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

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The Hematology Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative has systematically reviewed the published literature and, through a consensus process, developed an evidence-based practice guideline assessing the role of stem-cell transplantation in patients with multiple myeloma. The conclusions were validated by solicited feedback from 221 practitioners across Ontario, Canada. The guideline comprises six recommendations: 1) Autologous transplantation is recommended for patients with stage II or III myeloma and good performance status. Evidence of benefit is strongest for patients who are younger than 55 years of age and have a serum creatinine level less than 150 μmol/L (<1.7 mg/dL). Physicians must use clinical judgment in recommending transplantation to other patients. 2) Allogeneic transplantation is not recommended as routine therapy. 3) Patients potentially eligible for transplantation should be referred for assessment early after diagnosis and should not be extensively exposed to alkylating agents before collection of stem cells. 4) Autologous peripheral blood stem cells should be harvested early in the patient’s treatment course. The best available data suggest that transplantation is most advantageous when performed as part of initial therapy. 5) The comparative data addressing the specifics of the transplantation process are insufficient to allow definitive recommendations. In the absence of such data, a single transplant with high-dose melphalan, with or without total-body irradiation, is suggested for patients undergoing transplantation outside a clinical trial. 6) At this time, no conclusions can be reached about the role of interferon therapy after transplantation.


For author affiliations, see end of text.

For members of the Hematology Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative, see Appendix.

After more than three decades of clinical trials testing various standard-dose chemotherapy regimens, the disease course of patients with multiple myeloma has not changed appreciably. Conventional chemotherapy can provide effective palliation but is not curative (1). Case series have described encouraging results in patients with myeloma undergoing allogeneic or autologous bone marrow or peripheral blood stem-cell transplantation (2). Other studies of transplantation, including randomized trials, have been reported in the past 6 years (3, 4).

To facilitate decisions about treatment options, practice guidelines have been developed for use by health care providers and consumers. In Ontario, Canada, cancer treatments and policies are led by a state-funded organization, Cancer Care Ontario. To help derive treatment options, Cancer Care Ontario has developed the Program in Evidence-Based Care, which includes the Practice Guidelines Initiative. Disease Site Groups (DSGs), which comprise physicians, epidemiologists, and consumers, develop guidelines through a systematic process that involves assessment of evidence, consensus, and a validation process involving practitioners from across the province. Guideline topics are chosen through a prioritization process that includes the burden of illness, availability of evidence, perceived variation in practice, the potential to affect treatment decisions, and resource utilization.

The Hematology DSG noted that the use of transplantation for patients with myeloma varied among practices across the province. Variability in practice and emerging evidence of higher quality made this a priority topic for guideline development. To approach this topic, the DSG addressed the following questions: What is optimal standard-dose chemotherapy for patients with myeloma? In terms of survival, is peripheral blood stem-cell or marrow transplantation better than conventional chemotherapy? What is the relative efficacy of autologous versus allogeneic transplantation? What specifics of the transplantation process can be recommended? When should transplantation be performed? Who should (or should not) receive a transplant?

METHODS

Overview of Guideline Development

This guideline was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) using...
the methods of the Practice Guidelines Development Cycle (5). Members of the CCOPGI’s Hematology DSG selected, reviewed, and interpreted the evidence. This DSG comprises 25 members, including hematologists, medical and radiation oncologists, an epidemiologist, and 2 lay representatives. Several of the physician members have background training in epidemiology; 8 hematologists regularly perform stem-cell transplantation in clinical practice.

The DSG’s draft recommendations were circulated through a mailed survey to hematologists and medical or radiation oncologists in Ontario for feedback and involvement in a consensus process. Responses were used to guide the reformating of the draft into the final guideline recommendations. The Practice Guidelines Co-ordinating Committee (PGCC), which ensures consistency of guideline development across the DSGs of various tumor sites, approved the guideline. The CCOPGI has a standardized process to update each guideline report; the current guideline was updated and reviewed by the PGCC in October 2000.

