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Recommendation Report SCT-1 IN REVIEW

Stem Cell Transplantation in Multiple Myeloma

C.T. Kouroukis and R.B. Rumble

Report Date: March 29, 2012

An assessment conducted in March 2018 placed Recommendation Report SCT-1 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#))

Recommendation Report SCT-1 is comprised of 2 sections. You can access the summary and full report here:

<https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/986>

Section 1: Recommendations

Section 2: Summary of Methods and Evidence

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IN REVIEW



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Recommendation Report SCT-1: Section 1

Stem Cell Transplantation in Multiple Myeloma: Recommendations

C.T. Kouroukis and R.B. Rumble

Report Date: March 29, 2012

CLINICAL QUESTION

What is the role of stem cell transplantation (SCT) in the treatment of multiple myeloma (MM)?

TARGET POPULATION

All adult MM patients considered for treatment that includes blood or marrow transplantation.

RECOMMENDATIONS AND SUPPORTING EVIDENCE

Autologous SCT is the recommended treatment option for patients with newly diagnosed MM, as part of the initial treatment plan.

Supporting evidence

Evidence included in four Clinical Practice Guidelines (CPGs) (1-4) suggests that a single transplant with autologous SCT should be offered to all MM patients who are free from severe co-morbidities and who are younger than 65 years of age, following the initial treatment with high-dose chemotherapy.

The SCT Steering Committee acknowledged that, while the evidence upon which the CPGs were based almost uniformly excluded patients older than age 65, there was no reason not to offer SCT to patients 65 or older who have good performance status and no co-morbidities that would be a contraindication to transplantation.

The SCT Steering Committee also acknowledges that ongoing trials are investigating the value of upfront treatment with combinations of novel agents and the deferring of transplantation to a later date.

Tandem (double) autologous SCT is an option for patients with MM who respond to the first autologous transplant with less than a very good partial response, but not progressive disease.

Supporting evidence

Evidence included in two CPGs (1,2) suggests that double autologous SCT should be offered to patients who did not achieve a complete remission after their initial autologous SCT.

While the CPGs recommended a second transplant be offered to patients who did not achieve

complete remission following their first transplant, the SCT Steering Committee acknowledged that offering a second transplant to patients who achieve less than a very good partial response is reasonable as long as there is no progressive disease.

Allogeneic transplantation is an option for patients with high-risk MM preferably within the context of an investigative study.

Supporting evidence

Evidence from three of the CPGs did not support the use of allogeneic SCT from HLA-matched related donors as a primary treatment, but the conclusion is that it may be offered to patients <50 years of age who are not expected to benefit from autologous SCT (e.g., chromosome 13 deletion) within the investigative setting only (1,2,4).

Repeat autologous transplantation is an option for patients with MM who relapse after a long remission (> 2 years) to a single autologous transplant.

Supporting evidence

Despite a lack of good quality evidence, the SCT Steering Committee's consensus opinion is that patients who relapse after a long remission following a single transplant should be offered a second transplant.

QUALIFYING STATEMENT

The patient selection process and the ultimate decision to perform an SCT should take into account not only disease-related characteristics, but also co-morbidities and patient preferences. Evidence on the role of SCT in the management of MM is emerging rapidly. This topic is also the subject of Program in Evidence-based Care (PEBC) Evidence-based Series (EBS) 6-6, which will be updated to incorporate new data. EBS 6-6 differs from this report in that it includes only evidence comparing high-dose chemotherapy and SCT in patients with MM, whereas this report includes comparisons of all interventions including SCT such as radiotherapy and other treatment modalities.

FUTURE RESEARCH

Future research in this setting should continue to explore novel chemotherapy and supportive therapy options along with SCT. Better management of co-morbidities may allow clinicians to offer SCT to patients currently not eligible for treatment.

IMPLICATIONS FOR POLICY

Transplantation for myeloma remains the most frequent indication in Ontario for autologous transplantation. As of this report, and in the foreseeable future, it is highly unlikely that the indication for transplant in such patients will change. With the use of more effective induction regimens, it is possible that more patients will be eligible for transplant with myeloma.

