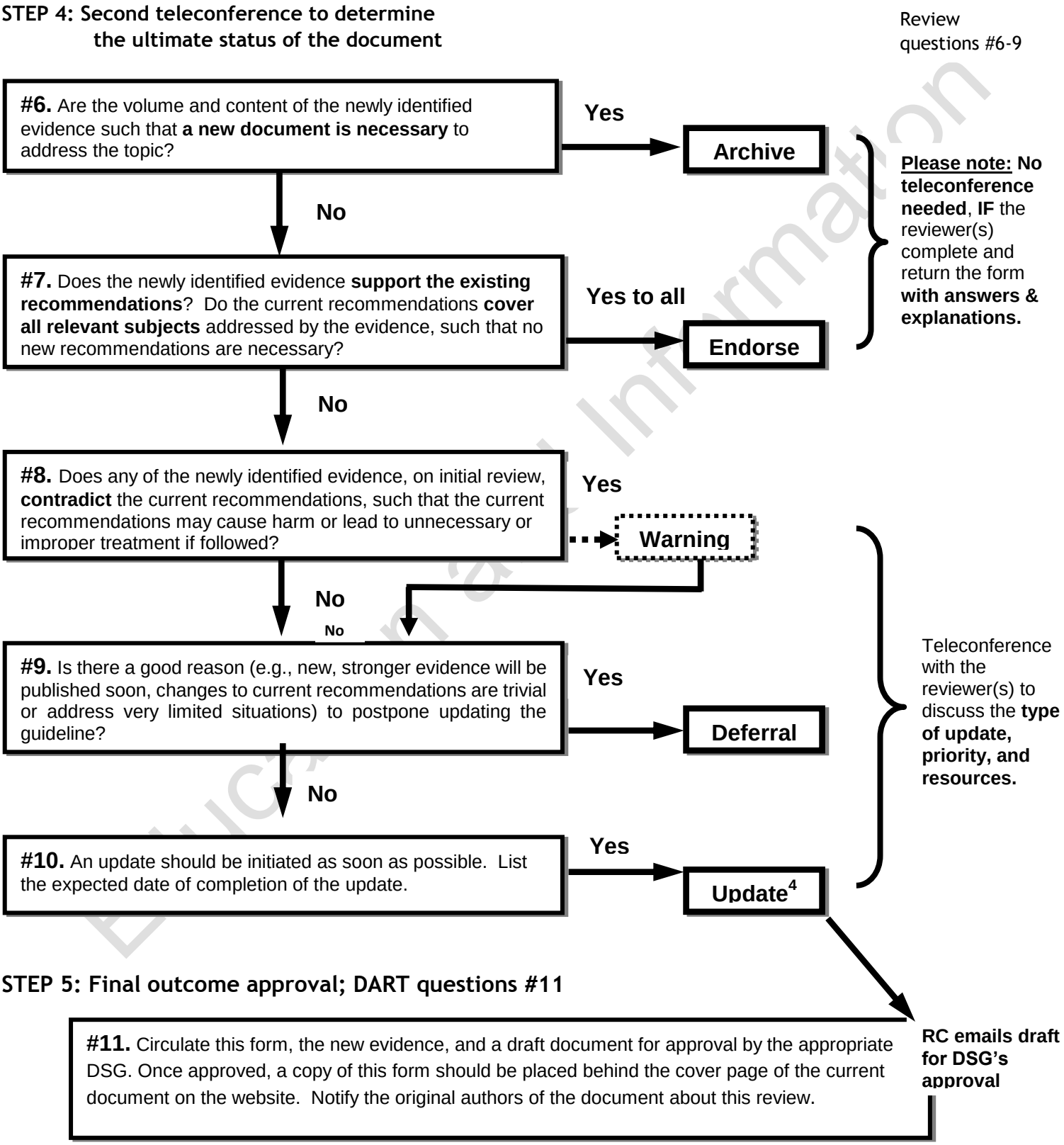
DART 5-STEP FLOW CHART



Guideline Information

Flow-chart (cont.)

STEPS	Outcomes	Action



Education and Information

DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

***DEFINITIVE RECOMMENDATIONS** – Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

[§]**SUFFICIENT RECOMMENDATIONS** – Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

[¶]**WARNING** – A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the Web site, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the website, and each page is watermarked with the term "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DEFERRAL** – A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.

Education and Information