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Recommendation Report

Stem 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

The full Recommendation Report report, which is available on the CCO Transplantation page, consists of the following sections:

Section 1: Recommendations
Section 2: Summary of Methods and Evidence

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Recommendation Report: Section 1

Stem Cell Transplantation in Adults: Recommendations

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INTENDED PURPOSE

This recommendation report is primarily intended to guide policy makers in their decision making regarding the indications for stem cell transplantation. This recommendation report may also be useful to inform clinical decision making regarding the appropriate role of stem cell transplantation and to guide priorities for future research.

QUESTIONS:

1. What are the accepted indications for stem cell transplantation?
2. What measures are commonly reported to assess transplant outcomes?
3. Are there published standards guiding performance of transplantation?

TARGET POPULATION

All adult cancer patients being considered for treatment that includes either bone marrow or stem cell transplantation.

SUPPORT FOR RECOMMENDATIONS

A systematic review and environmental scan was conducted that searched for synthesized evidence reports and identified 14 clinical practice guidelines, 12 review articles, nine review articles including expert panel consensus, seven systematic reviews, four technology assessments, and nine other documents or articles containing relevant data and/or recommendations. This review and environmental scan is described in detail in Section 2 of this report. Where possible, the Advisory Panel on Bone Marrow and Stem Cell Transplantation (the Panel) and the Hematology Disease Site Group (DSG) developed these recommendations on the basis of clinical trial evidence identified in this review. In the absence of clinical trial evidence, the Panel and the Hematology DSG developed recommendations through the consensus of world opinion shown by the identified documents, as well as their own expert opinion. These recommendations represent a summary of current knowledge and opinion regarding stem cell transplantation in adults both in Ontario and

around the world. Please refer to Section 2 for more details regarding the evidence used for these recommendations and the process of their development.

RECOMMENDATIONS

Indications

The following recommendations address the role of stem cell transplantation for the following indications:

Acute Lymphoblastic Leukemia (ALL) (Including lymphoblastic lymphoma)

- *First complete remission:*
  - Allogeneic stem cell transplantation is an option for patients with ALL with poor prognostic features such as Philadelphia chromosome or t(4;11) positivity or delayed time to first complete remission.
  - Autologous stem cell transplantation is not recommended for patients with ALL in first complete remission.
- *Beyond first complete remission:*
  - Allogeneic transplantation is the recommended treatment option for eligible patients with ALL who achieve a second remission.
  - There is insufficient evidence to support or refute the use of autologous stem cell transplantation beyond first remission for patients with ALL.
- *Qualifying Statement:* The role of BCR-ABL inhibitors (e.g., imatinib, dasatinib) in the management of Philadelphia chromosome positive ALL is currently being explored as therapy prior to or following allogeneic transplantation.

Acute Myeloid Leukemia (AML)

- First complete remission:
  - Allogeneic transplantation is a treatment option for selected patients with AML in first complete remission with high-risk features such as high-risk cytogeneic or molecular phenotypes and secondary AML.
  - Autologous stem cell transplantation is not recommended for patients with AML in first complete remission.
- Beyond first complete remission:
  - Allogeneic transplantation is the recommended option for eligible patients with AML who achieve a second or subsequent remission.
  - There is insufficient evidence to support or refute the use of autologous stem cell transplantation for patients with AML in the second or subsequent remission.

Acute Promyelocytic Leukemia: (APL)

- First complete remission: Stem cell transplantation is not recommended for patients with APL in first complete remission.
- Beyond first complete remission: There is insufficient evidence to support or refute the use of stem cell transplantation for patients with APL in the second or subsequent remission.

Aplastic Anemia (AA)

- Allogeneic stem cell transplantation is the recommended treatment option for eligible patients under age 30-40 years of age with severe or very severe AA.
- Allogeneic stem cell transplantation is an option for selected patients with severe or very severe AA over the age of 30-40 years of age.
- Autologous stem cell transplantation is not recommended for patients with AA.

- *Qualifying Statement:* The choice of stem cell transplantation or immunosuppressive therapy with agents such as ATG and cyclosporine must take into consideration the expected toxicities of the two treatments as well as patient preference.

Chronic Lymphocytic Leukemia (CLL)
- Allogeneic stem cell transplantation is an option for selected patients with CLL, including those with high-risk cytogenetics who have failed purine analog therapy.
- Autologous stem cell transplantation is not recommended for patients with CLL.
- *Qualifying Statement:* The management of CLL is in evolution with the emergence of new treatment options, including targeted therapy. These options must be considered when recommending stem cell transplantation.

Chronic Myeloid Leukemia (CML)
- Allogeneic stem cell transplantation is an option for patients with CML for whom medical therapy has failed, as well as those in accelerated phase or blast crisis.
- Autologous stem cell transplantation is not recommended for patients with CML

Hodgkin's Lymphoma (HL)
- Autologous stem cell transplantation is the recommended treatment option for eligible chemosensitive patients with HL who are refractory to or who have relapsed after primary chemotherapy.
- Allogeneic stem cell transplantation is an option for chemosensitive patients with refractory or relapsed HL who are not candidates for autologous stem cell transplantation or who have a syngeneic (identical twin) donor.
- Stem cell transplantation is not recommended as part of primary therapy for HL.

Multiple Myeloma (MM)
- 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.

Myelodysplastic Syndrome (MDS)
- Allogeneic transplantation is an option for selected patients with MDS.
- Autologous stem cell transplantation is not recommended for patients with MDS.

The Non-Hodgkin's Lymphomas

Aggressive Histology NHL Including Diffuse Large B Cell Lymphoma and Aggressive T Cell Lymphomas (AH-NHL)

- Autologous stem cell transplantation is the recommended option for eligible chemosensitive patients with AH-NHL refractory to or relapsed after primary therapy.
- Allogeneic stem cell transplantation is an option for eligible chemosensitive patients with refractory or relapsed AH-NHL who are not candidates for autologous stem cell transplantation or who have a syngeneic (identical twin) donor.
- Stem cell transplantation is not recommended for patients with AH-NHL as part of primary therapy.

Follicular Lymphoma (FL)

- Autologous or allogeneic transplantation are options for selected patients with poor prognosis FL that progresses after second-line therapy.

Burkitt's Lymphoma

- Autologous and allogeneic transplantation are options for selected patients with Burkitt's lymphoma beyond first remission.
- Stem cell transplantation is not recommended for patients with Burkitt's lymphoma in first complete remission.

Mantle Cell Lymphoma (MCL)

- Autologous stem cell transplantation is an option for eligible patients with MCL in first remission.
- Autologous or allogeneic transplantation are options for selected patients with MCL in second remission.

Solid Tumours

- Autologous stem cell transplantation (single or tandem) is a treatment option for patients with gonadal or retroperitoneal germ cell tumours refractory to or relapsed after cisplatin-based chemotherapy.
- Stem cell transplantation is not recommended in patients with other solid tumours including breast, ovarian, and lung cancers.

Assessment and Performance

The following recommendations address what measures should be assessed when reporting transplant outcomes:

Measures to assess transplant outcomes

- Treatment-related mortality
- Relapse-free survival
- Disease-free survival
- Event-free survival
- Outcome at 12 months and annual follow-up: current survival status (alive/dead/unknown), current disease status (refractory, response, relapse), further treatment since initial treatment program (yes/no)
- Overall survival (including date of death, cause of death)

Demographic Information

- Patient identification: date of birth, postal code, sex (male/female), OHIP number, General Practitioner's name

Procedure Information

- Immediate plan for transplantation versus (vs.) deferred ("rainy day") harvest (yes/no; date collected)
- autograft (yes/no; date)
- allograft (yes/no; date)

The following recommendations address published standards guiding performance:

Published standards guiding performance

- Treatment-related mortality is a reliable measure of performance between centres.

Qualifying Statement: The choice of whether to use an autologous or allogeneic procedure must be made by the patient in consultation with his/her clinician in consideration of the expected benefits and harms associated with each procedure in this disease setting.

Qualifying Statement: Age is generally considered a surrogate for co-morbidity as toxicity and treatment-related mortality with transplantation increase with age.

RELATED PEBC REPORTS

- 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 Apr 16;136(8):619-29.

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Recommendation Report: Section 2

Stem Cell Transplantation in Adults: Summary of Methods and Evidence

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INTRODUCTION

High-dose therapy and stem cell transplantation (SCT) is the process of administering high doses of chemotherapy with or without radiation, followed by the infusion of stem cells, progenitor cells capable of repopulating the bone marrow. The development of this procedure in the 1950s by Dr. Donnall Thomas was later recognized with a Nobel Prize (1). Since that time, SCT has been reported to offer the potential of cure for a number of cancers and other conditions (2). SCT consists of two distinct procedures characterized by the source of the stem cells used to repopulate the bone marrow (3): autologous transplantation, in which the cells are collected from the patients themselves, and allogeneic transplantation, in which the stem cells are collected from a separate compatible donor. The mechanism of action of these two forms of therapy differs significantly. Autologous transplantation allows for the administration of doses of chemotherapy with or without radiation that are many times higher than the maximum otherwise tolerated. Allogeneic transplantation also allows for the administration of high doses of chemotherapy and/or radiation but also has a graft-versus-cancer effect in which transplanted donor immune cells are able to target some cancer cells (4). Allogeneic transplantation requires the identification of a compatible donor. Donors are matched according to the expression of Human Leukocyte Antigens (HLA) and may be related (typically sibling) or unrelated to the patient, with each full sibling having a 25% chance of being HLA compatible. For patients without a sibling donor, unrelated donors are sought though donor registries. As the distribution of HLA antigens differs amongst ethnic groups, diversity in the donor registries is essential. At the current time, not all ethnic groups are well represented in the donor pool, leading to uneven access to compatible unrelated donors.

Allogeneic transplantation is typically a more toxic and technically complex procedure as it requires the suppression of the immune system with medication to prevent graft rejection and graft-versus-host disease (GVHD), a potentially fatal complication in which transplanted immune cells attack host tissue. Because of this, transplant-related mortality (TRM) is higher with allogeneic transplantation and increases with recipient age. This had led transplant centres to institute age limits on transplantation (historically age 55-60), though improvements in donor compatibility testing and, supportive care and the advent of less

intensive, "non-myeloablative" transplants are allowing centres to offer allogeneic transplantation to selected older patients.

Autologous transplantation is available to a larger population of patients, because each patient is potentially their own donor, with no risk of GVHD. The lack of GVHD is associated with a lower reported TRM (3), but the lack of a graft-versus-cancer effect and the potential for graft contamination with malignant cells may offset this advantage. The selection of the appropriate type of transplant for a given patient is complex and depends on a number of patient, donor, and disease-specific factors.

A second classification of transplantation involves the collection of stem cells, historically through the harvesting of bone marrow to recover hematopoietic stem cells. Transplants performed using stem cells obtained in this manner are referred to as bone marrow transplants (BMT). In the 1980s, it was discovered that stem cells could be mobilized from the bone marrow into the peripheral blood using chemotherapy and hematopoietic growth factors (5), a technique referred to as peripheral blood stem cell collection (PBSC). PBSC has been reported to result in long-term outcomes comparable to BMT but allows donors to avoid the general anesthetic associated with bone marrow harvesting (6,7). In addition, peripheral blood stem cell transplantation (PBSCT) results in a more rapid recovery of bone marrow function (engraftment) and shorter hospital stays. For this reason, PBSCT has supplanted BMT for many indications, although BMT continues to be performed for a number of reasons, including the inability to mobilize stem cells in some patients (8). For the purpose of this report, the term SCT will be used to refer to the two types of procedures.