RELATED PROGRAM IN EVIDENCE-BASED CARE REPORTS

- Imrie K, Rumble RB, Crump M; Advisory Panel on Bone Marrow and Stem Cell Transplantation; Hematology Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Stem cell transplantation in adults. Report Date: January 30, 2009 (5). Available from:

<http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=35448>

RELATED PROGRAM IN EVIDENCE-BASED CARE GUIDELINES

- 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;136:619-29. Available at:
<http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34315>

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Recommendation Report SCT-1: Section 2

Stem Cell Transplantation in Multiple Myeloma: Summary of Methods and Evidence

C.T. Kouroukis and R.B. Rumble

Report Date: March 29, 2012

QUESTION

What is the role of stem cell transplantation (SCT) in the treatment of multiple myeloma (MM)?

INTRODUCTION

Multiple myeloma (MM) is a plasma cell malignancy identified by an accumulation of clonal plasma cells, predominately in the bone marrow, which can cause bone loss, anemia, hypercalcemia, renal dysfunction (1,2), recurrent infections, and peripheral neuropathy (2). Myeloma is the second most common hematologic malignancy (after lymphoma) (1) and is responsible for approximately 20% of all deaths relating to cancers of the blood and bone marrow (2).

MM can be preceded by a stage of monoclonal gammopathy of undetermined significance (MGUS), which differs from MM by having fewer plasma cells in the bone marrow and no organ damage due to plasma cell proliferation (1). Following the MGUS stage, the disease may enter a stage referred to as smouldering multiple myeloma (SMM), where the markers of tumour burden are higher than the threshold for MGUS (1), but still not progressing to MM.

The current standard of care for these patients is to provide treatment for those who have myeloma who are symptomatic or who have or are expected to have end organ damage. With MGUS or of SMM, disease monitoring at regular intervals is required, and therapy is initiated if there is evidence of progression (1). The typical treatment for newly diagnosed MM in younger patients is induction chemotherapy followed by high-dose therapy (HDT) with autologous SCT (ASCT) (3,4). MM remains incurable, however, and advancements in the treatment of these patients have been complicated by the introduction of newer agents and combinations of newer agents (1). For this reason, a systematic review of the available evidence is warranted.

The goal of this Recommendation Report is to review the most current evidence comparing treatment modalities that include an SCT component, and to

make a series of clinical recommendations to inform clinicians, patients, and other stakeholders of the treatment options available.

METHODS

This advice report, produced by the PEBC, CCO, is a convenient and up-to-date source of the best available evidence on SCT in MM, developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ministry.

Literature Search Strategy

The MEDLINE (OVID) database (2006 through August (week one) 2010) was systematically searched for evidence on August 18, 2010, using the strategy that appears in Appendix A. This search strategy was used for EBS 6-6, a completed Clinical Practice Guideline covering the use of high-dose chemotherapy along with stem cell support for patients with MM. For the purposes of this review, only the papers including data on SCT were retained.

A total of 634 hits were obtained; after excluding irrelevant papers according to a title and abstract review, 27 were ordered for full-text review. Of these 27, only seven met the inclusion criteria and were retained.

Study Selection Criteria

Inclusion Criteria

Articles were selected if they were the following:

1. Systematic reviews with or without meta-analysis or CPGs if the evidence was obtained with systematic review.
2. Fully published randomized controlled trials (RCTs) on patients with MM who received SCT that reported on survival and/or quality of life (QoL).
3. Fully published non-randomized studies on patients with MM who received SCT that had an appropriate contemporaneous control group that reported on survival or QoL.
4. Reports published in English only, because of a lack of translation funding.

Synthesizing the Evidence

While no pooling of data was planned for this report, it would be considered if data allow.

