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**Recommendation Report SCT-2 Version 2**

# Stem Cell Transplantation in Primary Systemic Amyloidosis

*Members of the Stem Cell Transplantation Expert Panel*

**An assessment conducted in February 2024 deferred the review of Recommendation Report SCT-2 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)**

**Recommendation Report SCT-2 Version 2 is comprised of 3 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/981**

Section 1: Recommendations (ENDORSED)
Section 2: Summary of Methods and Evidence
Section 3: Document Assessment and Review

**November 18, 2019**

For further information about this series, please contact:
Dr. Tom Kouroukis through the PEBC at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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

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**Recommendation Report History**

| GUIDELINE VERSION | SYSTEMATIC REVIEW | | PUBLICATIONS | NOTES and KEY CHANGES |
|---|---|---|---|---|
| | Search Dates | Data | | |
| Original March 29, 2012 | 2006 to Oct 2010 | Full Report | Web publication | N.A. |
| Version 2 November 18, 2019 | 2010 to Jun 2019 | New data found in Section 3: Document Assessment and Review | Updated web publication | 2012 recommendations are ENDORSED |

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**Recommendation Report SCT-2 Version 2: Section 1**

# Stem Cell Transplantation in Primary Systemic Amyloidosis: Recommendations

The 2012 recommendations have been ENDORSED. This means that the recommendations are still current and relevant for decision making. Please see Section 3: Document Assessment and Review for a summary of updated evidence published between 2010 and 2019, and for details on how this Recommendation Report was ENDORSED.

## CLINICAL QUESTION

What is the role of stem cell transplantation (SCT) in the treatment of primary systemic (AL, amyloid light-chain) amyloidosis?

## TARGET POPULATION

All adult patients with primary (AL) amyloidosis who are being considered for treatment that includes either bone marrow or SCT.

## RECOMMENDATIONS AND KEY EVIDENCE

| |
|---|
| High-dose chemotherapy (CT) and autologous SCT is an option for selected patients with primary systemic amyloidosis, preferably within an investigative setting. |
| **Evidence**<br>A single meta-analysis (1) met the inclusion criteria for this review, and that meta-analysis found no significant difference between autologous stem cell transplantation (ASCT) and CT for AL patients in survival outcomes. An RCT included in that meta-analysis (Jaccard et al, 2007) found treatment with ASCT to be associated with a significant increase in treatment-related mortality (TRM).<br>This meta-analysis has some limitations that must be considered when making evidence-based recommendations. The quality of the included evidence was low and consisted of a small RCT and non-RCTs with likely patient selection bias. The single included RCT needed 340 patients to detect a 15% survival difference at $\propto$=0.05, but only 100 were accrued. Secondly, AL patients typically also have significant co-morbidities precluding them from study enrolment.<br>In consideration of the lack of curative treatment options and the limitations of the evidence reviewed, the Expert Panel believes that offering ASCT may be a reasonable option for some patients, depending on performance status, co-morbidities, patient preferences, and ultimate treatment goals. |
| Allogeneic SCT is not recommended for patients with primary systemic amyloidosis. |

**Evidence**
There is no evidence supporting the use of allogeneic SCT for patients with AL.

## 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 comorbidities and patient preferences.

**Added to the 2019 Endorsement:**

Careful patient selection based on degree of light chain amyloidosis involvement and organ function is an emerging concept in amyloidosis that should be considered to reduce transplant-related mortality.

Transplantation in amyloidosis is an evolving area. New emerging areas include consideration of transplantation in first relapse and the impact of novel proteasome inhibitors on outcomes. New evidence is expected within a time frame of 2 to 3 years.

## FUTURE RESEARCH

Newer agents are being investigated in the treatment of AL amyloidosis. At this time it is not known how they may impact the need for SCT.

## IMPLICATIONS FOR POLICY

The number of transplants provincially for systemic AL amyloidosis remains very low, and is unlikely to change in the foreseeable future.

## 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] (2). Available from: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=35448

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**Dr. Tom Kouroukis**; Chair, Hematology Disease Site Group
Juravinski Cancer Centre

3rd Floor, 699 Concession Street
Hamilton, ON, L8V 5C2
Phone: 905-575-7820 Fax: 905-575-6340 E-mail: kourouk@hhsc.ca

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

## REFERENCES

1. Mhaskar R, Kumar A, Behera M, Kharfan-Dabaja MA, Djulbegovic B. Role of high-dose chemotherapy and autologous hematopoietic cell transplantation in primary systemic amyloidosis: a systematic review. Biol Blood Marrow Transplant. 2009;15(8):893-902.
2. Imrie K, Rumble RB, Crump M. Stem cell transplantation in adults. Toronto: Cancer Care Ontario; 2009 [cited 2011 March 28, 2011]; Available from: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=35448.

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# Recommendation Report SCT-2 Version 2: Section 2

The 2012 recommendations have been ENDORSED. This means that the recommendations are still current and relevant for decision making. Please see Section 3: Document Assessment and Review for a summary of updated evidence published between 2010 and 2019, and for details on how this Recommendation Report was ENDORSED.