In the early years of transplantation, evidence of its effectiveness was largely restricted to case reports and publications of single-centre experiences; however, its role is increasingly being defined by controlled trials and by published practice guidelines. Such trials are increasingly important because the role of SCT must be continually readdressed with the introduction of other novel cancer treatments.

SCT is a complex and resource-intensive treatment associated with significant toxicity. Given this reality, not all centres can be expected to offer SCT and not all transplant centres will necessarily offer all types of transplantation for all disease entities. For this reason, coordination between transplant centres is required to ensure equitable access to all transplant services.

Recently, concern has been expressed that the gap between the demand for SCT and the ability to provide the therapy in Ontario is growing, and there is a perception of uneven access for patients across the province. The Ontario Ministry of Health and Long Term Care has requested that Cancer Care Ontario (CCO) provide advice regarding issues of access, quality, and funding. This recommendation report was developed in response to that request, and to provide recommendations to policy makers and clinicians in Ontario on how best to ensure optimal access to evidence-based SCT both in the immediate term and in the future.

ADVISORY PANEL AND HEMATOLOGY DSG INVOLVEMENT

In order to develop the necessary recommendations, CCO created the Advisory Panel on Bone Marrow and Stem Cell Transplantation (referred to as the Panel) (membership: Appendix 1). At the request of the Panel, the standing Hematology Disease Site Group (DSG) of the Program in Evidence-based Care (PEBC) was asked to participate in the recommendations process and to assume responsibility for the dissemination and periodic updating of the document.

EVIDENCE REVIEW

In order to ensure that any recommendations were informed to the greatest extent feasible by the clinical evidence, and to determine what the consensus of world opinion on this subject was in the absence of good clinical evidence, the PEBC was asked to conduct a systematic review and environmental scan. Due to the time constraints involved in developing the recommendations, the PEBC decided to limit this search to only summary

sources of evidence and recommendations, including clinical practice guidelines, systematic reviews with or without meta-analyses, review articles, technology assessments, and similar documents and articles. Primary research articles (e.g., randomized controlled trials, observational studies) were not considered. The methods and results of this evidence review are described below.

Methods

The systematic review of the literature and the environmental scan of the unpublished gray literature were intended to gather evidence to answer the following questions:

1. What are the accepted indications for stem cell transplantation?
2. What measures are commonly reported to assess transplant outcomes?
3. Are there published standards guiding performance of transplantation?

For this project, the core methodology used to develop the evidentiary base was a systematic review of the indexed literature along with an environmental scan of non-indexed evidence and other relevant sources of information. Evidence was selected and reviewed by two members of the expert panel and one methodologist. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through CCO. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

Using OVID, the MEDLINE (1996 through January (week 4), 2008), EMBASE (1996 through week 5, 2008), and Cochrane Database of Systematic Reviews (CDSR) (through December 31, 2007) databases were searched for evidence. For the MEDLINE and EMBASE searches, terms for bone marrow transplantation were combined with terms for stem cell transplantation, autologous and allogeneic transplantation, the various diseases included, and evidence-based medicine (EBM) publication types. These results were then limited to the English language, reports on human subjects, and reports published after 1999. The search terms varied depending on the database being used, and the search strategies used appear in Appendix 2 and 3. A flow diagram of the literature search appears in Appendix 4.

An environmental scan of the non-indexed evidence was also performed on October 26, 2007. The environmental scan was comprised of two parallel processes, one a targeted search of known organizations that produce evidence-based medicine products and the other an untargeted search to identify previously unknown sources of evidence. A listing of the organizations that were examined in the targeted search is given in Appendix 5. For the untargeted search, the Google™ online internet search engine was used with the keywords "bone marrow transplantation" + "guideline", "bone marrow transplantation" + "standards", "stem cell transplantation" + "guideline", and "stem cell transplantation" + "standards".

Evidence Selection Criteria

The types of evidence eligible for inclusion in this review were:

1. Existing evidence synthesis and summary reports, including clinical practice guidelines, systematic reviews with or without meta-analyses, review articles, technology assessments, consensus statements, and standards documents.
2. Published papers discussing indications where SCT is appropriate (including disease site/state; any data on proven indications if available).
3. Published papers of short and long term outcomes, current and proposed models for monitoring, and quality planning/improvement.

Excluded Evidence
Papers reporting on non-malignant disease were excluded. The Panel is aware that SCT is performed in adults for non-malignant indications such as myleoproliferative disorders, immune deficiency syndromes, and hemoglobinopathies but is also aware that these indications account for a very small proportion of the transplants performed in Ontario and other jurisdictions and that, therefore, evidence on which to base recommendations is extremely limited.

Synthesizing the Evidence
As the evidence review was intended to locate summary documents of evidence and recommendations, and not clinical trial reports themselves, no pooling was planned or performed.

Results
Literature Search Results
From the MEDLINE search, 170 potentially relevant articles were identified, of which 68 were ordered for further review. On reviewing these 68 articles, 53 were deemed to be relevant and were included (2,9-60). For the EMBASE search, seven potentially relevant articles not found in the MEDLINE search were identified, of which one was ordered for full review but then excluded. For the CDSR search, six potentially relevant articles not found in the MEDLINE search were identified, and upon review of the abstract, were excluded without being ordered (all were protocols of reviews in development). Two additional papers, one by Koreth et al (61) and a Cochrane Review by Greb et al (62), that were not found in the literature search were identified by one of the authors (K.I.), bringing the total number of papers obtained to 55. This search process is summarized in Table 1.

Table 1. Summary of literature search.

Database	Number of hits	Number ordered for review	Number retained for inclusion	References
MEDLINE	168	66	53	(2,9-60)
EMBASE	7	1	0	-
CDSR	6	0	0	-
Other	2	2	2	(61,62)

The articles obtained were comprised of 14 clinical practice guidelines; 12 review articles; nine reviews with an expert panel consensus; six systematic reviews; five position statements, consensus statements, monographs, or special reports; four technology assessments; two meeting reports or grand rounds reports; and two database audits using population-based data. The results are summarized in Table 2.

Table 2. Summary of literature search results by document type.

EBM type	Number	References
Clinical Practice Guidelines	14	(15,16,20,23,24,28,33,39,40,43,44,46,48,52)
Review articles	12	(14,18,21,27,29,30,34,35,49,55,59,60)
Review + expert panel consensus	9	(11,13,25,26,37,41,42,50,53)
Systematic review	7	(17,22,36,54,56,61,62)
Position statement/Consensus statement/Monograph/Special report	5	(2,10,45,47,51)
Technology assessment	4	(9,38,57,58)
Meeting report/grand rounds report	2	(19,31)
dB audit	2	(12,32)
TOTAL:	**55**	

Environmental Scan Results

The information obtained in the environmental scan was comprised of two systematic reviews with expert panel consensus, one hospital Standard of Care report, and one government publication (Certificate of Need), for a total of four reports (63-66).

Table 3. Summary of environmental scan results by document type

Document type:	Number:
Systematic review and expert panel consensus (F.A.C.Tsite.org)	2
Hospital standard of care report (Brigham & Women's Hospital, Boston, MA, USA)	1
Government documents (Certificate of Need document) (State of Michigan, USA)	1
TOTAL:	**4**

Outcomes – Systematic Review of the Literature

Evidence was obtained and summarized for the following diseases: acute lymphoblastic leukemia, acute myeloid leukemia, acute promyelocytic leukemia, aplastic anemia, chronic lymphocytic leukemia, chronic myeloid leukemia, Hodgkin's disease, multiple myeloma, myelodysplastic syndrome, the non-Hodgkin's lymphomas, and solid tumours.

Acute lymphoblastic leukemia (ALL)

Three papers were retrieved providing data on stem cell transplantation in ALL (2,9,10), one on SCT (10) and the other two on SCT including PBSCT (9) and PBSCT and Cord Blood Stem Cell Transplantation (CBSCT) (2). These papers are summarized in Table 4. One reported on both allogeneic and autologous procedures (9), and the remaining two reported on allogeneic procedures only (2,10). One of the papers was a technology assessment (9), one was a position statement (10), and the last was a special report (2). The recommendations are based on small uncontrolled studies. The reports do not recommend transplantation for standard-risk patients in first complete remission. Two papers suggest that allogeneic transplantation is indicated in Philadelphia chromosome positive ALL or as an investigational indication (2,10). The reports provide conflicting recommendations on the role of transplantation beyond first complete remission, with the Medical Advisory Panel of Blue Cross and Blue Shield finding no indication for either allogeneic or autologous transplantation and the report of the American Society of Bone Marrow Transplantation recommending allogeneic stem cell transplantation as the treatment of choice in this situation (9,10). A synopsis of the indications/contraindications for ALL supported by the identified papers is found in Table 5.

Table 4. Summary of papers pertaining to acute lymphoblastic leukemia (ALL).

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
Medical Advisory Panel (MAP), 2000 (8) Sponsor: Blue Cross, Blue Shield	PBSCT	Both	Contraindicated. The evidence reviewed does not support high dose chemotherapy and allogeneic SCT as salvage treatment after relapse or progression following high dose chemotherapy and autologous SCT in patients with ALL.	Technology assessment Four studies involving 35 patients
Hahn T et al, 2006 (10) Sponsor: American Society for Blood & Marrow Transplantation	SCT	Allogeneic	Indicated: SCT is recommended as the treatment of choice during second CR. Contraindicated: SCT is not recommended as a treatment option during first CR. Under investigation: Early data suggest a survival advantage for related allogenic SCT compared with CT in Ph+ adult patients in CR1 or later remission.	Position Statement
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow Transplantation	BMT/ PBSCT/ CBSCT	Allogeneic	Indicated: Patients with poor prognostic features (e.g. t(9;22) or t(4;11)) or with delayed time to CR1 are candidates for allogenic SCT from either an HLA-matched sibling or unrelated donor.	Special Report

Table 5. Acute lymphoblastic leukemia (ALL) supported indications/contraindications.

Indications/Contraindications	References
Indicated: Allogeneic SCT during second CR, or in patients with poor prognostic features, or delayed time to first CR.	(2,10)
Contraindicated: There is no evidence to support allogeneic SCT as salvage treatment after relapse or progression following high dose chemotherapy and autologous SCT, or during CR1.	(9,10)

Acute myeloid leukemia (AML)

Nine papers (2,9,11-17) were retrieved reporting on either BMT (2,11,14,16) or SCT (9,12,13,15,17) in AML. Two papers reported on allogeneic procedures (12,16), and seven reported on both allogeneic and autologous procedures (2,9,11,13-15,17). None reported on autologous alone. Two of the papers were reviews with an expert panel consensus (11,13), one was a technology assessment (9), one was a database audit (12), one was a review (14), two were clinical practice guidelines (15,16), one was a special report (2), and one was a systematic review (17). These papers are summarized in Table 6.

Two papers report SCT (from a sibling or HLA-matched donor) as being potentially curative in the treatment of AML (14,16).