Assessment of Study Quality

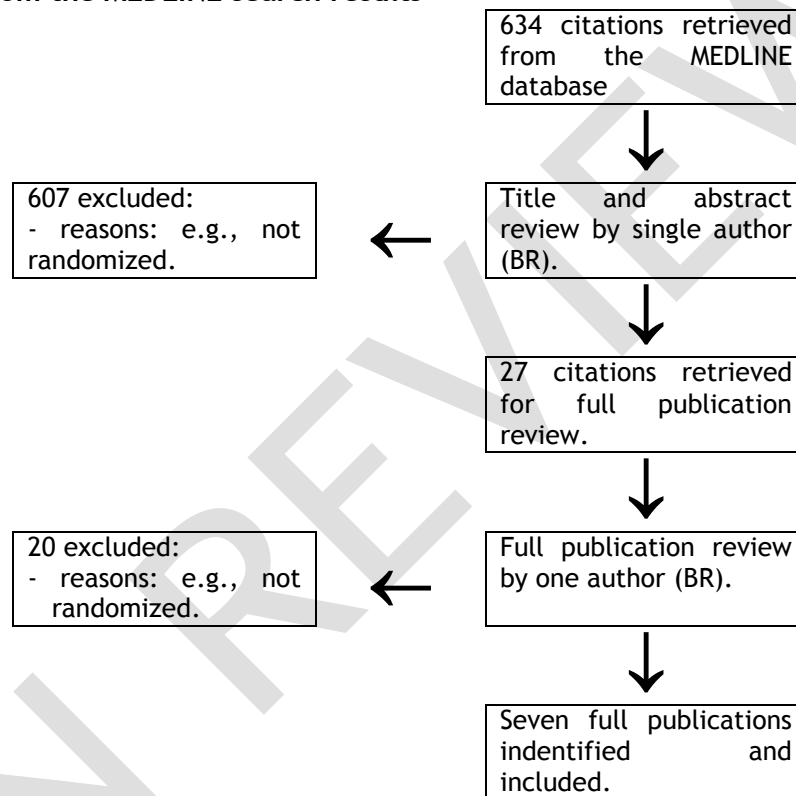
The quality of the included evidence was assessed as follows. For systematic reviews that would be used as the sole evidence base for our recommendations, the Assessment of Multiple Systematic Reviews (AMSTAR) tool would be used to assess quality. For CPGs, the Appraisal of Guidelines for Research and Evaluation (AGREE) II Instrument would be used, but only if an adaptation of the recommendations was being considered. Where recommendations from CPGs were not adapted, the evidence base in those CPGs would be informally assessed for completeness, and any relevant evidence within would be considered as a basis for recommendations in this report. Any meta-analysis would be assessed for quality using criteria similar to that used for RCTs, where appropriate. RCTs would be assessed for quality by examining the following seven criteria: the method of randomization, reporting of blinding, the

power and sample size calculation, length of follow-up, reporting details of the statistical analysis, reporting on withdrawals to treatment and other losses to follow-up, and reporting on the sources of funding for the research. Comparative, but non-randomized, evidence would be assessed according to the full reporting of the patient selection criteria, the interventions each patient received, and all relevant outcomes.

RESULTS: Literature Search Results and Quality Appraisal

A total of seven papers were retained (5-11), two RCTs (6,7), one individual patient data (IPD) meta-analysis (10) and four CPGs (5,8,9,11). Results appear in Tables 1-3.

Figure 1. Selection of studies investigating stem cell transplantation in multiple myeloma from the MEDLINE search results



Quality of Included Studies

Meta-analysis

One individual patient data meta-analysis, reported by Levy et al (10), was obtained. This meta-analysis compared the IPD from three RCTs (IFM 90, MAG 90, and MAG 91) that enrolled a total of 575 patients from 1993 to 1998 and that compared high-dose therapy (HDT) followed by autologous SCT (ASCT) (either BMT or PBSCT) with conventional therapy. Evidence was obtained through a systematic search of the literature using MEDLINE as well as a search of relevant conference proceedings and a search for the protocols of eligible trials. To avoid publication bias, both fully published and unpublished RCTs were considered. Inclusion criteria for this meta-analysis were RCTs that compared HDT-ASCT with conventional therapy in the first-line treatment of myeloma (regardless of the regimen used in the comparator arm)