**Literature Search Strategy**

We searched the MEDLINE, CANCERLIT, and Cochrane Library databases for literature published from 1992 to December 1997 and subsequently updated the search in October 1998, June 1999, and April 2000. For the searches, we combined multiple myeloma (as a Medical Subject Heading [MeSH] and text word) with bone marrow transplantation (MeSH and text word) and drug therapy (MeSH). Then, we combined these terms 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, we searched the PubMed and Physician Data Query (PDQ) (www.cancer.gov/search/clinical_trials/) databases and reviewed relevant conference proceedings (American Society of Hematology, 1997 to 1999, and American Society of Clinical Oncology, 1999 to 2000), article bibliographies, and personal files. To address the issue of optimal chemotherapy, we performed an additional search of the same databases using the term multiple myeloma (MeSH) combined with randomized controlled trials (MeSH) and the text word random in the title.

**Inclusion Criteria**

We selected study reports meeting one of the three following criteria: randomized trial or meta-analysis of therapy for patients with myeloma that reported survival or quality-of-life outcomes; nonrandomized comparative trial that addressed transplantation strategy, including a contemporaneous control group, and that reported survival or quality-of-life outcomes; or economic evaluation that addressed transplantation strategy. Because of insufficient data on the specifics of the transplantation process and the patients who would be most likely to benefit from transplantation, we performed a second search, which identified data from noncomparative case-series studies.

**Data Extraction and Interpretative Summary**

Three members of the DSG, including an epidemiologist, determined eligibility of the articles and abstracts obtained from the literature search. The lead DSG member for this guideline extracted and summarized relevant data according to the guideline question addressed. The DSG members then reviewed the summarized data and key articles. The DSG met formally three to four times annually; at these meetings, the members methodologically assessed the articles, interpreted the data, and debated specific points in an attempt to reach a consensus.

**Synthesizing the Evidence**

Because all of the nine randomized trials on transplantation addressed different questions, we did not statistically pool the data.

**DSG Consensus Process**

Through an iterative process that included debate at formal meetings and circulation of draft recommendations, we considered the implications of the appraised data for each guideline question. With this process, attempts were made to reach consensus; when this was impossible, minority opinions were recorded. Approval by each member of the DSG was required before circulation of the draft version for practitioner feedback and submission of the final guideline to the PGCC.

**Practitioner Feedback**

To obtain practitioner feedback, we mailed a survey to 211 practitioners in Ontario (94 hematologists, 93...
medical oncologists, and 24 radiation oncologists). The survey consisted of standardized items asking the practitioner to rate the quality of each draft guideline and to judge whether the draft recommendations should serve as a practice guideline. Written comments were invited. Follow-up reminders were sent at 2 weeks (by postcard) and 4 weeks (entire package). After exclusion of 18 retired practitioners, 137 of 193 practitioners (71%) responded; 90 of 137 respondents (66%) indicated that the guideline was relevant to their practice. Approval of the draft guideline was strong among these 90 practitioners: 91% agreed or strongly agreed that the summary of the evidence was acceptable, 87% agreed with the draft recommendations, and 81% approved of the recommendations as a practice guideline. Thirty-nine respondents provided written comments; these comments were, like the other responses, incorporated in the final guideline.

RESULTS

Sixty-six reports met the criteria for inclusion and are categorized in Table 1. In each section below, we describe the studies, summarize results, and describe the guideline development.

What Is Optimal Standard-Dose Chemotherapy for Patients with Multiple Myeloma?

To properly compare transplantation with conventional chemotherapy, we must define optimal conventional chemotherapy. We identified 30 randomized trials comparing therapies in previously untreated patients. Four meta-analyses (6–9) evaluated these data.

The Myeloma Trialists’ Collaborative Group (7) compared combination chemotherapy with melphalan plus prednisone in a meta-analysis of 27 trials. Twenty of these trials supplied individual-patient data. No difference in survival was detected. The proportional reduction in the annual odds of death was 1.5% in favor of combination chemotherapy (95% CI, −8% to 5%; P > 0.2), with an odds ratio (OR) of 0.99 (CI, 0.93 to 1.05). An earlier literature-based meta-analysis (6) of 18 trials also failed to detect a survival difference between groups (OR, 1.04 [CI, 0.90 to 1.19]; P > 0.2). Two meta-analyses evaluated interferon for multiple myeloma. An overview of 24 randomized trials published in abstract form (8) demonstrated that interferon improved

recurrence-free survival by 6 months and improved 3-year overall survival by 4%. Another meta-analysis (9) measured survival by a unique measure called the “mean lifetime survival.” This meta-analysis found no difference in survival rate between the group receiving interferon and the group not receiving interferon (3.9 vs. 3.4 years, respectively; P = 0.095).