First complete remission

The recommendations on the role of SCT in AML in first complete remission are based on a number of controlled trials. Of the six reports that make recommendations regarding allogeneic transplantation (2,11-13,15,17), all recommend it should be offered to patients with an HLA-identical sibling; three recommend it for all such patients (12,13,17), with three recommending it to patients felt to be at higher risk (generally intermediate and high-risk karyotype) (2,11,12,15). Of the seven reports making recommendations regarding autologous transplantation (11-16), four consider it investigational (12-16), while three recommend that it should be offered to selected patients without an HLA-identical sibling (2,11,17). One report suggests that the outcome of autologous and allogeneic transplantation may be comparable. Only one report (11) specifically addresses the role of unrelated SCT in AML in first remission. This paper recommends it for patients with unfavourable karyotype over age 30 years. A synopsis of the indications/contraindications for AML in first complete remission supported by the identified papers is found in Table 7.

Beyond first remission

Few of the identified reports address transplantation for AML beyond first remission, with one technology assessment indicating that there is insufficient data to support its use (9) and one guideline from the British Committee for Standards in Hematology recommending HLA-matched sibling transplant as the treatment of choice for younger patients in second remission (15). A synopsis of the indications/contraindications for AML beyond first remission supported by the identified papers is found in Table 7.

Table 6. Summary of papers pertaining to acute myeloid leukemia (AML).

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
Gale RP et al, 1999 (11) Sponsor: Salik Health Care, Inc. (in part)	BMT	Both	Accepted indications: AML patients in 1st remission: In patients with an HLA-identical sibling and cytogenics unfavourable or intermediate/untested and age <30y → HLA-identical sibling transplant. In patients without an HLA-identical sibling with unfavourable cytogenics and age <30y → autologous or alternative donor. In patients without an HLA-identical sibling with unfavourable cytogenics and age >30y → autologous. Under Investigation: In patients with an HLA-identical sibling and cytogenics intermediate/untested age <30y or favourable cytogenics → HLA-identical sibling transplant or CT. In patients without an HLA-identical sibling with intermediate, favourable or not tested cytogenics → autotransplant.	Review + expert panel consensus
Medical Advisory Panel (MAP), 2000 (9) Sponsor: Blue Cross, Blue Shield	PBSCT	Both	Not accepted indications: The evidence reviewed is insufficient to support HDC/AlloSCS as salvage treatment after relapse or progression following HDC/AuSCS in patients with either: AML, NHL, HD, AML, or ALL.	Technology assessment Three studies involving 43 patients
Visani G et al, 2001 (12) Sponsor: MURST, FONDI (in part)	SCT	Allogeneic	Accepted indications: Patients should receive allogenic SCT following induction/consolidation CT instead of standard CT. Data show this approach results in a significant improvement in DFS in patients in "favourable" and "intermediate" karyotype group.	dB audit (Chart review of data from 11 Italian centres)
Fey et al for ESMO, 2003 (13) Sponsor: European Society for Medical Oncology	SCT	Both	Accepted indications: Patients with HLA-identical sibling should be offered allogenic SCT at first remission. Under investigation: Patients with poor risk features and no family donor may qualify for allogenic transplant from an unrelated matched donor. The role of high-dose consolidation CT with autologous PBSCT is still under investigation.	Review + Expert panel consensus
Rund D et al, 2004 (14)	BMT	Both	Accepted indications: Allogenic BMT, myeloablative or non-myeloablative, is potentially curative in	Review

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
Sponsor: None listed			therapy-related AML/MDS. Not accepted indications: While autologous BMT is less risky than allogeneic BMT, survival is poorer.	
Milligan DW et al, 2006 (15) Sponsor: British Committee for Standards in Haematology	SCT	Both	Accepted indications: For high-risk patients in first CR that have an HLA-identical donor SCT is recommended, although only a minority of patients will benefit. HLA-matched sibling allogeneic SCT is recommended as the treatment of choice for younger patients that are in second remission. Under investigation: The role of autologous SCT is under investigation and should only be considered within a clinical trial.	Practice guideline
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow Transplantation	BMT/ PBSCT/ CBSCT	Both	Accepted indications: Patients with AML in CR1 may be considered for treatment with allogeneic or autologous SCT on an individual basis, or within the context of a clinical trial. Not accepted indications: In AML patients in CR1 with cytogenetically favourable subtypes allogeneic SCT is not recommended.	Special Report
O'Donnell MR et al, 2006 (16) Sponsor: National Comprehensive Cancer Network	BMT	Allogeneic	Accepted indications: Allogeneic SCT from a sibling or an unmatched donor offers the best chance for long-term disease control.	Practice Guideline
Visani G et al, 2006 (17) Sponsor: MURST, AIL (in part)	SCT	Both	Accepted indications: In patients in CR1 allogeneic SCT is the proven method of reducing the risk of relapse, but is associated with high TRM. Although allogeneic has been shown to extend DFS, OS remains unchanged and use of it in this setting remains controversial. Newer data suggest that there is no overall survival difference between allogeneic and autologous SCT, and autologous SCT might be considered in patients lacking a HLA-matched sibling donor.	Systematic review

Table 7. Acute myeloid leukemia (AML) supported indications/contraindications.

	References
INDICATED	
Overall: BMT and allogeneic SCT (from a sibling or HLA-matched donor) are potentially curative in the treatment of AML.	(14,16)
First CR: Allogeneic transplantation should be offered to all patients with an HLA-identical sibling.	(2,11-13,15,17)
Three recommend allogeneic transplantation for all patients.	(12,13,17)
Three recommend allogeneic transplantation to patients felt to be at higher risk (generally intermediate and high-risk karyotype).	(2,11,12,15)
Four papers consider autologous transplantation investigational.	(12-16)
Three recommend that autologous transplantation should be offered to selected patients without an HLA-identical sibling.	(2,11,17)
One report addresses the role of unrelated SCT in AML in first remission recommending it for patients with unfavourable karyotype over age 30 years.	(11)
Post-first CR: There is insufficient data to support the use of transplantation beyond first CR.	(13)
HLA-matched sibling transplant is the treatment of choice for younger patients in second remission.	(15)
CONTRAINDICATED	
While autologous BMT may hold less risk than allogeneic BMT survival is also poorer.	(14)
UNDER INVESTIGATION	
The role of high-dose consolidation CT with autologous peripheral SCT is still under investigation.	(13)
There may be no overall survival difference between allogeneic and autologous SCT, and for patients without an HLA-matched donor, autologous transplantation may be considered, but this is still under investigation.	(15,17)

Acute promyelocytic leukemia (APL)

One paper was retrieved that reported on BMT (PBSCT) in APL (18). This review paper reported on autologous procedures only. The recommendations were that patients in second remission or greater either BMT or PBSCT should be offered as postconsolidation therapy. While SCT is not considered standard treatment during first remission, it might be offered to high-risk patients, but this is still under investigation. This paper is summarized in Table 8. A synopsis of the indications/contraindications for APL supported by the identified papers is found in Table 9.

Table 8. Summary of the paper pertaining to Acute promyelocytic leukemia (APL).

Author	Intervention	Allogeneic /autologous/both	Indicated/contraindicated/under investigation	Evidence base
Douer D et al, 2003 (18) Sponsor: None listed	BMT/ PBSCT	Autologous	Accepted indications: Either BMT or peripheral SCT is recommended as post-consolidation therapy for patients with APL in ≥2 CR. Under investigation: SCT is not indicated in first CR but might be offered to high-risk patients.	Review

Table 9. Acute promyelocytic leukemia (APL) supported indications/contraindications.

	References
INDICATED	
BMT or peripheral SCT is recommended as post-consolidation therapy for patients in second or greater remission.	(18)
UNDER INVESTIGATION	
SCT is not indicated in first response but might be offered to high-risk patients	(18)

Aplastic anemia (AA)

Three papers were retrieved that reported on allogeneic BMT in AA (2,19,20). One paper was a meeting report (19), one was a clinical practice guideline (20), and one was a special report of the European Group for Blood and Marrow Transplantation (EBMT) (2). These papers are summarized in Table 10.

All three papers agree that allogeneic BMT is the treatment of choice for severe or very severe AA patients with an HLA-matched sibling donor that are under 30 years of age (2,19,20). Two of the papers extend the appropriate age from 30 to 40 years of age (19,20), with one of these recommending that, in patients in this age group, immunosuppression and BMT have comparable outcomes (2). Two papers suggest that, in selected patients over the age of 40 years with a compatible donor (related or unrelated), transplantation can be considered after failure of immunosuppressive therapy (2,20).

Haplo-identical transplantation using purified CD34+ cells is addressed in one paper and still under investigation and is not recommended (20). A synopsis of the indications/contraindications for AA supported by the identified papers is found in Table 11.

Table 10. Summary of papers pertaining to aplastic anemia (AA).

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
Kojima S et al, 2000 (19) Sponsor: None listed	BMT	Allogeneic	<u>Accepted indications:</u> Allogenic BMT is the treatment of choice for severe AA patients <40y who have an HLA-identical sibling. Patient lacking an HLA-identical sibling may choose an unrelated donor. In the case of non-HLA-identical family donor transplants, mismatches of one locus are acceptable, but haplo-identical transplantation using purified CD34+ cells is considered experimental and cannot be recommended. Non-responders should receive two cycles of immunosuppressive therapy prior to BMT	Meeting report
Marsh et al, 2003 (20) Sponsor: The British Committee for Standards in Hematology	BMT	Allogeneic	<u>Accepted indications:</u> Allogenic BMT from an HLA-identical sibling is the initial treatment of choice for newly diagnosed patients with aplastic anemia if they have severe or very severe AA, and if they are younger than 40y.	Practice guideline
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow Transplantation	BMT/ PBSCT/ CBSCT	Allogeneic	<u>Accepted indications:</u> In AA patients under 30y allogenic BMT is the treatment of choice. In AA patients 30-45y BMT and immunosuppression give acceptable results. In older patients, or where there is no HLA-matched sibling donor, CT should be offered.	Special Report

Table 11. Aplastic anemia (AA) supported indications/contraindications.

	References
INDICATED	
Allogeneic BMT is the treatment of choice for severe or very severe AA for patients with an HLA-matched sibling donor that are under 30 years of age.	(2,19,20)
The appropriate age can be up to 40 years of age, if all patients over the age of 30 receive immunosuppression therapy along with BMT.	(19,20)
When a non-HLA-identical sibling donor is used, mismatches of one locus are acceptable.	(2)
UNDER INVESTIGATION	
Haplo-identical transplantation using purified CD34+ cells is still under investigation and cannot be recommended.	(20)

Chronic lymphocytic leukemia (CLL)

Six papers were obtained that reported on the use of transplantation in CLL (2,21-25), three on SCT (21,22,24), one on BMT alone (23), and two on BMT and PBSCT or CBSCT (2,25). Four of the papers reported on both allogeneic and autologous procedures (2,22-24), one reported on allogeneic procedures only (25), and one did not specify (21). One of the obtained papers was a review (21), one was a systematic review (22), two were clinical practice guidelines (CPGs) (23,24), one was a special report (2), and one was a review with expert panel consensus (25). These papers are summarized in Table 12.