and that had a median follow-up of five years or more. The data items collected for each patient were age, sex, Durie-Salmon stage, M-band type, albumin, creatinine, beta-2 microglobulin, treatment received, date of diagnosis, randomization, ASCT, date of first relapse, and date of death (or last contact). Data on each patient's cytogenetics were not available. Data were analyzed using the intent-to-treat principle. Survival outcomes were calculated from the date of randomization for all patients. Differences between treatment groups were compared using a Cox regression model and expressed as hazard ratios. Heterogeneity was considered in the following ways: in presentation features across trials via adjustment, in baseline patient characteristics using mixed effects models and stratified Cox models, and in treatment effects using the Gail and Simon test for quantitative interactions. The Gail and Simon test was also used to examine potential subsets of patients who would benefit from HDT-ASCT based on interactions between baseline patient characteristics and treatment effects. A sensitivity analysis was performed to explore differences in the conventional treatment arms. Treatment-related mortality (TRM) was estimated by cumulative incident curves, using relapse as the competing risk, and compared between groups, using a mixed effect model. The mean TWiST (time without symptoms disease or toxicity) was calculated by estimating the mean duration of toxic effects due to treatment, time without symptoms of disease or toxicity, and time after relapse until death for each treatment group, with data censored at median follow-up. Standard errors were estimated through the non-parametric Bootstrap method. Attempts were made to obtain all available RCTs via the systematic review, and an effort was made to avoid publication bias by including unpublished data. In summary, this was a well-performed, comprehensive meta-analysis.

Clinical Practice Guidelines

As none of the four CPGs obtained (5,8,9,11) were suitable for adaptation, no formal assessment of quality was performed. A description of the evidence included in each CPG is described in the Results section, and a summary of the recommendations along with the type of supporting evidence appears in Appendix C.

Randomized Controlled Trials

The randomized trial reported by Cavo et al (6) allocated patients to either single or double autologous SCT. Randomization was computer generated at each coordination centre with patients stratified according to Durie-Salmon staging. Blinding was not reported. The study was powered to detect a 15% increase in complete response (CR) or near CR rate with double autologous SCT compared with single transplant (based on an expected single transplant CR/near CR rate of 30%). Using a two-sided test at $\alpha=0.05$ and $1-\beta=0.80$, 162 patients were needed in each arm. Comparisons between baseline characteristics of the two arms were done using the X^2 test. CR and near CR were calculated using the Kaplan-Meier method and compared using the log-rank test. The median follow-up was 55 months (2-112 months) for all patients. Only three patients were lost to follow-up, all from the single transplant group. Funding for this study was provided by various sources, including the Università di Bologna, Progetti di Ricerca Fondamentale Orientata (M.C.); Ministero dell'Università e Ricerca Scientifica, progetto FIRB, RBAU012E9A_001 (M.C.); and Fondazione Carisbo.

The RCT reported by Facon et al (7) allocated elderly patients to melphalan and prednisone (MP), melphalan and prednisone plus thalidomide (MPT), or higher dose chemotherapy followed by ASCT. Patients were randomized to MP, MPT, or ASCT

in 3:2:2 ratios. Blinding was not reported. The primary outcome in this trial was overall survival (OS), and the trial was powered to detect an 18-month increase in median survival in either the MPT or the ASCT groups based on an expected median survival of 30 months in the MP group. Therefore, using a two-sided $\alpha=0.05$ and $1-\beta=0.80$, 500 patients in total were required. Comparisons between baseline characteristics were performed using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Time-to-event survival outcomes were analyzed according to the Kaplan-Meier method and calculated using an unstratified proportional hazards model. All analyses were performed using the intent-to-treat principle. Median follow-up for all patients was 36.8 months (Interquartile range [IQR], 20.8 to 51.2). There were no losses to follow-up. Funding for this study was provided by various sources, including the Centre Hospitalier et Universitaire de Lille (Lille University Hospital), Ministry of Health, France (Projet Hospitalier de Recherche Clinique, CHRU Lille 1998, number 1951), and the Swiss Group for Clinical Cancer Research (SIAC).