## QUESTION

What is the role of stem cell transplantation (SCT) in the treatment of primary systemic (AL) amyloidosis?

## INTRODUCTION

Systemic amyloidosis is a protein-misfolding disease caused by deposits of amyloid fibrils within various tissues (1-4). These amyloid fibrils are monoclonal light chains produced by plasma cell clones within bone marrow that enter circulation as free light chains and are ultimately deposited within susceptible tissues (1-3). In the West, AL amyloidosis is the most common form of amyloidosis, with an incidence of approximately 10 patients per million persons per year (3,4). Of these patients, between 10% to15% will develop overt AL amyloidosis (3). The goal of treatment is to suppress the clone with chemotherapy (1,2,4), similar to the approach taken for multiple myeloma patients; however, in amyloidosis, any outcome achieved is dependent upon the amount of organ dysfunction caused by the deposited amyloid fibrils. When treating amyloidosis patients, the treatment approach must consider that although multiorgan damage does make patients more susceptible to adverse effects, reducing the concentration of free light chains results in rapid clinical and survival benefits (2). Typically, the plasma cell clone is treated using two methods, conventional chemotherapy (CT) or high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) (1-4). While both CT and ASCT have shown clinical and survival benefits, ASCT is associated with both higher complete response and treatment related mortality (TRM) (1,2). This higher TRM is associated with the extent of prior organ damage caused by the disease; therefore, patients considered for ASCT treatment should be assessed for suitability by measuring the concentration of free light chains and the cardiac biomarkers N-terminal pro-natriuretic peptide type-B (NT-proBNP) and troponin (cTn). By carefully considering the patient selection criteria for ASCT, TRM rates have dropped from the 1998 rate of 12% to the current 7% (2).

The goal of this recommendation report is to review the most current evidence comparing these two treatment modalities, 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 multiple myeloma, 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 October (week two) 2010) was systematically searched for evidence on October 21, 2010 using the strategy that appears in Appendix A. A total of 23 hits were obtained, and after excluding irrelevant papers according to a title and abstract review, three were ordered for full-text review. Of these three, only one met the inclusion criteria and was retained.

### Study Selection Criteria

#### *Inclusion Criteria*

Articles were selected if they were the following:

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

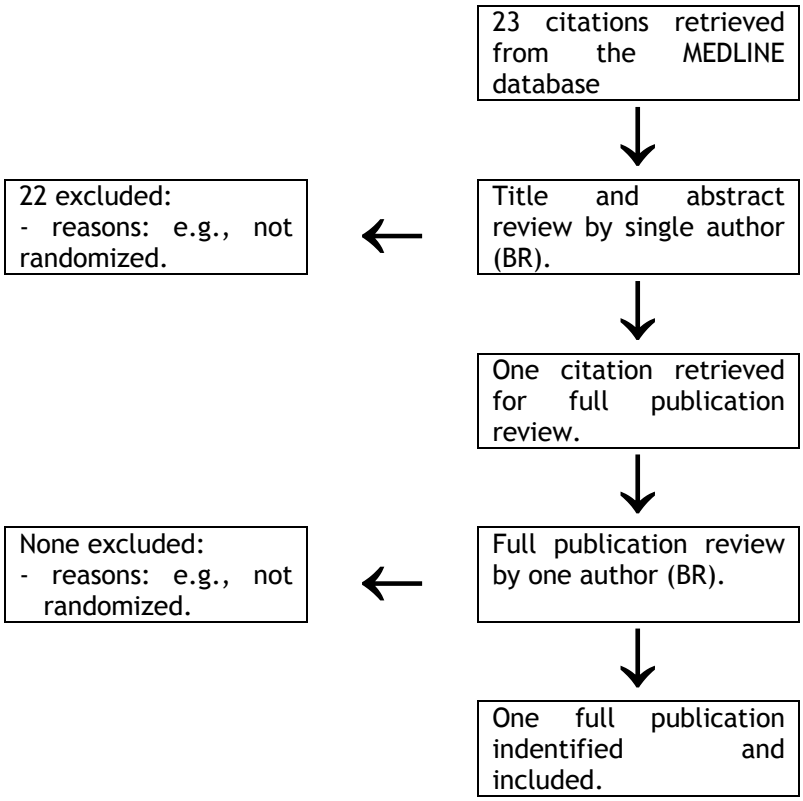
### Synthesizing the Evidence

While no pooling was planned, 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 adaptation of the recommendations was being considered. 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 a full reporting of the patient selection criteria, the interventions each patient received, and of all relevant outcomes.

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




**RESULTS: Literature Search and Quality of the Included Evidence**

Only one report, a systematic review with meta-analysis, was obtained (5). This systematic review with meta-analysis only covered AL amyloidosis.

**Quality of the Included Study**

A formal assessment of quality was performed on the SR reported by Mhaskar et al (5) using the AMSTAR instrument. Details of the assessment can be found in Appendix B. As the SR was of high quality overall, it was deemed appropriate to use it as the body of evidence in this review.