The retrieved reports do not identify any controlled clinical trials of transplantation in CLL. Five of the reports consider allogeneic transplantation to be an option for selected patients with CLL, with three of the papers reporting curative potential (21,23,25). A number of papers comment on the high observed treatment-related mortality (22,24,25). There are no consistent criteria for transplantation proposed in the identified reports, although one states that it should be considered an option only for younger patients who have been previously treated and have poor-risk disease, as defined by cytogenic and clinical assessments (2). Currently, there are no randomized controlled trial data supporting the use autologous SCT in this setting (23), and the majority of the retrieved reports identify autologous transplantation as investigational in CLL.

One paper recommended that measures to evaluate treatment outcomes should be treatment-related mortality, relapse incidence for disease control, event-free survival, and overall survival (25). A synopsis of the indications/contraindications for CLL supported by the identified papers is found in Table 13.

Table 12. Summary of papers pertaining to chronic lymphocytic leukemia (CLL).

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
Walshe R et al, 1999 (21) Sponsor: None listed	SCT	NR	Accepted indications: SCT is an accepted treatment for CLL.	Review
Kimby E et al, 2001 (22) Sponsor: Swedish Council of Technology Assessment in Health Care	SCT	Both	Under investigation: High dose CT with allogenic or autologous SCT has been evaluated in young patients with B-cell CLL with a survival benefit being demonstrated, however this is limited by transplantation-related mortality, and this treatment should still be considered experimental in this setting.	Systematic review
Oscier D et al, 2004 (23) Sponsor: The British Committee for Standards in Hematology	BMT	Both	Accepted indications: Allogenic SCT is potentially curative in CLL. Under investigation: There are no randomized controlled trial data supporting the use autologous SCT although trials are underway.	Practice guideline
Brugiatelli M et al, 2006 (24) Sponsor: Novartis	SCT	Both	Under investigation: Younger high-risk patients should be considered candidates for high-dose CT with either autologous or allogenic SCT within a clinical trial setting. Patients that do not respond to, or that relapse shortly after, fludarabine CT should be considered for therapy using non-cross-reactive agents such as alemtuzumab, followed with high-dose CT and autologous or allogenic SCT within a clinical trial setting.	Practice Guideline
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow Transplantation	BMT/ PBSCT/ CBSCT	Both	Accepted indications: Allogenic SCT is an option for younger patients who have been previously treated and have poor-risk disease, as defined by cytogenic and clinical assessments.	Special Report
Dreger P et al, 2007 (25) Sponsor: German CLL Study Group	BMT/ PBSCT	Allogeneic	Accepted indications: In patients with poor-risk CLL allogeneic SCT is potentially curative. Under investigation: Early data suggest that the success rate of SCT decreases with the number of cytotoxic pretreatments given. Measures to determine treatment outcomes: TRM, relapse incidence for disease control, event-free survival, overall survival.	Systematic review + expert consensus

Table 13. Chronic lymphocytic leukemia (CLL) supported indications/contraindications.

	References
INDICATED	
Allogeneic SCT is potentially curable in CLL.	(21,23,25)
Allogeneic SCT should only be considered an option for younger patients who have been previously treated and have poor-risk disease, as defined by cytogenic and clinical assessments.	(2)
There are no randomized controlled trial data supporting the use autologous SCT in this setting.	(23)
UNDER INVESTIGATION	
A survival benefit has been demonstrated in younger patients with B-cell CLL that received high-dose CT with either allogeneic or autologous SCT, but TRM was high and this should remain an experimental procedure only.	(22,24)
One paper suggests that for patients that either do not respond to or relapse shortly after fludarabine CT should be offered using non-cross-reactive agents such as alemtuzumab followed with high-dose CT and autologous or allogeneic SCT, but within a clinical trial setting only.	(24)
Multiple agents must be used with caution as early data suggest that the success rate of SCT decreases with the number of cytotoxic pretreatments given.	(25)
MEASURES TO ASSESS TRANSPLANT OUTCOMES	
Measures to evaluate treatment outcomes should be treatment-related mortality, relapse incidence for disease control, event-free survival, and overall survival.	(25)

Chronic myeloid leukemia (CML)

Eleven papers were obtained that reported on CML (2,21,26-34). Three of the papers reported on BMT procedures (2,29,31), seven papers reported on SCT procedures (21,24,28,30,32-34), and one reported on both BMT and SCT procedures (27). One of the obtained papers was a review with an expert panel consensus (26), five were reviews (21,27,29,30,34), two were CPGs (28,33), two were grand rounds or special reports (2,31), and one was a database audit (32). These papers are summarized in Table 14.

Nine of the papers report that allogeneic transplantation is potentially curative in patients with CML, depending on the availability of an HLA-matched donor (21,26-31,33,34). HLA-matched sibling allogeneic transplantation has been considered as the standard of care for patients with newly diagnosed CML (2); however, with the advent of tyrosine kinase inhibitors such as imatinib, the place of transplantation is being re-assessed. The EBMT recommends allogeneic SCT for younger patients who have been previously treated and have poor-risk disease, as defined by cytogenic and clinical assessments only (2). None of the other reports recommend specific criteria for the use of allogeneic transplantation in this disease. One paper reported that this benefit is dependent on graft versus leukemia effect (30). Another paper recommended allogeneic SCT as salvage treatment for relapse following transplantation (28). One older trial recommended that transplantation be offered to patients within one to two years of diagnosis (26); this same trial noted that younger patients, and patients not previously treated with busulfan, are more likely to benefit.

One paper reported that treatment-related mortality is the optimum measure of transplant centre performance (32). A synopsis of the indications/contraindications for CML supported by the identified papers is found in Table 15.

Table 14. Summary of papers pertaining to chronic myeloid leukemia (CML).

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
Silver RT et al, 1999 (24) Sponsor: American Society of Hematology	SCT	Allogeneic	Accepted indications: Allogeneic BMT is an option if the patient has a suitable HLA-matched donor and is in acceptable health to tolerate the procedure. BMT should be offered to patients within 1-2y of diagnosis. Younger patients are more likely to benefit from allogeneic BMT. BMT is also more successful if the donor is an HLA-matched sibling or other relative. Patients receiving CT before allogeneic BMT appear less likely to benefit from transplant if they have been treated with busulfan.	Review + expert panel consensus (all reccs based on uncontrolled observational studies)
Walshe R et al, 1999 (21) Sponsor: None listed	SCT	NR	Accepted indications: Myeloid leukemias	Review
Hehlmann R et al, 2000 (partially based on Silver RT et al, 1999) (27) Sponsor: German Bundesminister für Forschung und Technologie	BMT	Allogeneic	Accepted indications: Allogeneic BMT is potentially curative in CML.	Review
NCCN, 2000 (28) Sponsor: National Comprehensive Cancer Network	SCT	Allogeneic	Accepted indications: Allogeneic SCT is curative treatment in CML. Allogeneic SCT is also indicated as salvage treatment for relapse following transplantation.	Practice guideline
Applebaum FR et al, 2001 (29) Sponsor: National Cancer Institute, National Institutes of Health (in part)	BMT	Both	Accepted indications: Allogeneic SCT is the only proven curative therapy for CML.	Review
Goldman JM and Druker BJ, 2001	SCT	Allogeneic	Accepted indications: Allogeneic SCT is potentially curative for CML, but this benefit is dependent on	Review

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
(30) Sponsor: None given			graft-vs-leukemia effect.	
Kalaycio ME, 2001 (31) Sponsor: None given	BMT	Allogeneic	Accepted indications: Allogeneic BMT is potentially curative in CML.	Grand rounds report
Russell NH et al, 2004 (32) Sponsor: British Society for Blood & Marrow Transplantation	SCT	NR	Standards guiding performance: TRM (defined as treatment related mortality) is a sensitive indicator of transplant centre excellence, and has been used in the past to study the effect of individual transplant centre size on outcome	dB audit (Chart review)
O'Brien S et al, 2005 (33) Sponsor: National Comprehensive Cancer Network	SCT	Allogeneic	Accepted indications: The NCCN guidelines recommend three primary treatments: Allogeneic SCT CT using imatinib mesylate Clinical trial Allogeneic SCT is recognized as being potentially curable in CML.	Practice guideline
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow Transplantation	BMT/ PBSCT/ CBSCT	Allogeneic	Accepted indications: Allogeneic SCT is an option for younger patients who have been previously treated and have poor-risk disease, as defined by cytogenic and clinical assessments.	Special Report
Mauro MJ et al, 2006 (34) Sponsor: None given	SCT	Allogeneic	Accepted indications: In patients with CML allogeneic SCT is potentially curative.	Review

Table 15. Chronic myeloid leukemia (CML) supported indications/contraindications.

	References
INDICATED	
Allogeneic SCT is potentially curative in CLL depending on the availability of an HLA-matched donor.	(21,26-31,33,34)
Allogeneic SCT is effective as salvage treatment for relapse following transplantation.	(28)
There may be a role for allogeneic SCT for younger patients who have been previously treated and have poor-risk disease, as defined by cytogenic and clinical assessments.	(2)
Transplantation should be offered to patients within 1-2 years of diagnosis.	(26)
Younger patients, and patients not previously treated with busulfan, are more likely to benefit.	(26)
PUBLISHED STANDARDS GUIDING PERFORMANCE	
Treatment-related mortality is the optimum measure of transplant centre performance.	(32)

Hodgkin's lymphoma (HL)

The recommendations regarding the role of SCT in HL are based on a number of randomized controlled trials. Six papers were obtained that reported on Hodgkin's lymphoma (HL) (2,9,21,32,35). Four papers reported on SCT procedures (11,21,32,35), and one reported on BMT (2). Two papers did not differentiate between allogeneic and autologous procedures and were categorized as NR (not reported) (21,32), one reported on both (9), two reported on autologous procedures (2,35), and one was NA (not applicable) as it reported on outcome measures only (32). These papers are summarized in Table 16.

Table 16. Summary of papers pertaining to Hodgkin's lymphoma (HL).

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
Walshe R et al, 1999 (21) Sponsor: None given	SCT	NR	Accepted indications: SCT is an accepted treatment option in HL.	Review
Medical Advisory Panel (MAP), 2000 (9) Sponsor: Blue Cross, Blue Shield	SCT	Both	Not accepted indications: The evidence reviewed is insufficient to support HDC/Allogeneic SCT as salvage treatment after relapse or progression following HDC/Autologous SCT in patients with HL.	Technology assessment 3 studies involving 12 patients
Reece DE, 2000 (35) Sponsor: University of Kentucky Blood & Marrow Transplant Program	SCT	Autologous	Accepted indications: There are data to support autologous SCT in patients with HL that has relapsed or recurred after initial CT. Not accepted indications: There are no data to support the use of SCT in the initial treatment of HL, and first-line treatment should remain CT with or without RT.	Review Data supporting SCT in HL that has relapsed: 2 RCTs, two cohort studies sing historic controls.
Russell NH et al, 2004 (32) Sponsor: British Society for Blood & Marrow Transplantation	SCT	NA	Standards guiding performance: TRM (defined as treatment related mortality) is a sensitive indicator of transplant centre excellence, and has been used in the past to study the effect of individual transplant centre size on outcome	dB audit (Chart review)
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow Transplantation	BMT/ PBSCT/ CBSCT	Autologous	Accepted indications: Autologous SCT is the standard treatment for patients that relapse.	Special Report

Three of the obtained papers report a role for SCT in the treatment of HL (2,21,35). None of the identified reports recommend transplantation as a component of first-line therapy for Hodgkin's disease. The EBMT recommends autologous SCT as the standard treatment for patients that relapse (2). Two other reports state that autologous transplantation should only be administered to patients who have relapsed or who are chemotherapy induction failures (2,35). None of the reports suggest an established role for allogeneic transplantation in Hodgkin's lymphoma (9).