RESULTS: Clinical Evidence Meta-analysis

An IPD meta-analysis reported by Levy et al (10) was obtained. In this meta-analysis, IPD from three RCTs (IFM 90, MAG 90, and MAG 91) comparing first-line HDT-ASCT with conventional therapy, with a median follow-up of five years or more, were pooled. The outcomes reported were OS, TRM, and TWiST. No significant differences were detected for any of the pooled comparisons. The results appear in Table 1.

Table 1. IPD meta-analysis.

Outcome	N	OS %	TRM %	TWiST (Months)
HDT-ASCT	285	26	5.26	+14
ConCT	290	23	2.1	-
		HR=0.89, p=ns	p=ns	

Note: N, number; OS, overall survival; TRM, treatment-related mortality; TWiST, time without symptoms of disease or toxicity of treatment; HDT-ASCT, high-dose therapy followed by autologous stem cell transplantation; ConCT, conventional chemotherapy; HR, hazard ratio; ns, not significant.

Clinical Practice Guidelines

Four CPGs were obtained (5,8,9,11). The evidence used to produce the recommendations for each of the included CPGs detailed in this report is shown below. The first CPG obtained, reported by Anderson et al (5), was a National Comprehensive Cancer Network (NCCN) guideline that made recommendations based on evidence that ranged from RCT-supported evidence to consensus interpretation of conflicting clinical evidence. No description of the methods used to obtain the included evidence was described in that report. The second CPG, reported by Harousseau et al (8), was a European Society for Medical Oncology (ESMO) guideline that made recommendations based on evidence ranging from an individual cohort study and/or a low-quality RCT to a systematic review of RCTs with homogeneity of results. No description of the methods used to obtain the included evidence was described in that report. The third CPG, reported by Barosi et al (9), was produced in cooperation with three Italian groups, including the Italian Society of Hematology (SIE), the Italian Society of Experimental Hematology (SIES), and the Italian Group for Bone Marrow Transplantation (GITMO). Recommendations in that CPG were made based on

evidence obtained using a systematic review process that ranged from RCTs to population-based studies. The final CPG obtained, reported by Smith et al (11), was produced by the UK Myeloma Forum, the Nordic Myeloma Study Group, and the British Committee for Standards in Haematology. Recommendations in that CPG were made based on evidence obtained using a systematic review process that ranged from systematic reviews and/or one RCT with narrow confidence intervals, case-series, and one prospective study. The type of evidence that supported each of the recommendations made in the CPGs is detailed in Appendix C.

The findings of the CPGs are as follows. According to the evidence obtained in all four of the CPGs, patients free of severe co-morbidities and who are younger than 65 years of age should receive high-dose chemotherapy followed by ASCT (5,8,9,11), and double ASCT should be offered to patients who did not achieve complete remission after their initial ASCT (5,9). Two of the guidelines included evidence suggesting an age over 65 should not be considered an exclusion criterion for SCT, and patients 65 to 70 years of age who are free from severe co-morbidities should be offered SCT within an approved clinical study (9,11). The evidence from one CPG stated that the preferred source of autologous stem cells is peripheral blood (9). The evidence included in three of the CPGs did not support the use of allogeneic SCT from HLA-matched related donors as a primary treatment but suggest it may be offered to patients less than 50 years of age who are not expected to benefit from ASCT (e.g., chromosome 13 deletion), within the investigative setting only (5,9,11).

Comparison of stem cell transplantation and conventional chemotherapy from RCTs

The RCT [IFM 99-06] in older patients reported by Facon et al (7) compared three regimens, melphalan, prednisone and thalidomide (M/P/T), melphalan and prednisone (M/P), and higher dose melphalan plus stem cell transplantation (MEL). For median event-free survival, statistically significant benefits were detected in favour of M/P/T compared with M/P ($p < 0.0001$) and in favour of M/P/T compared with MEL ($p = 0.0002$). No difference in median event-free survival was detected between M/P and MEL. For overall survival, statistically significant benefits were detected in favour of M/P/T compared with M/P ($p = 0.001$) and in favour of M/P/T compared with MEL ($p = 0.004$). No OS difference was detected between M/P and MEL. The results appear in Table 2.