**RESULTS: Clinical evidence**

**Methods Used by Mhaskar et al, 2009**

Evidence was systematically searched for using the PubMed database (dB). The search was performed in two stages: the first gathered RCT evidence, searching from 1966 through March 2008, and the second gathered single-arm prospective studies searching from January 2001 through March 2008. Meeting abstracts from the American Society of Hematology (ASH), the European Society of Hematology, and the American Society of Clinical Oncology (ASCO) were also searched from 2001 through 2008.

**Inclusion Criteria Used by Mhaskar et al, 2009**

- RCTs comparing ASCT with CT with at least 10 patients in each arm.
- Prospective nonrandomized single-arm studies, with or without historical controls, regardless of the number of patients.
- Each study had to report on at least one of the outcomes of interest: overall survival (OS), event-free survival (EFS), hematological response (complete (CHR) or partial

(PHR)), renal response, treatment-related morbidity, or treatment-related mortality (TRM).

**Exclusion Criteria Used by Mhaskar et al, 2009**

- Retrospective study designs

***Study Selection and Quality of Evidence Assessment***

The studies to be included were determined by four reviewers, with disagreements resolved by consensus. All studies included were critically appraised on their methods, using the GRADE instrument. Three reviewers independently extracted the data.

**Details of the Analysis used by Mhaskar et al, 2009**

***Comparative Studies (Including RCTS)***

Time-to-event data and dichotomous data were pooled and reported using a random-effects model. If these data were not available, the hazard ratio (HR) was assessed using the Parmar method.

**Non-Comparative Studies Used by Mhaskar et al, 2009**

Proportions were converted into quantities according to the Freeman-Tukey variant of the arcsine square root-transformed proportion. The pooled proportion was calculated from the weighted mean of the transformed proportions, also using the random-effects model.

Heterogeneity was tested for using the $I^2$ test, and was explored through sensitivity tests, where warranted. Publication bias was assessed using the funnel plot methods of Begg and Mazumdar and also Egger et al, and none was detected.

All meta-analysis was performed using Stata (Release 9) in accordance with the guidelines published in the Quality of Reporting of Meta-Analyses statement.

**Funding Sources Reported by Mhaskar et al, 2009**

This systematic review with meta-analysis was funded by a grant from Johnson & Johnson Pharmaceutical Research & Development. The details of the studies included in the obtained systematic review appear in Table 1.

**Table 1: Details of the individual studies included in the systematic review.**

| Authors, year | Patient characteristics (median age, performance status, N) | Arm 1 (N) | Arm 2 (N) | Overall survival | Complete hemato-logic response |
|---|---|---|---|---|---|
| *RCT* | | | | | |
| Jaccard et al, 2007 | Age 58 (40-69), ECOG status: 0-2, International multicentre trial, N=100 | IV HDM+ASCT (50) | Oral Mel+oral Dex (50) | HR: 1.78, p=0.04 (95%CI, 1.03-3.08) in favour of CT | NR |
| *Non-randomized two-arm trial* | | | | | |
| Gono et al, 2004 | Age 59.5 (44-78), SWOG | VAD+Mel+ASCT (NR) | VAD (NR) | HR: 0.80, p=ns | NR |

| | | | | | |
|---|---|---|---|---|---|
| | status: 0-2, N=31 | | | (95%CI, 0.14-4.61) | |
| Van Gameren et al, 2002 | Age 53 (43-62), SWOG status: 0-2, N=18 | VAD+HDM+ASCT (NR) | Mel+prednisone (historical control) (NR) | HR: 2.83, p=ns (95%CI, 0.82-9.77) | NR |
| *Single-arm studies with no controls* | | | | | |
| Gertz et al, 2004 | Age 54 (42-71), ECOG status: 0-2, N=30 | SCT+IV Mel | NA | 39% (95%CI, 0.19-0.59) | NR |
| Gertz et al, 2002 | Age 54 (31-70), N=66 | SCT+IV Mel (17/66 received Mel+total body RT) | NA | 21% (95%CI, 0.11-0.32) | NR |
| Blum et al, 2003 | Age 56 (35-67), ECOG status: 0-2, N=13 | CTx+PBSCT+total body RT+ASCT. For CTx Dex alone was recommended, but other regimens were allowed | NA | 54% (95%CI, 0.23-0.85) | NR |
| Skinner et al, 2004 | Age 56.9 (0-80), SWOG: <2, N=394 | IV Mel+ASCT | NA | 44% (95%CI, 0.39-0.50) | NR |
| Perz et al, 2004 | Age 54 (34-65), WHO status: 0-2, N=28 | 2-5 cycles of VAD followed by HDM+ASCT | NA | 29% (95%CI, 0.10-0.47) | NR |
| Perfetti et al, 2006 | Age 51 (31-65), ECOG status: 0-2, N=22 | IV HDM+ASCT Mel | NA | 50% (95%CI, 0.27-0.73) | NR |
| Sanchorawala et al, 2007 | Age 55.5 (32-65), SWOG status: <2, N=62 | HDM+SCT, 2 cycles | NA | NR | 56% (95%CI, 0.43-0.70) |
| Cohen et al, 2007 | Age 57 (34-73), N=45 | Mel+SCT (Mel followed with adjuvant Dex+Thal) | NA | 24% (95%CI, 0.11-0.38) | NR |
| Gertz et, 2007 | Age 55-59 | HDM+SCT | NA | 33% (95%CI, 0.27-0.39) | NR |