One of the obtained papers reported on outcome measures stating that TRM is a representative indicator of transplant centre performance, and can be used to study the effect of individual transplant centre size on outcome (32). A synopsis of the indications/contraindications for HL supported by the identified papers is found in Table 17.

Table 17. Hodgkin's lymphoma (HL) supported indications/contraindications.

	References
INDICATED	
While CT with or without RT remains the standard first-line treatment, SCT has a role in the treatment of HL.	(2,21,35)
SCT should only be administered to patients that have relapsed or who are CT induction failures.	(2,35)
CONTRAINDICATED	
There is no evidence to support allogeneic SCT at this time.	(9)
MEAUSURES TO ASSESS TRANSPLANT OUTCOMES	
One of the obtained papers reported on outcome measures stating that TRM is a representative indicator of transplant centre performance, and can be used to study the effect of individual transplant centre size on outcome.	(32)

Multiple myeloma (MM)

Twelve papers were obtained that reported on multiple myeloma (2,21,37-45,61). The recommendations are informed by multiple randomized controlled trials. Seven papers reported on SCT procedures (21,37,39,41-44), two reported on PBSCT alone (40,45), and two reported on BMT with PBSCT and/or CBSCT (2,61). Three of the papers reported on both allogeneic and autologous procedures (37,43,45), eight reported on autologous procedures (38-42,44,61), one did not specify either (21), and one reported on allogeneic procedures only (2). One of the papers was a review with expert panel consensus (37), one was a technology assessment (38), one was a review (21), two were clinical practice guidelines (39,40), five were systematic reviews (41-44,61), and the remaining two were comprised of a special report (2) and a consensus statement (45). These papers are summarized in Table 18.

All 12 papers report a role for SCT in the treatment of MM (2,21,37,39-45,61), with the majority reporting autologous SCT as the treatment of choice for younger patients with myeloma as a component of primary therapy, except for the technology assessment (38) which did not find a role for treatment with SCT in resistant MM only. The majority of papers report that this treatment is limited by the age of the patient (39-41,43,45). This recommended upper age limit varied significantly among the obtained papers, with some reporting the maximum age ranging from 55 (40) to 70 years of age (39,42). One paper reported that, for standard risk patients under age 65, it is the treatment of choice, and in patients aged 65-75 without any significant co-morbidities, it is a treatment option (45).

Recently, increasing evidence evaluating the role of double or tandem transplantation is emerging (43-45,61), on the basis of randomized trials suggesting a survival benefit when compared to a single transplant. A number of the reports recommend tandem transplantation as an option for patients who fail to obtain a complete remission or near complete remission with a single transplant (43-45).

Few of the reports address autologous transplantation beyond initial treatment. The CCO guideline suggests that transplantation should be performed early, before extensive exposure to alkylating agents (40). Other reports suggest a role for transplantation at the time of disease progression (37).

Allogeneic transplantation is reported to be associated with significant treatment-related mortality. The CCO guideline recommends that there is insufficient evidence to recommend allogeneic transplantation as routine therapy for MM (40), while the EBMT considers that, given the high treatment-related mortality, it should be offered only to selected high-risk patients (2). Only one paper addresses unrelated transplantation. This report, from the British Committee for Standards in Haematology, does not recommend unrelated allogeneic transplantation in myeloma (43).

Table 18. Summary of papers pertaining to multiple myeloma (MM).

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
Anderson KC et al, 1999 (37) Sponsor: None given	SCT	Both	Accepted indications: In patients responding to CT or that have stable disease: Allogeneic BMT until disease progression, then salvage treatment in clinical trial, OR Autologous BMT until disease progression, then salvage treatment in clinical trial or allogeneic BMT. In patients that respond to salvage CT or that have stable disease following salvage CT, salvage in clinical trial or allogeneic BMT or autologous BMT.	Review + expert panel consensus
Medical Advisory Panel (MAP), 1999 (38) Sponsor: Blue Cross, Blue Shield	BMT	Autologous	Not accepted indications: A single cycle of high-dose CT with autologous SCT has no demonstrated efficacy in resistant MM. A single cycle of tandem high-dose CT with autologous SCT has no demonstrated efficacy in resistant MM.	Technology assessment
Walshe R et al, 1999 (21) Sponsor: None given	SCT	NR	Accepted indications: SCT is accepted treatment in MM	Review
Samson D et al, 2001 (39) Sponsor: International Myeloma Foundation (UK) (in part)	SCT	Autologous	Accepted indications: High-dose CT with autologous SCT should be considered primary treatment in newly diagnosed patients up to 60y. Initial induction therapy should be chosen accordingly. Patients aged 60-70y with good performance status may also be considered suitable candidates. Not accepted indications: There are no data supporting high-dose CT with SCT for patients over 70y and the combination of melphalan and prednisone remains standard treatment. Recommended measures to assess outcomes: Patient identification: date of birth, postcode, sex (male/female), NHS number (if known), GP name. Transplantation/stem cell procedure: "rainy day" harvest (yes/no; date collected), autograft (yes/no; date); allograft (yes/no; date). Outcome at 12 months and annual follow-up: current survival status (alive/dead/unknown), current disease	Practice guideline

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
			status (refractory, response, regression), further treatment since initial treatment program (yes/no). Death: date of death, cause of death.	
Imrie K et al, 2002 (40) Sponsor: Cancer Care Ontario	PBSCT	Autologous	Accepted indications: Autologous transplantation is recommended for patients with advanced-stage myeloma and good performance status. The evidence is strongest for patients under 65 years of age without significant renal dysfunction following hydration and remission-induction chemotherapy. Physicians must use their clinical judgement in recommending transplantation to patients over 65 years of age or those with renal impairment. • There is insufficient evidence to recommend allogeneic transplantation as routine therapy for multiple myeloma. Patients who are potentially eligible for transplantation should be referred for transplant assessment early after diagnosis and should not be given extensive exposure to alkylating agents such as melphalan prior to the collection of stem cells. High-dose glucocorticoid-based regimens such as vincristine, doxorubicin (adriamycin), dexamethasone (VAD) are preferable for such patients. • Harvesting of autologous peripheral blood stem cells or bone marrow should be performed early in the patient's treatment course. The best available data demonstrate that transplantation is most advantageous when performed as part of the initial therapy. • No conclusions can be reached about the role of interferon alpha following transplantation at this time.	Practice guideline
Durie BGM et al, 2003 (41) Sponsor: International Myeloma Foundation	SCT	Autologous	Accepted indications: High-dose CT with autologous SCT should be considered initial therapy for newly diagnosed patients under 70y with symptomatic myeloma. The standard conditioning regimen is melphalan 200 mg/m^2. Peripheral blood stem cells are recommended over bone marrow.	Systematic review + expert consensus
Hahn T et al, 2003 (42) Sponsor:	SCT	Autologous	Accepted indications: SCT is the preferred de novo therapy over standard CT. Autologous peripheral SCT is preferred to BMT.	Systematic review + expert panel consensus

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
American Society for Blood & Marrow Transplantation			Melphalan is preferred to melphalan plus whole body RT as the conditioning regimen for autologous SCT.	
Smith A et al, 2005 (43) Sponsor: British Committee for Standards in Haematology	SCT	Both	<u>Accepted indications:</u> High-dose CT with autologous SCT is recommended primary treatment in newly diagnosed patients up to 65y with adequate performance status and organ function. High-dose CT with autologous SCT is an option for primary treatment in newly diagnosed patients over 65y with good performance status and organ function. It is recommended that enough stem cells are collected to support two high-dose procedures. Patients up to age 50 who have at least a partial remission following initial therapy may be considered for HLA-matched sibling allogeneic SCT. <u>Under investigation:</u> The role of allogeneic SCT using HLA-matched sibling donors can result in long-term survival and may play a treatment role in younger patients, but is an option for a selected few only. <u>Not accepted indications:</u> Matched unrelated donor SCT is not recommended	Practice guideline
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow Transplantation	BMT/ PBSCT/ CBSCT	Allogeneic	<u>Accepted indications:</u> Allogeneic SCT is potentially curative in myeloma, but has significant TRM, and might be offered only to selected high-risk patients.	Special Report
Anderson KC et al, 2007 (44) Sponsor: National Comprehensive Cancer Network	SCT	Autologous	<u>Accepted indications:</u> For patients receiving follow-up treatment after induction CT autologous SCT is recommended. Patients in CR or near-CR experience the greatest benefit, and do not show a benefit from a second transplantation. Patients with a partial response or stable disease after the first transplantation are candidates for a second transplantation.	Practice guideline
Dispenzieri A et al, 2007 (45) Sponsor: None given	PBSCT	Both	<u>Accepted indications:</u> For standard risk patients under 65y early autologous SCT, followed by a second SCT if the patient does not experience a PR or better with the first transplant.	Consensus Statement

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
			For standard risk patients 65-75y without any other significant comorbidities, high-dose CT followed by SCT is a treatment option. Allogeneic SCT can lead to CR rates between 22-67%, but is associated with high TRM.	
Koreth J et al, 2007 (61) Sponsor: None given	BMT/ PBSCT	Autologous	Accepted indications: Single autologous transplantation performed early in treatment can result in a PFS benefit, but not an OS benefit compared with chemotherapy. PBSC is preferred over BMT as a stem cell source due to faster engraftment and lower adverse effects.	Systematic review + meta-analysis

One paper reported on the following recommendations for outcome measures (39):

- Patient identification: date of birth, postcode, sex (male/female), National Health Service (NHS) number (if known), General Practitioner's name.
- Transplantation/stem cell procedure: "rainy day" harvest (yes/no; date collected), autograft (yes/no; date); allograft (yes/no; date).
- Outcome at 12 months and annual follow-up: current survival status (alive/dead/unknown), current disease status (refractory, response, regression), further treatment since initial treatment program (yes/no).
- Death: date of death, cause of death.

A synopsis of the indications/contraindications for MM supported by the identified papers is found in Table 19.