Guideline Recommendation. Multiagent chemotherapy or melphalan plus prednisone is appropriate therapy for a control group in a comparison of transplantation versus standard-dose therapy. The addition of interferon is unlikely to influence outcomes in the control group.

In Terms of Survival, Is Autologous Peripheral Blood Stem-Cell or Bone Marrow Transplantation Better than Conventional Chemotherapy?

We reviewed two randomized and three nonrandomized comparisons (Table 2). Attal and colleagues (3) randomly assigned 200 previously untreated patients younger than 65 years of age with stage II or III (40) myeloma to conventional chemotherapy or to a strategy that included autologous bone marrow transplantation. Patients were randomly assigned before therapy began. Conventional therapy consisted of 12 months of vincristine, melphalan, cyclophosphamide, and prednisone—

Table 1. Evidence Included in This Practice Guideline Report

<table>
<thead>
<tr>
<th>Question</th>
<th>Studies Identified (References)</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is optimal standard-dose chemotherapy?</td>
<td>4 Meta-analyses (6–9)</td>
</tr>
<tr>
<td>In terms of survival, is peripheral blood stem-cell or autologous bone-marrow transplantation better than conventional chemotherapy?</td>
<td>2 Randomized trials (3, 4) 3 Nonrandomized comparisons (10–12) 1 Economic analysis (13)</td>
</tr>
<tr>
<td>What is the relative efficacy of autologous and allogeneic transplantation?</td>
<td>3 Nonrandomized comparisons (14–16)</td>
</tr>
<tr>
<td>What specifics of the transplantation process can be recommended?</td>
<td>6 Randomized trials (17–22) 4 Nonrandomized comparisons (23–26) 2 Noncomparative case series (27, 28) 2 Economic analyses (29, 30)</td>
</tr>
<tr>
<td>When should transplantation be performed?</td>
<td>1 Randomized trial (31)</td>
</tr>
<tr>
<td>Who should (or should not) receive a transplant?</td>
<td>2 Randomized trials (3, 4) 6 Nonrandomized comparisons (32–37) 2 Noncomparative case series (38, 39)</td>
</tr>
</tbody>
</table>
vincristine, carmustine, doxorubicin, and prednisone (VMCP–BVAP). Beginning with the ninth chemotherapy cycle, patients in this group received interferon, 3 million units/m² three times weekly. Patients randomly assigned to transplantation first received four to six cycles of VMCP–BVAP; patients who had a good performance status (World Health Organization performance status below grade 3), a serum creatinine level less than 150 μmol/L (<1.7 mg/dL), and an adequate bone marrow harvest collected after the fourth chemotherapy cycle received melphalan, 140 mg/m², and total-body irradiation, 800 cGy, followed by reinfusion of autologous bone marrow. After hematologic recovery, patients received interferon. The investigators analyzed the data on an intention-to-treat basis. Event-free and overall survival improved with autologous transplantation. In a subset analysis, this benefit appeared confined to patients younger than 61 years of age.

A second randomized trial (median follow-up, 56 months) assessed patients 55 to 65 years of age and was published in abstract form (4). The investigators detected no difference in event-free or overall survival between those receiving high-dose therapy and autologous bone marrow transplant and those receiving conventional VMCP. Three nonrandomized studies compared autologous bone marrow or peripheral stem-cell transplantation with matched (10, 11) or historical (12) controls receiving conventional therapy. All three reported superior outcomes in the patients undergoing transplantation.

A cost-effectiveness analysis using pooled data from published reports concluded that high-dose therapy with stem-cell reinfusion was cost-effective (13). The marginal cost increase associated with autologous transplantation was approximately $26 000 per life-year gained compared with conventional treatment.

**Guideline Recommendation.** When the DSG initially assessed this question, only the data from Attal and colleagues were available. The DSG agreed that the trial by Attal and colleagues was well conducted, but opinions varied about whether this evidence warranted a statement that autologous transplantation should be “recommended” or “offered” to specific patient groups. While remaining committed to principles of patient participation and autonomy in treatment decision making, there was consensus that the evidence supported transplantation as the “preferred” option and should be “recommended” to appropriate patients with stage II or III disease.