Table 2. Comparison of peripheral blood stem cell or marrow transplantation from RCTs.

Authors, year	Arm 1 (N)	Arm 2 (N)	Arm 3	Response-to-treatment (%)	Median event-free survival (Months)	Overall survival (%)
Facon et al, 2007 (7) [IFM 99-06]	M/P/T N=125 elderly patients	M/P N=196 elderly patients	MEL N=126 elderly patients	-	M/P/T v M/P, HR=0.45; $p < 0.0001$ M/P/T v MEL, HR=0.54; $p = 0.0002$ MEL v M/P, ns	M/P/T v M/P, HR=0.56; $p = 0.001$ M/P/T v MEL, HR=0.58; $p = 0.004$ MEL v M/P, ns

Note: N, number; ASCT, autologous stem cell transplantation; M/P/T, melphalan, prednisone, thalidomide; M/P, melphalan, prednisone; MEL, reduced intensity stem cell transplantation plus melphalan; ns, not significant.

Comparison of single versus double transplantations from RCTs

In the RCT reported by Cavo et al (6), double ASCT was found to have statistically significant benefits when compared with single ASCT for both response-to-treatment ($p=0.008$) and median event-free survival ($p<0.001$). No difference was detected in OS at seven years ($p=0.9$). The results appear in Table 3.

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 (%)
Cavo et al, 2007 (6) [Bologna 96]	163	158	33 v 47; $p=0.008$	23 v 35; $p=0.001$	46 v 43; $p=0.9$	3 v 4; $p=0.7$

Note: TRM, transplantation-related mortality.

DISCUSSION

High-dose chemotherapy followed by ASCT remains a standard therapy for patients with newly diagnosed MM who are in need of treatment. The committee discussed the current recommendations in light of the evidence and the previous set of recommendations from the 2009 report.

The committee has moved away from defining a specific age limit to high-dose chemotherapy and SCT in patients with MM, stating that exclusions based on performance status and co-morbidities would be more relevant than age. The study by Facon et al (7) did show that combination chemotherapy is superior to SCT in an older group of patients, up to the age of 75 years, and the committee recognizes that doing an SCT in those aged 70 to 75 years could be more problematic and associated with increased toxicities. An IPD meta-analysis (10) did not detect a difference between regimens containing chemotherapy and regimens containing both chemotherapy and SCT. Final decision-making between clinicians and patients regarding the value of SCT would take into account all factors, including co-morbidities. In Ontario, there are relatively few SCTs performed for patients with MM over the age of 70 years.

The committee also discussed the value of a second transplant. The wording was changed from 'complete response' to 'very good partial response' as a measure to help in the decision regarding whether to perform a second tandem transplant. This recommendation was consistent with the association in the literature between very good partial responses and better responses and successful outcomes post-transplantation. The committee also recognizes that, with the availability of newer agents in the treatment of MM, the value of a second tandem transplant may be less attractive.

The committee did not substantially change the earlier recommendations regarding SCTs at the time of relapse or the use of allogeneic transplants.

CONCLUSIONS

High-dose chemotherapy followed by ASCT remains a standard therapy for patients with newly diagnosed MM, and the decision to offer this treatment to patients

is dependent on performance status and the presence of contraindicating co-morbidities.

RECOMMENDATIONS

- ASCT is the recommended treatment option for patients with newly diagnosed MM free from contraindications to treatment (e.g., co-morbidities, poor performance status).
- Tandem (double) ASCT is an option for patients with MM who obtain less than a very good partial response, but not progressive disease, to their first autologous transplant.
- Repeat autologous transplantation is an option for patients with MM who relapse after a long remission (> 2 years) after a single autologous transplant.
- Allogeneic transplantation is an option for patients with high-risk MM, within the context of an investigative study.

These recommendations are in concordance with the recommendations made in the other CPGs obtained (5,8,9,11), which are summarized in Appendix C.

ONGOING TRIALS (www.clinicaltrials.gov) (updated August 30, 2011).