Table 19. Multiple myeloma (MM) supported indications/contraindications

	References
INDICATED	
There is a role for SCT in the treatment of MM.	(2,21,37,39-45,61)
There is no role for SCT in the treatment of resistant MM.	(38)
Allogeneic SCT is potentially curative but has significant TRM, and therefore might only be offered only to high-risk patients.	(2)
This treatment is limited by the age of the patient.	(40,41,43,45)
The recommended upper age limit varies: some reporting the maximum age for high-dose CT with autologous SCT as first-line treatment being up to age 55, age 60, age 65, and age 70.	(40,42,43,45)
Despite the high TRM, one of the papers obtained states that SCT is the preferred first-line treatment over standard CT.	(42)
Patients that respond to CT or that have stable disease should receive allogeneic BMT until disease progression, at which time it is recommended that receive salvage treatment within a clinical trial, or, alternatively, autologous BMT until disease progression, then salvage treatment in a clinical trial.	(37)
Patients that respond to salvage CT or that have stable disease following salvage CT should receive salvage treatment in a clinical trial or allogenic BMT or autologous BMT.	(37)
Patients up to age 50 who have at least a partial remission following initial therapy also be considered for HLA-matched sibling allogeneic SCT.	(43)
Patients with a partial response or stable disease after the first transplantation are candidates for a second transplantation.	(44)
Peripheral blood stem cell collection is recommended over BMT due to poor engraftment rates observed with BMT.	(40,41,42)
CONTRAINDICATIONS	
There are no data supporting high-dose CT with SCT for patients over 70y and the combination of melphalan and prednisone should remain the standard treatment.	(40)
UNDER INVESTIGATION:	
Allogeneic SCT using HLA-matched sibling donors is still experimental.	(43)
MEASURES TO ASSESS TRANSPLANT OUTCOMES	
Patient identification: date of birth, postcode, sex (male/female), NHS number (if known), General Practitioner's name.	(40)
Transplantation/stem cell procedure: "rainy day" harvest (yes/no; date collected), autograft (yes/no; date); allograft (yes/no; date).	(40)
Outcome at 12 months and annual follow-up: current survival status (alive/dead/unknown), current disease status (refractory, response, regression), further treatment since initial treatment program (yes/no).	(40)
Death: date of death, cause of death.	(40)

Myelodysplastic syndrome (MDS)

Six papers were obtained that reported on myelodysplastic syndrome (2,14,46-49). Two of the papers reported on SCT procedures (46,48), two reported on BMT procedures (14,47), and two reported on BMT with PBSCT or CBSCT (2,49). Two of the obtained papers reported on allogeneic procedures (2,49), three reported on both allogeneic and autologous procedures (14,46,48), and one did not report on the type of procedure (47). Two of the papers were clinical practice guidelines (46,48), two were reviews (14,49), one was a monograph (47), and one was a special report (2). These papers are summarized in Table 20.

Four papers state that allogeneic BMT is the only known potentially curable treatment for MDS (2,14,47,48). The optimal timing of transplantation in myelodysplasia is controversial. MDS is a heterogeneous entity with variable outcome, with some patients having a life expectancy of greater than five to ten years with conservative treatment (49). One paper recommends that allogeneic BMT offers the best chance for long-term DFS, if performed early or during the first complete response (2). Other papers indicate that it is unclear whether or not allogeneic transplantation should be performed early (before initial complete response) (40) or recommend that transplantation should be restricted to younger patients with shorter disease duration, human leukocyte antigen compatibility, primary MDS, <10% blasts, and good-risk cytogenetics, as in this setting.

While autologous BMT is less risky than allogeneic BMT, survival is also poorer and for this reason is not recommended as standard therapy in any of the retrieved articles (14,46,48). A synopsis of the indications/contraindications for MDS supported by the identified papers is found in Table 21.

Table 20. Summary of papers pertaining to myelodysplastic syndrome (MDS).

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
Bowen D, 2003 (46) Sponsor: None given	SCT	Both	Accepted indications: For younger patients with shorter disease duration, human leucocyte antigen compatibility, primary MDS, <10% blasts, and good-risk cytogenics, allogeneic stem cell transplantation results in long-term event-free survival (32-54% of patients). Under investigation: Autologous SCT may also prolong survival though stem cell mobilization is commonly problematic.	Practice guideline
Rund D et al, 2004 (14) Sponsor: None given	BMT	Both	Accepted indications: Allogeneic BMT, myeloablative or non-myeloablative, is potentially curative in t-AML/MDS. Not accepted indications: While autologous BMT is less risky than allogenic BMT, survival is poorer.	Review
Latsko JM et al, 2005 (47) Sponsor: Education Grant from Pharmion Corporation	BMT	NR	Accepted indications: BMT is the only known potentially curable treatment for MDS.	Monograph (Clinical Roundtable Monograph)
Greenberg PL et al, 2006 (48) Sponsor: National Comprehensive Cancer Network	SCT	Both	Accepted indications: For patients with high-risk disease treatment with allogeneic SCT from an HLA-matched sibling donor is the preferred approach. Under investigation: Whether transplantation should be performed before or after patients experience remission after induction CT is yet to be established. The role of autologous BMT or peripheral SCT is also under investigation.	Practice guideline
Deeg J, 2006 (49) Sponsor: National Institutes of Health (in part)	BMT/ PBSCT	Allogeneic	Accepted indications: Allogeneic SCT is potentially curative therapy in patients with MDS. In older patients, who may have a life-expectancy of 5-10y, conservative CT therapy may be a more appropriate treatment option due to transplant related mortality.	Review
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow Transplantation	BMT/ PBSCT/ CBSCT	Allogeneic	Accepted indications: Allogeneic SCT is the preferred treatment for MDS and offers the best chance for long-term DFS. This is optimized if performed early, or during CR1.	Special Report

Table 21. Myelodysplastic syndrome (MDS) supported indications/contraindications

	References
INDICATED	
Allogeneic BMT is the only known potentially curable treatment for MDS.	(2,14,47,48)
Allogeneic BMT offers the best chance for long-term DFS, and is optimized if performed early or during the first complete response.	(2)
For younger patients with shorter disease duration, human leucocyte antigen compatibility, primary MDS, <10% blasts, and good-risk cytogenics, allogeneic stem cell transplantation results in long-term event-free survival (32-54% of patients).	(46)
CONTRAINDICATIONS	
For older patients who may have a life-expectancy of five to 10 years, conservative CT therapy may be a more appropriate treatment option.	(49)
Autologous BMT is less risky than allogeneic BMT but has poorer survival, and therefore cannot be recommended at this time.	(14,46,48)
DISCREPANCIES	
It is unknown whether or not patients should receive transplantation before or after the initial complete response.	(48)

Non-Hodgkin's Lymphomas

Diffuse large B-cell non-Hodgkin's lymphoma

Four papers were identified that reported on diffuse large B cell Non-Hodgkin's lymphoma (2,50-52). Three papers reported on SCT procedures (50-52), and one reported on BMT including PBSCT or CBSCT (2). Two of the papers reported on both autologous and allogeneic procedures (51,52), and two reported on autologous procedures alone (2,42). One of the papers was a systematic review (42), one was a position statement (51), one was a practice guideline (52), and one was a special report (2). These papers are summarized in Table 22.

The role of autologous stem cell transplantation as a component of primary therapy for diffuse large B cell non-Hodgkin's lymphoma has been extensively studied through a number of randomized controlled trials and remains the subject of active investigation (2,51,52). Transplantation in this setting is considered investigational as there is no clear evidence that transplantation results in superior survival compared to conventional chemotherapy. None of the retrieved reports recommend allogeneic transplantation as a component of primary therapy (52).

All of the identified reports recommend that autologous transplantation be considered the standard of care for selected patients who are refractory to, or relapse after, therapy (2,50-52). Younger patients (<age 65 years) and those who have a demonstrated sensitivity to chemotherapy, have a good performance status, and have no significant co-morbidities are typically considered to be suitable candidates for transplantation (52). Allogeneic transplantation may be considered in some cases where patients have refractory or relapsed disease, but in general, autologous transplantation is preferred over allogeneic transplantation in DLBCL (51).

Follicular lymphoma

Two papers were identified that reported on follicular lymphoma (2,53). One reported on autologous SCT procedures (53) and the other reported on SCT with either PBSCT or CBSCT (2). One paper was a review with an expert panel consensus (53) and the other was a special report of the EBMT (2). These papers are summarized in Table 22.

Both papers report that first-line treatment with autologous SCT remains investigational (2,53), with one stating that there may be a role for a limited subgroup of high-risk patients (2). One of the papers reported that autologous SCT is the standard treatment for patients in early relapse, but the same paper noted that the advantages, if any, for patients in late relapse were less clear (2).

Lymphoblastic and Burkitt's lymphoma

Only one paper, a special report of the EBMT was obtained that reported on both lymphoblastic and Burkitt's lymphoma (2). Both autologous and allogeneic SCT procedures were reported on. This paper is summarized in Table 22.

For patients with lymphoblastic lymphoma who experience remission, the paper reported that they may be consolidated with autologous SCT. As well, for younger patients in first remission, allogeneic SCT may be a treatment option, but this is still considered experimental. For Burkitt's lymphoma, the paper reported that autologous SCT may be considered for patients in first remission. Data supporting allogeneic SCT in this setting remains investigational only.

Table 22. Summary of papers pertaining to non-Hodgkin's lymphomas.

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
Diffuse large B cell Non-Hodgkin's lymphoma				
Hahn T et al, 2001 (51) Sponsor: American Society for Blood and Marrow Transplantation	SCT	Autologous	Accepted indications: There are data to support autologous BMT/SCT in patients with diffuse large B cell lymphoma that are experiencing the first CT-sensitive relapse. There are data to support autologous BMT/SCT in patients with diffuse large B cell lymphoma that are CT resistant, that have relapsed, or that have refractory disease.	Systematic review + expert panel consensus
Hahn T et al, 2003 (50) Sponsor: American Society for Blood and Marrow Transplantation	SCT	Both	Accepted indications: SCT In diffuse large B cell lymphoma is more effective than standard CT and is recommended for patients in first CT relapse, first complete remission in high/intermediate-high risk IPI patients, as high-dose sequential therapy in intermediate-high/high risk IPI untreated patients. Autologous SCT is currently the standard of care preferred over allogenic SCT. Autologous PBSCT is preferred over autologous BMT. Not accepted indications: SCT is not more effective than standard CT in patients with first complete remission in low/intermediate-low risk IPI patients, and after abbreviated induction therapy with fewer than 6 cycles of CHOP, 12 or less of MACOP-B, or 12 or less of VACOP-B.	Position Statement
Barosi G et al, 2006 (52) Sponsor: Italian Society of Hematology (SIE)/GITMO	SCT	Both	Accepted indications: Patients with an intermediate-high/high IPI score and who are less than 65y may receive first-line high-dose CT with autologous SCT within a clinical trial only. Patients with good performance status showing chemosensitivity to rescue CT should receive high-dose CT followed by autologous SCT. These patients are typically under 65y with chemosensitve disease, with a good performance status, no comorbidities, and good availability of autologous stem cells. At first CR, patients should receive CT and autologous SCT. Not accepted indications: Allogeneic SCT is not recommended as first line treatment for any patient.	Practice guideline

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow Transplantation	BMT/ PBSCT/ CBSCT	Autologous	Accepted indications: Autologous SCT is the standard treatment for early relapsing diffuse large B cell lymphoma patients.	Special Report
Follicular lymphoma				
ESMO Guidelines Task Force, 2003 (53) Sponsor: European Society for Medical Oncology	SCT	Autologous	Under investigation: Following initial treatment or RT or CT, the role of autologous SCT in this setting is still under investigation.	Review + Expert panel consensus
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow Transplantation	BMT/ PBSCT/ CBSCT	Autologous	Accepted indications: Autologous SCT is the standard treatment for early relapsing patients. In late relapsing patients, the advantages are less clear. Under investigation: First-line therapy with autologous SCT remains investigational, but there may be a role for a subgroup of high-risk patients.	Special Report
Lymphoblastic and Burkitt's lymphoma				
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow Transplantation	BMT/ PBSCT/ CBSCT	Both	*Lymphoblastic lymphoma:* Accepted indications: Lymphoblastic lymphoma patients may be consolidated in remission by autologous SCT. Under investigation: Allogeneic SCT may be considered for younger adults in CR1. *Burkitt's lymphoma:* Under investigation: Autologous SCT may be considered for patients in CR1. Data supporting allogeneic SCT remains limited.	Special Report
Mantle cell lymphoma				
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow	BMT/ PBSCT/ CBSCT	Autologous	Accepted indications: Early intensification with autologous SCT is a treatment option for these patients due to its poor prognosis.	Special Report