The DSG revisited this debate after receiving practitioner feedback on the draft recommendations. Nine respondents thought that one randomized trial provided insufficient evidence for the DSG to “recommend” stem-cell transplantation. They suggested that publication of the guideline be delayed until further evidence emerged or that the guideline be reworded to say that physicians should “offer” transplantation to appropriate candidates. After considering these options, the DSG again concluded that Attal and colleagues’ study supporting the recommendation was well done and represented the “preferred” option.

After a literature search update located a second randomized trial (in abstract form) (4), the DSG reconsidered its recommendation. The DSG concluded that while this trial was large and appeared well conducted, the nature of the publication (preliminary results reported in abstract form) was insufficient to cause a substantial change in the initial recommendations. However, as with the subset analysis performed by Attal and colleagues, which demonstrated that transplantation benefits were specifically identified in patients 60 years of age or younger, we recognized the potential for an interaction between age and treatment effect. The statement to “recommend” transplantation was thus re-

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**Table 2. Comparison of Autologous Peripheral Blood Stem-Cell or Marrow Transplantation with Conventional Therapy**

<table>
<thead>
<tr>
<th>Study (Reference), Report Type</th>
<th>Total Participants, n</th>
<th>Median Event-Free Survival*</th>
<th>Overall Survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, controlled trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attal et al. (3), full paper</td>
<td>200</td>
<td>At 5 y, 28% vs. 10%; P = 0.01</td>
<td>At 5 y, 52% vs. 12%; P = 0.03</td>
</tr>
<tr>
<td>Fermard et al. (4), abstract</td>
<td>190</td>
<td>Median, 24.3 vs. 18.7 mo; P = 0.07</td>
<td>Median, 55.3 vs. 50.4 mo; P &gt; 0.2</td>
</tr>
<tr>
<td>Nonrandomized comparisons</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barlogie et al. (10), full paper</td>
<td>239</td>
<td>Not reported</td>
<td>At 5 y, 61% vs. 39%; P = 0.01</td>
</tr>
<tr>
<td>Lennhoff et al. (11), full paper</td>
<td>548</td>
<td>Median, not reached vs. 44 mo; P &lt; 0.01</td>
<td>Not reported</td>
</tr>
<tr>
<td>Musto et al. (12), abstract</td>
<td>69</td>
<td>Median disease-free survival, 33 vs. 11 mo; P &lt; 0.02</td>
<td>Median, 49 vs. 25 mo; P &lt; 0.03</td>
</tr>
</tbody>
</table>

* Data reported as experimental (transplantation) group versus control group.
Worded to indicate that the supporting data were strongest for patients younger than 55 years of age.

**What Is the Relative Efficacy of Autologous and Allogeneic Transplantation?**

No reported randomized trial has compared autologous with allogeneic transplantation. Table 3 summarizes three nonrandomized comparisons. The European Bone Marrow Transplant Registry (14) reported a case-control comparison of 189 patients receiving allogeneic sibling donor transplants and 189 patients receiving autologous stem-cell transplants. Median survival was superior with autologous transplantation. The treatment-related mortality rate was 41% with allogeneic transplantation compared with 13% with autologous transplantation ($P < 0.001$). Meanwhile, the relapse rate was higher in patients undergoing autologous transplantation (70% vs. 50% at 48 months; $P = 0.04$).

Table 3 also summarizes two smaller concurrent cohort comparisons (15, 16) from single centers. Neither report detailed the reasons for assignment to autologous or allogeneic transplantation. Varterasian and colleagues (15) detected no difference in median event-free or overall survival; Couban and colleagues (16) reported superior median survival for the group undergoing autologous transplantation.

**Guideline Recommendation.** Although comparative data are limited, survival appears superior with autologous transplantation. The DSG members unanimously decided to recommend autologous transplantation as the standard transplantation option. Two practitioners responded to this draft recommendation by indicating a potential future role of allogeneic transplantation. The DSG agreed that while ongoing clinical trials to improve allogeneic transplantation technology should be encouraged, autologous transplantation should be considered the present standard option.