Protocol ID	Title, details
NCT01208662	Randomized Trial of Lenalidomide, Bortezomib, Dexamethasone vs High-Dose Treatment With SCT in MM Patients up to Age 65 (DFCI 10-106) Study ID: 10-106 Status: recruiting Updated: July 20, 2011
NCT01091831	Cyclophosphamide, Lenalidomide and Dexamethasone (CRD) Versus Melphalan (200 mg/m ²) Followed By Autologous Stem Cell Transplant (ASCT) In Newly Diagnosed Multiple Myeloma Subjects Study ID: RV-MM-EMN-441 Status: recruiting Updated: March 23, 2010
NCT00217438	Melphalan and Amifostine Followed By One or Two Autologous or Syngeneic Stem Cell Transplants and Maintenance Therapy in Treating Patients With Stage II-III Multiple Myeloma Study ID: 2004.00, NCI-2009-01543 Status: recruiting Updated: July 11, 2011

CONFLICT OF INTEREST

The authors of this recommendation report disclosed potential conflicts of interest relating to the topic of this special advice report and declared there were none.

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4. Stephanie Pow, Erin Rae, and Sherrie Hertz, CCO Staff for project support

UPDATING

This document will be reviewed in three years time to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. The outcome of the review will be posted on the CCO website. If new evidence that will result in changes to these recommendations becomes available before three years have elapsed, an update will be initiated as soon as possible.

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Appendix A. Literature search strategy.

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/
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="2006 -Current"
54. from 53 keep
26,32,91,94,99,146,178,207,212,226,279,304,344,361,369,410,414,419,479,518,525,549,588,596

Appendix B. Development & review.

This recommendation report was created to update the 2009 Stem Cell Transplantation in Adults report¹. Using the recommendations in that report as a starting point, a literature search from the original report's literature search dates to the date current for this study was performed to gather the most evidence.

TENTATIVE RECOMMENDATIONS₁

[Replaced with Definitive Recommendations (see below)]

- Autologous stem cell transplantation is the recommended treatment option for eligible younger patients (under age 65-70 years) with newly diagnosed MM.
- Tandem (double) autologous stem cell transplantation is an option for patients who obtain less than a complete response to the first autologous transplant.
- Repeat autologous transplantation is an option for patients with MM who relapse after a long remission (> 2 years) to a single autologous transplant.
- Allogeneic transplantation is an option for selected patients with MM including those with high-risk cytogenetics and those whose disease is unresponsive to primary therapy.
- *Qualifying Statement:* Evidence on the role of stem cell transplantation in the management of MM is rapidly emerging. This topic is the subject of Program in Evidence-based Care Evidence-based Series 6-6, which will be updated to incorporate new data.

¹Stem Cell Transplantation in Adults, K. Imrie, R.B. Rumble, M. Crump, the Advisory Panel on Bone Marrow and Stem Cell Transplantation, and the Hematology Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care [Report Date: January 30, 2009].

Definitive recommendations and supporting evidence.

Autologous stem cell transplantation is the recommended treatment option for patients with newly diagnosed MM as part of the initial treatment plan.

Supporting evidence:

Recommendations from four Clinical Practice Guidelines (CPG) (1-4) were that single transplant with autologous SCT should be offered to all multiple myeloma patients that are free from severe co-morbidities and that are younger than 65 years of age following initial treatment with high-dose chemotherapy.

The SCT Steering Committee acknowledged that while the evidence upon which the CPGs were based almost uniformly excluded patients older than age 65, there was no reason not to offer SCT to patient 65 or older that have good performance status and no co-morbidities that would be a contraindication to transplantation.

The SCT Steering Committee also acknowledges that ongoing trials are investigating the value of upfront treatment with combinations of novel agents and deferring transplantation to a later date.

Tandem (double) autologous stem cell transplantation is an option for patients with MM who obtain less than a very good partial response, but not progressive disease, to the first autologous transplant.

Supporting evidence:

Recommendations from two Clinical Practice Guidelines (1,2) were that double autologous SCT should be offered to patients that did not achieve complete remission after initial autologous SCT.