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
Transplantation				
T-cell lymphoma				
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow Transplantation	BMT/ PBSCT/ CBSCT	Both	Under investigation: Early intensification with autologous SCT is a treatment option for these patients due to its poor prognosis, however there are no prospective data to support this. Allogeneic SCT can be considered as consolidation treatment following first-line therapy.	Special Report
Other Non-Hodgkin's lymphomas				
Kimby E et al, 2001 (54) Sponsor: The Swedish Council of Technology Assessment in Health Care (SBU)	SCT	NR	*Aggressive Non-Hodgkin's lymphoma:* Accepted indications: Salvage therapy with high-dose CT and SCT is recommended for patients with chemosensitive relapse. Unproven/little or no evidence indications: In younger patients with a poor prognosis, further intensified induction therapy with SCT may be beneficial, but there are no data to support this. In patients that did not experience a CR following initial CT, high dose CT with SCT may improve response, but there are no data showing an improvement in survival. In patients refractory to initial standard CT there is no data to support a survival benefit from high dose CT with SCT, although it is suspected a subset of patients might benefit.	Systematic review
Greb A et al, 2008 (62) Sponsor: Cochrane Review	SCT	Autologous	*Aggressive Non-Hodgkin's lymphoma:* Not accepted indications: There is no evidence that high-dose CT with SCT improves either overall or event-free survival over standard CT alone in first-line treatment. Under investigation: Poor risk patients may benefit from high-dose CT with SCT in first-line treatment, but data are unavailable.	Systematic review
Brandt L et al, 2001 (36) Sponsor: Swedish Council of Technology Assessment in Health Care	SCT	NR	*Indolent Non-Hodgkin's lymphoma:* Accepted indications: High dose CT with SCT is a treatment option for patients who are CT induction failures, who relapse after a short initial remission, or who have had multiple relapses.	Systematic review: 113 papers total
Medical Advisory	SCT	Both	*Intermediate or high-grade non-Hodgkin's lymphoma:*	Technology assessment

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
Panel (MAP), 2000 (9) Sponsor: Blue Cross, Blue Shield			Not accepted indications: The evidence reviewed is insufficient to support HDC/Allogeneic as salvage treatment after relapse or progression following HDC/Autologous in patients with NHL.	4 studies involving 20 patients
Reni M et al, 2001 (55) Sponsor: None given	PBSCT	Both	*Refractory or relapsed primary central nervous system lymphomas:* Under investigation: For aggressive NHL that has relapsed, the use of high-dose CT supported by autologous or allogeneic PBSCT provides an option currently under investigation. In a case-series 5 of 5 patients experienced a CR and remained alive after 26 months of follow-up.	Review (of three small non-comparative studies)
Lewis A, 2005 (56) Sponsor: None given	BMT/ PBSCT	Autologous	*Unspecified non-Hodgkin's lymphoma:* Accepted indications: Peripheral SCT is superior to BMT in platelet and neutrophil engraftment speed.	Systematic review, four RCTs

Mantle cell lymphoma

Only one paper, a special report of the EBMT, was obtained that reported on mantle cell lymphoma (2), and only autologous BMT procedures with either PBSCT or CBSCT were discussed. While controlled data evaluating the role of autologous SCT in mantle cell lymphoma are limited, it is recommended that it be considered as a treatment option. This paper is summarized in Table 22.

T-Cell lymphoma

Only one paper, a special report of the EBMT, was obtained that reported on T-cell lymphoma (2). Both autologous and allogeneic BMT with either PBSCT or CBSCT procedures were reported on. The findings were that, due to the poor prognosis of this illness, early intensification with autologous SCT should be considered as an investigational treatment option, but the paper noted that there are no prospective data to support this. For patients with refractory or relapsed disease, autologous and allogeneic transplantation should be considered as treatment options. This paper is summarized in Table 22.

Other Non-Hodgkin's lymphomas

Six papers were obtained reporting on other Non-Hodgkin's lymphomas (9,36,54-56,62). These generally antedated modern lymphoma classification systems, with the terms aggressive or intermediate grade lymphoma including diffuse large B-cell lymphoma or peripheral T-cell lymphoma, among other subtypes. These papers are summarized in Table 22.

Two papers were obtained reporting on aggressive non-Hodgkin's lymphoma, a systematic review by Kimby et al (54), and a Cochrane Review by Greb et al (62). Kimby et al report that, for patients with chemosensitive relapse, salvage treatment with high-dose chemotherapy and SCT should be offered. This same paper states that the following may be

considered treatment options, but recognized that supporting data may be limited: for younger patients with a poor prognosis, further intensified induction therapy with SCT may be beneficial; for patients that did not experience a complete response following initial chemotherapy, high-dose chemotherapy with SCT may improve response; and for patients refractory to initial standard chemotherapy, some may experience a survival benefit from high dose chemotherapy with SCT. The Cochrane Review by Greb et al (62) reports that, in first-line treatment, there is no evidence that high-dose chemotherapy with SCT improves either overall or event-free survival, and there is some evidence that, in patients considered a good risk, overall survival is actually worse. These same data also suggest that, in patients considered poor risks, there may be a benefit from high-dose chemotherapy with SCT, but conclusive data are not available. The Cochrane Review recommends that chemotherapy alone remain the standard first-line treatment for aggressive non-Hodgkin's lymphoma.

One systematic review (36) comprising 113 papers, by the Swedish Council of Technology Assessment in Health Care, found high-dose chemotherapy with SCT is a treatment option for patients who are chemotherapy-induction failures, who relapse after a short initial remission, or who have had multiple relapses with indolent non-Hodgkin's lymphoma.

A technology assessment reported by the Medication Advisory Panel of Blue Cross/Blue Shield (9) on intermediate or high-grade non-Hodgkin's lymphoma found that there was no evidence to support allogeneic SCT with high-dose chemotherapy as salvage treatment for patients after relapse or progression following autologous SCT with high-dose chemotherapy.

A review paper by Reni et al (55) on refractory or relapsed primary central nervous system lymphomas states that high-dose chemotherapy with either autologous or allogeneic PBSCT for aggressive disease is a treatment option, but this option is still considered investigational.

A systematic review by Lewis et al (56) comparing SCT to BMT in non-Hodgkin's lymphoma concluded that peripheral blood SCT is superior to BMT in platelet and neutrophil engraftment speed.

Non-Hodgkin's lymphoma indications/contraindications

A synopsis of the indications/contraindications for non-Hodgkin's lymphoma supported by the identified papers is provided in Table 23.

Table 23. Non-Hodgkin's lymphomas supported indications/contraindications

	References
Diffuse large B cell Non-Hodgkin's lymphoma	
Autologous BMT or SCT should be offered to patients that are CT resistant, that have relapsed, or that have refractory disease.	(50,51)
Patients with good performance status showing chemosensitivity to rescue CT should receive high-dose CT followed by autologous SCT.	(52)
SCT is not more effective than standard CT in patients with first complete remission in low/intermediate-low risk IPI patients after abbreviated induction therapy with fewer than 6 cycles of CHOP, 12 or less of MACOP-B, or 12 or less of VACOP-B.	(51)
Autologous SCT is the standard treatment for early relapsing diffuse large B cell lymphoma patients.	(2)
Where SCT is chosen, autologous SCT is preferred over allogeneic SCT, and autologous PBSCT is preferred over autologous BMT.	(51)
Allogeneic SCT is not recommended as first line treatment for any patient.	(52)
Suitable patients (typically under 65 years of age with chemosensitive disease, good performance status, no comorbidities, and good availability of autologous stem cells) with an intermediate-high/high IPI score and who are less than 65 years of age may receive first-line high-dose CT with autologous SCT within a clinical trial only.	(52)
Follicular lymphoma	
First-line treatment with autologous SCT remains investigational.	(2,53)
There may be a role for a limited sub-group of high-risk patients.	(2)
Autologous SCT is the standard treatment for patients in early relapse.	(2)
Treatment with autologous SCT for patients in late relapse remains investigational	(2)
Lymphoblastic lymphoma	
For patients that experience remission may be consolidated with autologous SCT.	(2)
For younger patients in first remission allogeneic SCT may be a treatment option, but this is still considered experimental.	(2)
Burkitt's lymphoma	
Autologous SCT may be considered for patients in first remission.	(2)
Data supporting allogeneic SCT in this setting remains investigational only.	(2)
Mantle cell lymphoma	
Due to the poor prognosis of this illness, early intensification with autologous SCT should be considered a treatment option.	(2)
T-Cell lymphoma	
Due to the poor prognosis of this illness, early intensification with autologous SCT should be considered a treatment option, despite the lack of prospective data.	(2)
Following first-line therapy, allogeneic SCT can also be considered consolidation therapy.	(2)
Other non-Hodgkin's lymphomas	
For patients with chemosensitive relapse, salvage treatment with high-dose CT and SCT should be offered.	(54)
For younger patients with a poor prognosis, further intensified induction therapy with SCT may be beneficial.	(54)
For patients that did not experience a CR following initial CT, high dose CT with SCT may improve response.	(54)
For patient's refractory to initial standard CT, some may experience a survival benefit from high dose CT with SCT.	(54)
In first-line treatment for aggressive non-Hodgkin's lymphoma there is no evidence that high-dose CT with SCT improves either overall or event-free survival.	(62)
There is evidence that in patients considered a good risk overall survival is actually worse with high-dose CT with SCT.	(62)
In patients considered poor risks, there may be a benefit from high-dose CT with SCT, but conclusive data are not available.	(62)

	References
CT alone remains the standard first-line treatment for aggressive non-Hodgkin's lymphoma.	(36)
High dose CT with SCT is a treatment option for patients who are CT induction failures, who relapse after a short initial remission, or who have had multiple relapses with indolent non-Hodgkin's lymphoma.	(62)
In intermediate or high-grade non-Hodgkin's lymphoma there is no evidence to support allogeneic SCT with high-dose chemotherapy as salvage treatment for patients after relapse or progression following autologous SCT with high-dose chemotherapy.	(9)
In refractory or relapsed primary central nervous system lymphomas high-dose chemotherapy with either autologous or allogeneic PBSCT is a treatment option, but this option is still considered investigational.	(55)
In non-Hodgkin's lymphoma concluded that peripheral SCT is superior to BMT in platelet and neutrophil engraftment speed.	(56)

Solid Tumours

Six papers were obtained reporting on various solid tumours (2,21,57-60). Three of these papers reported on SCT procedures (21,57,58), and three reported on BMT (2,59,60). Four papers reported on autologous procedures (2,57-59), and two did not specify the type of procedure (21,60). Two papers were technology assessments (57,58), three were reviews (21,59,60), and one was a special report (2). These papers are summarized in Table 24.