**What Specifics of the Transplantation Procedure Can Be Recommended?**

Autologous transplantation is a complex procedure with several distinct components. We attempted to evaluate optimal pretransplantation chemotherapy, stem-cell source, role of stem-cell purging or selection, high-dose therapy regimen, single versus double transplant, and posttransplantation therapy.

### Table 3. Nonrandomized Comparisons between Autologous and Allogeneic Transplantation

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Patients Receiving Autologous Transplant</th>
<th>Patients Receiving Allogeneic Transplant</th>
<th>Median Survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Björkstrand et al. (14)</td>
<td>189</td>
<td>189</td>
<td>34 vs. 18; $P = 0.001$</td>
</tr>
<tr>
<td>Varterasian et al. (15)</td>
<td>24</td>
<td>24</td>
<td>33.5 vs. 38.6; $P &gt; 0.2$</td>
</tr>
<tr>
<td>Couban et al. (16)</td>
<td>40</td>
<td>22</td>
<td>$\geq 48$ vs. 7; $P &lt; 0.001$</td>
</tr>
</tbody>
</table>

* Data reported as autologous versus allogeneic transplantation.

**Pretransplantation Chemotherapy**

Pretransplantation chemotherapy could influence ultimate disease control; we identified no study assessing this question. Initial chemotherapy may also affect the ability to harvest sufficient stem cells and might therefore affect stem-cell engraftment (41). This concern has been suggested regarding melphalan use. In Attal and colleagues’ study (3), patients received four to six cycles of alkylating agent–based chemotherapy (VMCP–BVAP) before bone marrow harvest. Ten percent of the patients in the transplantation group had insufficient harvests and could not receive the assigned transplant.

No randomized trial has assessed pretransplantation therapy. Two case series addressed the effect of cumulative alkylating agent exposure on stem-cell harvest quality (27, 28). Tricot and colleagues (27) performed a multivariate analysis of factors predicting engraftment in 225 patients with myeloma undergoing double autologous stem-cell transplantation. The end points of the study were time to platelet ($> 50 \times 10^9/L$) and neutrophil ($> 0.5 \times 10^9$ cells/L) engraftment; both were inversely correlated with alkylating agent exposure (for granulocytes, any exposure; for platelets, exposure for $> 1$ month). Prince and colleagues (28) evaluated the effect of previous melphalan exposure on the ability to harvest stem cells in 54 consecutive collections of peripheral blood stem cells in 37 patients (28). Only 32% of patients receiving more than four courses of melphalan had collections meeting threshold values compared with 85% of those receiving zero to four courses ($P = 0.001$).

**Guideline Recommendation.** Previous exposure to alkylating agent may reduce the ability to harvest sufficient stem cells. A threshold melphalan dose that precludes successful harvesting has not been conclu-
sively identified. Given these data and available alternatives, the DSG concluded that it is prudent to avoid exposure to melphalan before stem-cell collection when transplantation is a consideration. High-dose glucocorticoid-based regimens, such as vincristine, doxorubicin, and dexamethasone (VAD), are preferable for these patients.

Source of Stem Cells: Bone Marrow versus Peripheral Blood

The use of peripheral blood stem cells results in faster engraftment of neutrophils and platelets (42). Evidence suggests that using peripheral blood stem cells in patients with myeloma might reduce malignant cell contamination of the autograft (43). One randomized trial, which was reported in abstract form, described a comparison between bone marrow and peripheral blood as the stem-cell source in patients with myeloma (17). In that trial, 133 patients received peripheral blood stem cells and 89 received autologous bone marrow. Neutrophil engraftment was faster in patients receiving peripheral blood stem cells (9.7 vs. 12.2 days; \( P/H_0.001 \)). The study detected no difference in toxic deaths, response rates, or 2-year survival. Three nonrandomized studies reported comparisons of peripheral blood stem cells with autologous bone marrow (23–25); one of these studies included patients with breast cancer (25). Each study demonstrated faster engraftment with peripheral blood stem cells, and one trial also detected an advantage in transfusion needs, antibiotic use, and hospital days (25).