Note: N, number; Mel, melphalan; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; HDM, high-dose melphalan; ASCT, autologous stem cell transplantation; HR, hazard ratio; CI confidence interval; CT, chemotherapy; Dex, dexamethasone; NR, not reported; PBSCT, peripheral blood stem cell transplant; SWOG, Southwest Oncology Group; VAD, vincristine+adriamycin + dexamethasone; NA, not applicable; Thal, thalidomide; VMCP, vincristine + melphalan+cyclophosphamide+prednisone.

**Meta-analysis results.**

| | OS | CHR | PHR | Renal response | TRM |
|---|---|---|---|---|---|
| Comparative studies | HR=1.79 (95%CI, 1.11-2.91, p=0.18) in favour of CC; $I^2$=0 (p=ns) | OR=0.64 (95%CI, 0.25-1.64, p=ns); $I^2$=0 (p=ns) | OR=0.35 (95%CI, 0.06-2.10, p=ns) | OR=0.88 (95%CI, 0.30-2.53, p=ns) | RR=22.0 (95%CI, 1.32-365.5, p=0.03) indicating significant risk with ASCT |
| Non-comparative studies | 65% (95%CI, 0.25-0.46); $I^2$=71.5% (p=0.002) | 0.35 (95%CI, 0.26-0.44); $I^2$=73.3% (p<0.05) | 0.34 (95%CI, 0.17-0.50); $I^2$=85.7% (p<0.05) | 0.34 (95%CI, 0.15-0.52); $I^2$=70.8% (p=0.03) | 0.12 (95%CI, 0.09-0.14); $I^2$=0 (p=ns) |

**Notes:** OS, overall survival; CHR, complete hematological response; PHR, partial hematological response; TRM, treatment-related mortality; HR, hazard ratio; CI, confidence interval; CC, conventional chemotherapy; ns, nonsignificant; OR, odds ratio; RR, risk ratio; ASCT, autologous stem cell transplantation.

### *Treatment-Related Morbidity:*

*Comparative Studies*

The RCT by Jaccard et al (2007) reported a TRM of 24% in the SCT arm and none in the CT arm, indicating a significant risk associated with the use of SCT compared with CT alone (RR, 22.0 95% CI, 1.324 to 365.5; p=0.03). One of the non-RCTs reported 21% (3/14) cytomegalovirus or *Pneumocystis carinii* infections on the ASCT arm compared with none on the CT arm. Another reported 100% ASCT patients experiencing neutropenia and mucositis compared with none in the CT arm.

*Non-Comparative Studies*

Infection was the most common treatment-related morbidity observed (14% to 63%), followed by adverse gastrointestinal effects (7% to 66%). Other adverse effects reported included central nervous system effects, including seizures, acute renal failure, and bacterial sepsis syndrome.

**Sensitivity analysis results**

### *Non-Comparative Studies*

Sensitivity analyses were conducted to explore the causes for the statistical heterogeneity detected for OS, CHR, PHR, and renal response. When three outliers were removed from the CHR analysis, heterogeneity was removed (0.45 (95% CI, 0.37 to 0.52; $I^2$, 17.7%; p=0.30). No explanation for the heterogeneity observed with OS, PHR, and renal response was found.

None of the other sensitivity analyses performed changed any of the findings.

## DISCUSSION

Systemic AL amyloidosis is characterized by multisystem involvement in many patients. Issues around the extent of cardiac involvement have been implicated in terms of early morbidity and mortality with high-dose melphalan and SCT. The committee acknowledged that in the only published RCT (Jaccard et al, 2007, included in (5)), patients with this disease who were randomized to SCT had a lower survival than those receiving standard-dose CT alone. That RCT has been noted to have a relatively high TRM in the transplant arm, 24%, and other authors have suggested that if patients are carefully selected, outcomes with SCT may be better than standard-dose CT. The committee has recommended that SCT remain an option for patients with systemic AL amyloidosis, but that a referral to a transplant centre be considered for a more detailed examination of the risks versus benefits of high-dose CT. Given the nature of this disease

and the poor prognosis, even with SCT, transplantation within the context of an investigative study would be preferred. The committee agreed that there is no role for allogeneic SCT for this disease.

**CONCLUSIONS**

High-dose CT and SCT remain an option for carefully selected patients with systemic AL amyloid, and such patients should be referred to a transplant centre for proper evaluation.