While the CPGs recommended a second transplant be offered to patients that did not achieve complete remission following first transplant the SCT Steering Committee acknowledged that offering a second transplant to patients that achieve less than a very good partial response is reasonable as long as there is no progressive disease.

Allogeneic transplantation is an option for patients with high-risk MM preferably within the context of an investigative study.

Supporting evidence:

Three of the Clinical Practice Guidelines did not recommend the use of allogeneic SCT from HLA-matched related donors as primary treatment, but acknowledge that it may be offered to patients <50 years of age that are not expected to benefit from autologous SCT (e.g. chromosome 13 deletion) within the investigative setting only (1,2,4).

Repeat autologous transplantation is an option for patients with MM who relapse after a long remission (> 2 years) to a single autologous transplant.

Supporting evidence:

Despite a lack of good quality evidence, it is the SCT Steering Committee's consensus opinion that patients that relapse after a long remission following a single transplant be offered a second transplant.

IN REVIEW

Appendix C. Clinical practice guidelines.

Authors, year	Endorsing Entity	Recommendations
Anderson KC, 2009 (5)	NCCN	<p><u>ASCT, single transplant:</u> For eligible patients, ASCT remains the standard of care following induction therapy (supported by RCT evidence).</p> <p><u>Tandem or repeat SCT:</u> A tandem transplant within six months of the initial transplant is an option for patients with partial response or stable disease after the first ASCT (consensus recommendation).</p> <p><u>Allogeneic SCT:</u> An option in the clinical trial setting for patients with responsive or primary progressive disease, or as salvage therapy following initial ASCT (consensus recommendation based on examining conflicting evidence).</p>
Harrouseau JL, 2009 (8)	ESMO	<p><u>Younger patients (<65 years of age):</u> High-dose therapy with ASCT is standard treatment (supported by an individual cohort study and/or a low-quality RCT).</p> <p><u>Elderly patients:</u> For patients ineligible for standard treatment, oral melphalan (9mg/m²/day for four days) with prednisone (30mg/m²/day for four days) is a suitable alternative (supported by an SR of RCTs with homogeneity of results).</p>
Barosi G et al, 2004 (9)	SIE, SIES, GITMO	<p><u>ASCT, single transplant:</u> Patients free of severe co-morbidities and who are younger than 65 years of age should receive high-dose chemotherapy followed by ASCT (supported by two prospective randomized trials and one population-based study).</p> <p><u>ASCT, double transplant:</u> Should be offered to patients that did not achieve complete remission after initial ASCT (supported by one study).</p> <p><u>Age restrictions:</u> Age over 65 is not an exclusion criteria for SCT, and patients 65-70 years of age who are free from severe co-morbidities should be offered SCT within an approved clinical study (supported by one study).</p> <p><u>Preferred source of stem cells:</u> Peripheral blood is the preferred source of autologous stem cells (supported by one RCT).</p> <p><u>Allogeneic SCT:</u> Evidence does not support the use of allogeneic SCT from match-related donors as primary treatment, but it may be offered to patients <50 years of age who are not expected to benefit from autologous SCT (e.g., chromosome 13 deletion), within the investigative setting only.</p>
Smith A et al, 2005 (11)	NMSG, BCSH	<p><u>ASCT, single transplant:</u> HDT-ASCT should be offered as first-line treatment for patients up to the age of 65 years with adequate performance status. It may be considered for patients older than 65 years of age with good performance status (supported by an SR and /or an RCT with narrow CI).</p> <p><u>ASCT, double transplant:</u> While planned double transplants are not recommended, enough stem cells should be gathered initially to support two procedures (supported by a case-series).</p>

		Allogeneic SCT: HLA-matched sibling allogeneic SCT should only be considered for patients 50 years of age or younger that achieved at least a partial remission after initial therapy within the investigative setting only (supported by one prospective study).
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Note: SIE, Society of Hematology (Italy); SIES, Society of Experimental Hematology (Italy); GITMO, Group for Bone Marrow Transplantation (Italy); NCCN, National Comprehensive Cancer Network; ESMO, European Society for Medical Oncology; SR, systematic review; RCT, randomized controlled trial; CI, confidence interval.

IN REVIEW