Two studies assessing economic end points have addressed this topic: Duncan and colleagues (29) performed a cost-minimization analysis to compare transplantation using peripheral blood stem cells with autologous bone marrow; Powles and colleagues (30) included data on cost in a nonrandomized comparison that assessed tolerance of post-transplantation interferon as the primary outcome. Both analyses demonstrated that peripheral blood stem-cell transplantation had economic advantages.

Guideline Recommendation. On the basis of differences in outcomes affected by engraftment rate, the DSG favored the use of peripheral blood stem cells as the stem-cell source.

Role of Stem-Cell Purging or Selection

The presence of malignant cells in harvested stem cells could contribute to disease recurrence. Investigators have attempted different methods to reduce malignant contamination. Stewart and colleagues (18) reported preliminary results of a randomized trial comparing outcomes in 93 patients receiving selected CD34+ stem cells with the outcomes in 97 patients receiving unselected peripheral blood stem cells. Molecular testing showed that tumor contamination decreased with stem-cell selection. During a median follow-up of 37.2 months, the study detected no difference in survival (\( P > 0.2 \)).

Guideline Recommendation. Insufficient data exist to recommend purging or stem-cell selection outside a clinical trial.

High-Dose Therapy Preparative Regimen

Two comparative trials—one randomized and one nonrandomized, both reported in abstract form (19, 26)—assessed the role of total-body irradiation. In a randomized trial comparing outcomes in newly diagnosed patients undergoing peripheral blood stem-cell transplantation, 113 patients received melphalan, 140 mg/m², plus total-body irradiation, and 108 received melphalan, 200 mg/m², alone (19). This study detected no difference in response rate or 2-year survival. Total-body irradiation was associated with longer durations of neutropenia and thrombocytopenia, increased red cell and platelet transfusion requirements, and more days of intravenous antibiotic therapy. Björkstrand and colleagues (26) analyzed data from the European Blood Marrow Transplantation Registry for 1905 patients who underwent autologous transplantation for myeloma. Regimens that included total-body irradiation were associated with an inferior survival rate.

Guideline Recommendation. In the randomized trial demonstrating a benefit for autologous transplantation compared with conventional-dose chemotherapy (3), the conditioning therapy received by transplant recipients included total-body irradiation. The DSG therefore initially considered this regimen to be the standard of care outside a clinical trial. On the basis of preliminary results of the above two studies reported in abstract form, the DSG concluded that either high-dose melphalan, 200 mg/m², alone...
or melphalan, 140 mg/m², with total-body irradiation could be considered standard therapy.

### Single versus Double Transplants

Three studies—two randomized trials (20, 21) and one nonrandomized comparison (26)—assessed the role of double autologous transplantations performed in succession; these data, which were published in abstract form, are shown in Table 4. This therapy, called “tandem transplantation,” includes a planned second transplant following recovery from a first transplantation. This practice is in contrast to performing a second transplantation after disease progression following a first transplantation. Both randomized studies failed to detect a difference in event-free or overall survival. In one of the three studies (26), a secondary analysis of the patients who received a second transplant demonstrated prolonged relapse-free and event-free survival (\( P = 0.03 \)) for patients receiving tandem transplant. A nonrandomized comparison of data submitted to the European Bone Marrow Transplant Registry demonstrated superior progression-free survival in the patients undergoing tandem transplantation (data points not reported); the study detected no survival difference (21).

**Guideline Recommendation.** Comparative trials are susceptible to selection bias when outcomes of patients who actually receive a second transplant are compared with those who received a single transplant. Randomized trials analyzed on an intention-to-treat basis are needed to address this question. The DSG concluded that the current data do not support the standard use of tandem transplants.

### Post-transplantation Therapy

Because transplantation appears noncurative, maintenance therapy, such as with interferon, may be used in an attempt to improve disease control and survival. In the randomized comparison of transplantation with conventional-dose chemotherapy (3), both groups received interferon until disease progression. It is not possible to factor out the contribution of this agent to the success of the high-dose treatment strategy. Two comparative trials tested use of maintenance interferon after autologous transplantation.

Cunningham and colleagues (22) reported outcomes in 84 patients randomly assigned to interferon, 3 million units three times weekly until disease progression, or to no maintenance therapy. The data suggested a trend toward prolonged progression-free survival in the interferon group (median, 48 vs. 27 months; \( P = 0.11 \)); the study found no difference in survival. A nonrandomized comparison assessing data from 1905 patients on file with the European Bone Marrow Transplant Group demonstrated that post-transplantation interferon as maintenance treatment was associated with prolonged survival (21).