**RECOMMENDATIONS**

- High-dose CT and ASCT are an option for selected patients with primary systemic amyloidosis but within an investigative setting only.
- Allogeneic SCT is not recommended for patients with primary systemic (AL) amyloidosis

**ONGOING TRIALS** (www.clinicaltrials.com) (updated August 31, 2011)

| Protocol ID | Title, details. |
|---|---|
| NCT01083316 | Bortezomib and Dexamethasone Followed by High-Dose Melphalan and Stem Cell Transplantation for Primary (AL) Amyloidosis<br>Study ID: H-28441, X05292<br>Status: recruiting<br>Last updated: June 21, 2011 |
| NCT00477971 | Low-Dose Melphalan and Dexamethasone Compared With High-Dose Melphalan Followed By Autologous Stem Cell Transplant in Treating Patients With Primary Systemic Amyloidosis<br>Study ID: CDR0000546745, P30CA015083, MC0482, 1691-05, NCI-2009-01329<br>Status: recruiting<br>Last updated: April 4, 2011 |
| NCT00075608 | Second Autologous Stem Cell Transplant in Treating Patients With Persistent or Recurrent Primary Systemic (AL) Amyloidosis<br>Study ID: CDR0000347379, BUMC-2001-0156<br>Status: recruiting<br>Last updated: June 21, 2011 |
| NCT00458822 | Melphalan and Autologous Stem Cell Transplant Followed By Bortezomib and Dexamethasone in Treating Patients With Previously Untreated Systemic Amyloidosis<br>Study ID: CDR0000537913, MSKCC-07006<br>Status: recruiting<br>Last updated: March 16, 2011 |
| NCT01273844 | Study of Bortezomib +HSCT in Primary Systemic Amyloidosis (AL)<br>Study ID: NJCT-1006<br>Status: recruiting<br>Last updated: January 10, 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.

**ACKNOWLEDGEMENTS**

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1. Hans Messersmith & Sheila McNair, Assistant Directors

2. Carol De Vito, Documents Manager
3. James Bao, Samia Qadir, and Esaba Kashem, Students for obtaining relevant papers and conducting the Data Audit
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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**Dr. Tom Kouroukis**; Chair, Hematology Disease Site Group
Juravinski Cancer Centre
3rd Floor, 699 Concession Street
Hamilton, ON, L8V 5C2
Phone: 905-575-7820 Fax: 905-575-6340 E-mail: tom.kouroukis@jcc.hhsc.ca

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3. Merlini G, Palladini G. Amyloidosis: is a cure possible? Ann Oncol. 2008;19 Suppl 4:iv63-6.
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5. Mhaskar R, Kumar A, Behera M, Kharfan-Dabaja MA, Djulbegovic B. Role of high-dose chemotherapy and autologous hematopoietic cell transplantation in primary systemic amyloidosis: a systematic review. Biol Blood Marrow Transplant. 2009;15(8):893-902.

## Appendix A. Literature search strategy.

1 exp Amyloidosis/
2 AA amyloidosis.mp.
3 AL amyloidosis.mp.
4 or/1-3
5 exp Bone Marrow Transplantation/
6 exp Stem Cell Transplantation/
7 exp Peripheral Blood Stem Cell Transplantation/
8 or/5-7
9 4 and 8
10 letter.pt.
11 comment.pt.
12 editorial.pt.
13 or/10-12
14 exp Randomized Controlled Trial/
15 randomised controlled trial.mp.
16 exp Clinical Trial/
17 Comparative Study/
18 or/14-17
19 pooling.mp.
20 pooled analysis.mp.
21 exp Meta-analysis/
22 meta-analyses.mp.
23 systematic review.mp.
24 health technology assessment.mp.
25 exp Evidence-Based Medicine/
26 clinical practice guideline.mp. or exp Practice Guideline/
27 or/19-26
28 18 or 27
29 28 not 13
30 9 and 29
31 limit 30 to (english language and humans and yr="2006 -Current") (23)

## Appendix B. AMSTAR results.

| | |
|---|---|
| **1. Was an a priori design provided?**<br>The research question and inclusion criteria should be established before the conduct of the review. | Yes |
| **2. Was there duplicate study selection and data extraction?**<br>There should be at least two independent data extractors and a consensus procedure for disagreements should be in place. | Yes |
| **3. Was a comprehensive literature search performed?**<br>At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. | No |
| **4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?**<br>The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc. | No |
| **5. Was a list of studies (included and excluded) provided?**<br>A list of included and excluded studies should be provided. | No |
| **6. Were the characteristics of the included studies provided?**<br>In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported. | Yes |
| **7. Was the scientific quality of the included studies assessed and documented?**<br>'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant. | Yes |
| **8. Was the scientific quality of the included studies used appropriately in formulating conclusions?**<br>The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. | Yes |
| **9. Were the methods used to combine the findings of studies appropriate?**<br>For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, $I^2$). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?). | Yes |
| **10. Was the likelihood of publication bias assessed?**<br>An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test). | Yes |
| **11. Was the conflict of interest stated?**<br>Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. | No |

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Recommendation Report SCT-2 Version 2: Section 3

# Stem Cell Transplantation in Primary Systematic Amyloidosis

## Document Review Summary

*S. Bhella, N. Varela, and members of the Stem Cell Transplantation Expert Panel*

November 18, 2019

***The 2012 recommendations are***

***ENDORSED***

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

## OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2012.

In March 2018, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (NV) conducted an updated search of the literature. A clinical expert (SB) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Stem Cell Transplant Expert Panel (see Appendix 1 for Expert Panel membership) endorsed the recommendations found in Section 1 (Recommendation Report) on November 18, 2019.

## DOCUMENT ASSESSMENT AND REVIEW RESULTS

### Questions Considered

1. What is the role of stem cell transplantation (SCT) in the treatment of primary systemic (AL, amyloid light-chain) amyloidosis?

**Literature Search and New Evidence**

The new search (October 2010 to June 2019) yielded 4 comparative retrospective studies that evaluated the role of autologous stem cell transplantation (SCT) in the treatment of primary systemic amyloidosis. An additional search in clinicaltrials.gov yielded no ongoing trials. No evidence was found addressing the use of allogeneic SCT for patients with primary systemic amyloidosis. Brief results of the identified publications are shown in the Document Review Tool; the search strategy is in Appendix 2.

**Impact on the Recommendation Report and Its Recommendations**

The original recommendation report concluded that high-dose chemotherapy and autologous stem cell transplantation is an option for selected patients with primary systemic amyloidosis, preferably within an investigative setting. The literature search updated to June 2019 provided new evidence that supports this recommendation. However, the quality of the evidence is low as it is derived from a limited number of retrospective, single center observational studies with small sample sizes. In addition, the selection of patients to receive treatment may have been biased due to treatment allocation based on baseline characteristics because patients who underwent autologous stem cell transplantation were significantly younger and had fewer comorbidities. Despite the limitations of the new evidence, the Stem Cell Transplantation Advisory Committee ENDORSED the 2012 recommendations on stem cell transplantation in primary systemic amyloidosis.

As suggested by a member of the Expert Panel, a qualifying statement was added to recommendation 1 to consider the degree of light chain amyloidosis when offering autologous stem cell transplantation.

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# Document Review Tool

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|---|---|
| **Number and Title of Document under Review** | SCT-2 Stem Cell Transplant in Primary Systematic Amyloidosis |
| **Current Report Date** | March 29, 2012 |
| **Date Assessed (by DSG or Clinical Program Chairs)** | March 9, 2018 |
| **Health Research Methodologist** | Norma Varela |
| **Clinical Expert** | Sita Bhella |
| **Approval Date and Review Outcome (once completed)** | November 18, 2019<br>ENDORSE |

Original Question(s):
What is the role of stem cell transplantation (SCT) in the treatment of primary systemic (AL, amyloid light-chain) amyloidosis?

Target Population:
All adult patients with primary (AL) amyloidosis who are being considered for treatment that includes either bone marrow or SCT.

Study Selection Criteria:
1. Systematic reviews with or without meta-analysis or clinical practice guidelines (CPGs) if the evidence was obtained with a systematic review (SR).
2. Fully published randomized controlled trials (RCTs) on patients with amyloidosis who received SCT that reported on survival and/or quality of life (QoL).
3. Fully published non-randomized studies on patients with amyloidosis who received SCT and had an appropriate contemporaneous control group that reported on survival or QoL.
4. Reports published in English only

Search Details:
October 2010 to June 2019: Cochrane Database of Systematic Reviews (intended to identify the most current systematic review/meta-analysis), MEDLINE (OVID), EMBASE (OVID), American Society of Clinical Oncology (ASCO) Abstracts, and clinicaltrials.gov.

Summary of New Evidence:

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| From 173 hits from MEDLINE and EMBASE, plus 2 from ASCO conference abstracts, 4 retrospective studies were found [1-4].<br><br>Clinical Expert Interest Declaration:<br>Dr. Bhella declared that she received more than $500 in 2017 and in 2019 from Celgene Corporation for acting in a consulting capacity. | |
| 1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed) | No |
| 2. Does the newly identified evidence support the existing recommendations? | Yes |
| 3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary) | Yes |
| **Review Outcome as recommended by the Clinical Expert** | ENDORSE |
| ***If the outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?*** | Not applicable |
| **DSG/GDG Commentary** | A qualifying statement was added to recommendation 1 to consider the degree of light chain amyloidosis when offering autologous stem cell transplantation for this condition. It was also stated that transplantation in amyloidosis is an evolving area and |