**Guideline Recommendation.** The evidence for benefit of interferon is conflicting, and the DSG could not reach a consensus on this issue. Some DSG members considered interferon to be an essential part of the therapeutic plan described by Attal and coworkers (3); these members believed that deleting this component could result in inferior outcomes. Other members believed that without data from randomized trials demonstrating a survival advantage, the toxicity of this agent precludes routine use.

### Table 4. Comparison of Single versus Double (Tandem) Transplantation of Autologous Peripheral Blood Stem Cells or Marrow

<table>
<thead>
<tr>
<th>Study (Reference), Report Type</th>
<th>Total Participants, ( n )</th>
<th>Median Event-Free Survival*</th>
<th>Overall Survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, controlled trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attal et al. (20), abstract</td>
<td>402</td>
<td>At 3 y, 31 vs. 39; ( P ) value not significant</td>
<td>At 3 y, 58 vs. 66; ( P ) value not significant</td>
</tr>
<tr>
<td>Tosi et al. (21), abstract</td>
<td>192</td>
<td>Data not provided; ( P ) value not significant</td>
<td>At 2 y, 90 vs. 90; ( P ) value not significant</td>
</tr>
<tr>
<td>Nonrandomized comparison</td>
<td></td>
<td>Data not provided; progression-free survival superior with double transplants</td>
<td>Data not provided; between-group differences not significant</td>
</tr>
</tbody>
</table>

* Data reported as single versus double transplant.
When Should Transplantation Be Performed?

In the randomized trial demonstrating superior event-free and overall survival in patients receiving an autologous transplant (3), bone marrow was harvested early after diagnosis and transplantation was performed at a median of 5.5 months after therapy began. One randomized trial compared early with late autologous transplantation in patients with stem-cell collection shortly after commencing therapy (31); among 202 patients, 185 were randomly assigned to receive an autologous transplant as part of initial therapy or upon disease progression. In an intention-to-treat analysis, disease progression was delayed in the 91 patients receiving early transplantation compared with the 94 patients assigned to late transplantation (median event-free survival, 39 months [CI, 29 to 48 months] vs. 13 months [CI, 9 to 18 months]; \( P \) value not reported). However, no difference in median survival between the groups was detected (64.6 vs. 64.0 months; \( P > 0.2 \)). Time without symptoms, treatment, and treatment toxicity (TWISTT) was 27.8 months (CI, 23.8 to 31.8 months) for the early transplantation group and 22.3 months (CI, 16.0 to 28.6 months) for the late transplantation group.

Guideline Recommendation. Although delaying transplantation until disease progression in patients who have stem cells collected shortly after therapy initiation does not adversely affect survival, it may decrease the time without symptoms of myeloma or treatment toxicity without a clear potential for benefit. The DSG believed that transplantation as part of initial therapy was potentially advantageous; patients need to be counseled to determine individual preferences. The need for early stem-cell harvesting deserves emphasis because no comparative data indicate the efficacy of harvesting stem cells during disease progression.

Who Should (or Should Not) Receive a Transplant?

Age

Age has been used as a proxy measure to determine the safety of performing autologous transplantation. A commonly stated upper-age threshold is 65 years. However, several reports described transplantation in older patients (32–36, 38, 39). The DSG identified two randomized trials and three nonrandomized comparisons addressing patient age. The study by Attal and colleagues comparing high-dose with standard-dose therapy enrolled patients up to 65 years of age (3); 42% of patients age older than 60 years did not complete the transplantation compared with 18% of patients 60 years of age or younger (\( P = 0.01 \)). In a subset analysis based on intention to treat, transplantation was superior to standard-dose therapy in patients 60 years of age and younger, with no benefits detected in patients older than age 60 years. A second randomized trial comparing transplantation with conventional therapy in patients 55 to 65 years of age was reported in abstract form (4); this study failed to detect a difference in event-free or overall survival. Two case-control studies (34, 35) and one cohort study (36) have reported that patients older than 65 years of age can safely receive an autologous transplant, with no differences in outcomes detected between the older and younger patients.