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| | therefore, new evidence is expected within a time frame of 2 to 3 years. |

| Observational Studies with Contemporaneous Control Group | | | | |
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| **Author [study years)** | **Patients characteristics (N, Study period, median age, median follow-up)** | **Arm 1 AUTO-SCT** | **Arm 2 CONTROL/ COMPARATOR** | **Brief Results OS, QoL** |
| Parmar et al., 2014 [1] [1998-2011] | N=145 RET<br><br>Only 100 patients alive at 1 year after initial diagnosis were included in the analysis<br><br>Patients in the ASCT were significantly younger than those in the control group (56 versus 61; *P*=0.0001)<br><br>Follow-up: 3-years | N=69<br>*Induction Therapy* n (%)<br>Pulse Dex 7 10<br>Mel/Pdn 4 6<br>Thal/Dex 4 6<br>Btz/Dex 17 25<br>Len/Dex 16 23<br>Btz/Thal 1 1<br>Btz/Len 4 6<br>Other 3 4<br>No treat. 13 19<br><br>*condition regimen*<br>MEL 200 87<br>Other 3 | N=31<br>*Induction Therapy* n (%)<br>Pulse Dex 3 10<br>Mel/Pdn 1 3<br>Thal/Dex 3 10<br>Btz/Dex 8 26<br>Len/Dex 3 10<br>Btz/Thal 0 0<br>Btz/Len 1 3<br>Other 2 6<br>No treat. 10 32 | Auto-SCT versus CTR<br>5-year OS<br>Overall: 63% versus 38%, *P*=0.0001<br>Patients alive at 1-year after diagnosis: 72% versus 65%, *P*=0.008<br><br>10-year OS<br>56% versus 10%, *P*=0.0001<br><br>Multivariable Analysis<br>The following factors were associated with improved survival<br>・ Age <60 years (*P*=0.01)<br>・ Novel agents Induction Therapy (*P*=0.04)<br>・ Kidney only involvement (*P*=0.04)<br>・ AUTO-SCT (*P*=0.004)<br><br>Among patients with overt cardiac involvement with or without other organ involvement (n=49), AUTO-SCT led to significant improvement in 5-year OS (51% versus 37%, *P*=0.03 |
| Raschle et al., 2014 [2] [1995-2012] | N=63 RET<br><br>Patients in the ASCT were significantly younger than those in the control group (59 versus 70; *P*<0.0006)<br><br>Follow-up: 31 months | N=13<br>*Induction Therapy* n (%)<br>VAD 1 8<br>Btz/Dex/CP 2 15<br>Btz/Dex 2 15<br>Thal/Dex 0 0<br>Mel/Dex 0 0<br>Len 0 0<br><br>*condition regimen*<br>MEL 200 mg/m$^2$ | N=50<br>*Induction Therapy* n (%)<br>VAD 6 12<br>Btz/Dex/CP 3 6<br>Btz/Dex 15 30<br>Thal/Dex 2 4<br>Mel/Dex 15 30<br>Len 2 4 | **NOTE**: Statistical Analysis did not control for confounding such as age.<br><br>Patients with Auto-SCT showed a trend towards better overall survival, with median survival not yet reached compared with 53 months in patients on conventional chemotherapy (*P*-0.065).<br><br>Possible factors contributing to the improved outcome, in addition to the more intensive treatment, in patients receiving Auto-SCT may be their better performance status and superior cardiac function. Patients undergoing Auto-SCT were younger (59 versus 70 year, *P*=0.0006), and their troponin-T values were lower (0.015 µg/l versus 0.08 µg/l, *P*=0.0279).<br><br>**NOTE**: Statistical Analysis did not control for confounding |

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| Miyazaki et al., 2019 [3]<br>[2007-2016] | N=232 RET<br>Patients in the ASCT were significantly younger than those in the control group (median age: 54 versus 67 years, *P*<0.001) | N=74<br>*Induction Therapy* n (%)<br>Mel-based 57 77<br>Btz-based 13 18<br>IMD-based 1 1<br>Btz+IMD 1 1<br>Other 2 3<br><br>*condition regimen*<br>MEL 200 mg/m$^2$ 34<br>MEL 120-140 mg/m$^2$ 31<br>MEL 70-100 mg/m$^2$ 8<br>Not available 1 | N=158<br>*Induction Therapy* n (%)<br>Mel-based 97 61<br>Btz-based 28 18<br>IMD-based 16 10<br>Btz+IMD 7 4<br>Other 10 6 | Multivariable Analysis<br>ASCT was significantly associated with better overall survival than chemotherapy alone<br>HR, 0.313; 95%CI, 0.155 to 0.636; *P*=0.0013.<br><br>Age, gender, brain natriuretic peptide, and creatinine were no associated with OS.<br><br>Overall, 14 and 85 patients died in the ASCT and CT group, respectively. The most common causes of death were amyloidosis (7 ASCT and 70 in the CT group) and infection (4 ASCT and 11 in the CT group) |
| Oke et al., 2017 [4] | N=74 RET<br><br>Patients in the ASCT were significantly younger and had higher ejection fractions, lower brain natriuretic peptide levels, and more severe proteinuria. | N=43<br>*Straight to Transplant* 14<br>*Induction Therapy* 29<br>MEL-based 3<br>Btz-based 24<br>IMD-based 2 | N=31<br><br>*CT Regimen*<br>MEL-based 1<br>Btz-based 30 | Auto-SCT versus CTR<br>OS: 74 months versus 8 months, *P*=0.03<br><br>Multivariable Analysis<br>ASCT was significantly associated with better overall survival than chemotherapy alone<br>HR, 5.6; 95%CI, 1.9 to 16; *P*<0.001. |
| **Abbreviations:** OS, overall survival; QoL, quality of life; ASCT, autologous stem cell transplantation; CTR, conventional therapies; RET, retrospective; Dex, dexamethasone; Mel, melphalan; Pdn, prednisone; Thal, thalidomide; Btz, bortezomib; Len, Lenalidomide; VAD, vincristine; IMD, immunomodulatory drug; CT, chemotherapy; HR, hazard ratio; CI, confidence intervals.. | | | | |

Appendix 1. Members of the Expert Panel

| Name | Affiliation | Conflict of Interest Declaration |
|---|---|---|
| Mohammed Aljama | Hamilton | No conflict declared |
| Chris Bredeson | Ottawa | No conflict declared |
| Michael Kennah | Ottawa | No conflict declared |
| Vishal Kukreti | Princess Margaret Hospital, Toronto | Received $500 or more in a single year acting in a consulting capacity for Janssen, Celgene, Takeda, and Amgen.<br>Principal Investigator on NEOD001 Prothena study for AL amyloidosis and Millenum study for AL amyloidosis relapsed disease. |
| Arleigh McCurdy | Ottawa | Received $500 or more in a single year acting in a consulting capacity for advisory boards of Janssen, Celgene, Takeda, and Amgen. |

Appendix 2. Search Strategy

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present; OVID EMBASE 1996 to June 2019

| # | Searches | Results |
|---|---|---|
| 1 | exp Amyloidosis/ | 23253 |
| 2 | AA amyloidosis.mp. | 1028 |
| 3 | AL amyloidosis.mp. | 1811 |
| 4 | or/1-3 | 23832 |
| 5 | exp Bone Marrow Transplantation/ | 44005 |
| 6 | exp Stem Cell Transplantation/ | 75893 |
| 7 | exp Peripheral Blood Stem Cell Transplantation/ | 3469 |
| 8 | or/5-7 | 114818 |
| 9 | 4 and 8 | 483 |
| 10 | letter.pt. | 1028674 |
| 11 | comment.pt. | 775545 |
| 12 | editorial.pt. | 491572 |
| 13 | or/10-12 | 1728027 |
| 14 | exp Randomized Controlled Trial/ | 483142 |
| 15 | randomised controlled trial.mp. | 20581 |
| 16 | exp Clinical Trial/ | 826944 |
| 17 | Comparative Study/ | 1830365 |
| 18 | or/14-17 | 2461091 |
| 19 | pooling.mp. | 11780 |
| 20 | pooled analysis.mp. | 7632 |
| 21 | exp Meta-analysis/ | 101169 |
| 22 | meta-analyses.mp. | 31779 |
| 23 | systematic review.mp. | 148123 |
| 24 | health technology assessment.mp. | 4232 |
| 25 | exp Evidence-Based Medicine/ | 70715 |
| 26 | clinical practice guideline.mp. or exp Practice Guideline/ | 27710 |
| 27 | or/19-26 | 322045 |
| 28 | 18 or 27 | 2762411 |
| 29 | 28 not 13 | 2702774 |
| 30 | 9 and 29 | 74 |
| 31 | limit 30 to (english language and humans) | 68 |
| 32 | limit 31 to yr="2010 -Current" | 28 |

***ASCO Annual Meeting*** - http://www.ascopubs.org/search

Amyloidosis AND Stem cell transplant

***Clinicaltrials.gov*** - http://www.clinicaltrials.gov/

Amyloidosis AND Stem cell transplant

**References**


1. Parmar S, Kongtim P, Champlin R, Dinh Y, Elgharably Y, Wang M, et al. Auto-SCT improves survival in systemic light chain amyloidosis: a retrospective analysis with 14-year follow-up. Bone Marrow Transplant. 2014;49(8):1036-41.
2. Raschle J, Banz Y, Suter T, Pabst T. A single-centre cohort of patients with systemic light chain AL-amyloidosis treated with conventional chemotherapy or with high-dose chemotherapy and autologous stem cell transplantation. Swiss Med Wkly. 2014;144:w13922.
3. Miyazaki K, Suzuki K. Autologous Hematopoietic Cell Transplantation Versus Chemotherapy Alone for Immunoglobulin Light Chain Amyloidosis: A Retrospective Study. Clin Lymphoma Myeloma Leuk. 2019.
4. Oke O, Sethi T, Goodman S, Phillips S, Decker I, Rubinstein S, et al. Outcomes from Autologous Hematopoietic Cell Transplantation versus Chemotherapy Alone for the Management of Light Chain Amyloidosis. Biol Blood Marrow Transplant. 2017;23(9):1473-7.

**DEFINITIONS OF REVIEW OUTCOMES**

1. **ARCHIVE – A**RCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document, however, may still be useful for education or other information purposes. The document is designated archived on the CCO website and each page is watermarked with the words "ARCHIVED."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel 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. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic 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 Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.