Guideline Recommendation. The DSG had already concluded that data supporting autologous transplantation were strongest for patients younger than 55 years of age. Although transplantation may be safely performed in older patients, improvements in event-free and overall survival have only been documented in randomized trials for patients up to 60 years of age. Because age may be a proxy measure for aspects of disease biology, other comorbid illness, and treatment tolerance, physicians must use clinical judgment in recommending transplantation to patients older than 60 years of age.

Renal Function

The randomized trial supporting use of autologous transplantation over standard-dose therapy (3) included patients with renal dysfunction but with a serum creatinine level correcting to less than 150 \( \mu \text{mol/L} \) (<1.7 mg/dL) before transplantation. In patients with significant renal dysfunction, transplant-related toxicity may be greater, and the magnitude of benefits compared with those of standard-dose treatment might therefore be reduced. One case–control study (37) of 42 patients with a serum creatinine level greater than 200 \( \mu \text{mol/L} \) (>2.26 mg/dL) demonstrated that treatment toxicity was greater in patients with renal dysfunction; the observed difference in 3-year survival in patients with renal dysfunction versus controls was not statistically significant (44% vs. 59%; \( P = 0.15 \)).

Guideline Recommendation. Although autologous transplantation is feasible in patients with serious renal dysfunction, whether these patients actually benefit from the treatment is unclear. Randomized data showing benefits for transplantation have been limited to patients with a serum creatinine level less than 150
µmol/L (<1.7 mg/dL); interpretation of the case–control study is limited by the study design and the small sample size. The DSG concluded that transplantation could not be recommended as standard therapy for patients with a creatinine level greater than 150 µmol/L (>1.7 mg/dL) until randomized trials can demonstrate a survival benefit for these patients. Renal dysfunction seen at diagnosis may improve with initial therapy for myeloma; these patients should be subsequently considered for high-dose therapy.

CONCLUSIONS

The Hematology DSG of the CCOPGI developed the guidelines presented here, which assess the role of stem-cell transplantation for patients with myeloma. These guidelines will be reviewed and updated every 6 months. Their recommendations are as follows:

1. Autologous transplantation is recommended for patients with stage II or III myeloma and good performance status. The evidence is strongest for patients younger than 55 years of age and a serum creatinine level less than 150 µmol/L (<1.7 mg/dL) after hydration and remission-inducing chemotherapy. Physicians must use their clinical judgment in recommending transplantation to other patients.

2. Allogeneic transplantation is not recommended as routine therapy.

3. Patients potentially eligible for transplantation should be referred for transplant assessment early after diagnosis and should not receive extensive exposure to alkylating agents, such as melphalan, before collection of stem cells. High-dose glucocorticoid-based regimens, such as VAD, are preferable for these patients.

4. Harvesting of autologous peripheral blood stem cells should be performed early in the patient’s treatment course. Best available data suggest that transplantation is most advantageous when performed during initial therapy.

5. Comparative data regarding the specifics of the transplantation process are insufficient to allow definitive recommendations. In the absence of such data, the use of a single transplant with high-dose melphalan, 200 mg/m², alone or melphalan, 140 mg/m², with total-body irradiation is suggested for patients undergoing transplantation outside of a clinical trial.

6. At this time, no conclusions can be reached about the role of interferon following transplantation.

Note added in proof: These guideline recommendations are based on work completed in March 2001. New information necessitates that practice guidelines undergo regular updating. Based on a recent publication (44), the Hematology Site Group of the Cancer Care Ontario Practice Guidelines Initiative now recommends that when patients with multiple myeloma undergo autologous transplantation, standard pretreatment therapy should consist of melphalan, 200 mg/m². Please see the Web site of the Cancer Care Ontario Practice Guidelines Initiative (www.cancercare.on.ca/ccopgi/) for updated recommendations.

APPENDIX: MEMBERS OF THE HEMATOLOGY DISEASE SITE GROUP OF THE CANCER CARE ONTARIO PRACTICE GUIDELINES INITIATIVE


*Has completed term with Hematology Disease Site Group.

A complete list of current Disease Site Group members is available on the Web site of the Cancer Care Ontario Practice Guidelines Initiative at www.cancercare.on.ca/ccopgi/.

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