Two of the publications report that autologous SCT is an option for patients with germ cell tumours (2,21). For other solid tumours in adult patients, SCT is considered to be investigational. High-dose chemotherapy with autologous SCT has not demonstrated efficacy in patients with advanced epithelial ovarian cancer (2,57,59), primary breast cancer (2,58-60), or small-cell lung cancer (2). A synopsis of the indications/contraindications for solid tumours supported by the identified papers is found in Table 25.

Table 24. Summary of papers pertaining to solid tumours.

Author	Intervention	Allogeneic /autologous /both	Indicated/contraindicated/under investigation	Evidence base
Medical Advisory Panel (MAP), 1999 (57) Sponsor: Blue Cross, Blue Shield	SCT in Advanced epithelial ovarian cancer	Autologous	Not accepted indications: High-dose CT with autologous SCT has no demonstrated efficacy in this disease setting.	Technology assessment
Medical Advisory Panel (MAP), 1999 (58) Sponsor: Blue Cross, Blue Shield	SCT in Women with primary breast cancer[1]	Autologous	Not accepted indications: High-dose CT with autologous SCT has no demonstrated efficacy in this disease setting.	Technology assessment
Walshe R et al, 1999 (21) Sponsor: None given	SCT in various solid tumours	NR	Accepted indications within a clinical trial setting: Breast cancer: adjuvant and metastatic disease Ovarian cancer: high-risk patients after operation Small cell lung cancer: limited disease Germ cell tumours: high risk patients and after relapse	Review
Mello MM and Brennan TA, 2001 (59) Sponsor: None given	BMT in breast cancer	Autologous	Not accepted indications: There is no benefit for high-dose CT with autologous BMT in patients with breast cancer compared with standard-dose CT alone.	Review (of five RCTs)
Welch HG et al, 2002 (60) Sponsor: VA Outcomes Group	BMT in breast cancer	NR	Not accepted indications: There are no data to support the use of BMT in the treatment of breast cancer.	Review
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow Transplantation	BMT/ PBSCT/ CBSCT in various solid tumours	Autologous	Accepted indications: Solid tumours: Autologous SCT may be considered a treatment option for patients with neuroblastoma, Ewing sarcoma, and extragonadal germ cell tumours. Not accepted indications: There are no data supporting the use of SCT in the treatment of breast cancer, ovarian cancer, small-cell lung cancer, or germ-cell tumours. Autologous SCT for solid tumours should only be undertaken within the context of a clinical trial.	Special Report

1. Either S2 or non-inflammatory S3 with 10 or more involved lymph nodes OR who have S2 or non-inflammatory S3 disease with 4-9 involved lymph nodes, OR who have non-metastatic inflammatory breast cancer.

Table 25. Solid tumours supported indications/contraindications.

	Grade	References
CONTRAINDICATIONS		
High-dose CT with autologous SCT has no demonstrated efficacy in advanced epithelial ovarian cancer, primary breast cancer, small-cell lung cancer, or germ-cell tumours.	C,A,D	(2,57-60)
There is also no benefit for high-dose CT with autologous BMT in patients with breast cancer compared with standard-dose CT alone.	D	(59)
UNDER INVESTIGATION		
Autologous SCT for solid tumours should only be undertaken within the context of a clinical trial, with possible sites being breast cancer (adjuvant and metastatic disease), ovarian cancer (high-risk patients after operation), small cell lung cancer (limited disease), or germ cell tumours (high risk patients and after relapse).	D	(2,21)

Outcomes – Environmental Scan

Four papers were retrieved through the environmental scan (63-66), none of which were found in the targeted search. All retrieved papers were found through the untargeted search using the Google™ internet search engine. One paper reported on accepted indications (65), none reported on performance standards, and three reported on outcome measures (63,64,66). These papers are summarized in Table 26.

A Standard of Care document from Brigham & Women's Hospital, Department of Rehabilitation Services (65) states that accepted indications for transplantation include leukemias, lymphomas, myelodysplasia, aplastic anemia, multiple myeloma, and solid tumours.

Three papers reported on recommended measures of transplant outcomes (63,64,66). The first paper, an Accreditation Manual from the Foundation for the Accreditation of Cellular Therapy (FACT) (63), stated that each procedure should detail the objectives of the procedure, acceptable end-points, and the range of expected results, and that all outcomes should be assessed by these criteria. The other two papers, another FACT standards document (64) and a State of Michigan Department of Community Health Certificate of Need document (66), stated more explicit outcome measures, including: 100-day (64,66), 6-month (66), 1-year (64,66), 2-year (66), and 5-year (66) survival rates, relapse rates at 6-months (66), 1-year (66), and 5-years post-transplant (66), median follow-up and patient loss to follow-up (66), causes of death (if applicable) (66), treatment related mortality (any death occurring within 100 days from transplant) (66).

Table 26. Summary of papers identified via environmental scan.

Author	Disease site	Intervention	Outcome (domain)	Evidence base
FACT[1], 2002 (63) Sponsor: Foundation for the Accreditation of Cellular Therapy	varied	Standards for stem cell collection, processing, and transplantation	<u>Transplant outcome assessment:</u> Each procedure should detail: • the objectives of the procedure • acceptable end-points • the range of expected results Outcomes are assessed by these criteria.	Systematic review + expert panel consensus
FACT[2], 2005 (64) Sponsor: Foundation for the Accreditation of Cellular Therapy	varied	Standards for cellular therapy product collection, processing, and administration	<u>Transplant outcome assessment:</u> • 100 day post-transplant data • 1 year post-transplant data, and annually thereafter	Systematic review + expert panel consensus
Brigham & Women's Hospital, 2007 (65) Sponsor: Brigham and Women's Hospital	varied	BMT	<u>Accepted indications:</u> Includes: leukemias, lymphomas, myelodysplasias, aplastic anemias, multiple myelomas, and some solid tumours	Review + expert panel consensus
State of Michigan Department of Community Health, 2007 (66) Sponsor: State of Michigan	varied	BMT	<u>Measures used to assess outcomes:</u> • 100-day, 6-month, 1-year, 2-year, and 5-year survival rates • Relapse rates at 6-months, 1-year, and 5-years post-transplant • Median follow-up, and patients lost to follow-up • Causes of death, if applicable • TRM (any death occurring within 100 days from transplant)	NR

1. Foundation for the Accreditation of Cellular Therapy
2. Joint Accreditation Committee of ISCT-EBMT

Discussion of Evidence Review

The Panel was asked to develop a comprehensive listing of indications for SCT in adult patients, measures to assess transplant outcomes, and standards guiding performance. This task is complex because SCT consists of a heterogeneous group of related procedures performed in a wide array of (mainly malignant) diseases. This process is also complicated by evidence that has emerged slowly over a period of two to three decades, a time during which the standard therapy for many of these diseases has evolved and improved. Randomized trials assessing the role of transplantation have been difficult to conduct given the relatively low incidence of some of the diseases in which transplantation is performed and issues of donor availability. Despite these limitations, an increasing number of controlled trials have recently been reported for selected indications. The Panel also considered the importance of considering mature data when assessing the place of SCT, given the occurrence of late toxicities of treatment that may offset survival gains achieved through greater disease control.

As noted above, this review was restricted to existing standards documents and published EBM papers such as systematic reviews, practice guidelines, position statements, and other evidence summaries. Given the large number of such documents identified, a systematic review of the primary RCTs assessing transplantation was not conducted. An inventory of the RCTs considered in these reviews is included in Appendix 6; however, these studies were not considered individually.

The Panel utilized the following factors in its deliberations: quality of available evidence, recency of publication, consistency in recommendations across published guidelines, and availability of alternative treatment options. Where existing evidence was weak or guidelines differed in their recommendations, a consensus process was utilized to develop recommendations.

Acute Lymphoblastic Leukemia

The Panel found the evidence evaluating the role of SCT in ALL to be scant, consisting of only three publications based on non-controlled studies and/or expert opinion; however, it noted consistency in the recommendations across the publications as well as the reports from registry studies of long-term survival following allogeneic transplantation (2). The Panel considered that the outcome with conventional chemotherapy is poor for patients with high-risk features (including, but not limited to, Philadelphia chromosome positivity) and agreed with the consistent recommendation from the retrieved publications that allogeneic transplantation is an option for such patients. For patients beyond first remission, the outcome is poor regardless of cytogenetic risk, and allogeneic transplantation is the recommended treatment option for eligible patients with a compatible donor. For patients without a compatible donor, the Panel considered autologous transplantation is to be an option.

Acute Myeloid Leukemia

The Panel considered the evidence evaluating the role of SCT in AML to be of good quality, with nine publications based on nine controlled trial reports.

The Panel considered that allogeneic transplantation has a clear role in AML, noting the consistent recommendation from the published literature that it is the recommended treatment for eligible patients with high-risk features in CR1. The Panel noted that some papers recommend allogeneic transplantation for all patients in first remission. However, given the risks associated with transplantation and the relatively favourable outcome of patients with good risk features with standard chemotherapy, the Panel recommended that the use of routine allotransplantation in CR1 be restricted to patients with high-risk features.

In addition, the Panel recommended allogeneic transplantation as the treatment option for patients in subsequent remission.

The Panel noted controversy in the retrieved publications regarding the role of autologous transplantation, but indicated that one systematic review considered it to be investigational given that a large number of RCTs have evaluated autologous SCT and not reported a survival benefit compared to standard chemotherapy in first complete remission (CR1). The panel considered autologous transplantation in AML in CR1 to be investigational. Beyond CR1, the panel considered autologous transplantation to be an option.

Acute Promyelocytic Leukemia

The Panel considered the evidence examining the role of SCT in APL to be scant but considers APL to be a favourable subtype of AML and that given this, SCT (autologous and allogeneic) should be reserved for patients beyond first remission.

Aplastic Anemia

The Panel noted that the recommendations from the published papers were relatively consistent regarding the role of SCT in AA. All recommended that allogeneic transplantation be the recommended treatment for patients under age 30 years with severe or very severe AA, while none recommended that autologous transplantation be considered. The recommendations differed over the maximum age for which SCT should be recommended as first-line therapy over immunosuppression. The Panel considered that the decision to recommend SCT or immunosuppression involved more than age and should consider patient co-morbidities as well as the nature of the donor. The Panel therefore recommended that allogeneic transplantation should be considered as the recommended treatment in patients up to age 30-40 years.

Chronic Lymphocytic Leukemia

The Panel noted that, while there were a number of papers addressing SCT in CLL, including a number of systematic reviews and practice guidelines, the primary evidence addressing SCT in CLL consists mainly of uncontrolled clinical trials. The published evidence does suggest that allogeneic transplantation has curative potential in CLL and should be an option for patients with high-risk features, including high-risk cytogenetics who have failed purine analog therapy. The Panel concurred that SCT should be restricted to patients with such features, given the relatively long survival expected for patients with favourable risk disease and the risks of this treatment. The Panel agreed with the consensus from the literature that autologous transplantation is considered investigational in CLL.

Chronic Myeloid Leukemia

Prior to the introduction of tyrosine kinase inhibitors such as imatinib (Gleevec), allogeneic SCT was considered the recommended first-line treatment for CML. The availability of more effective medical therapy for CML has altered the place of SCT in this disease. There is consensus amongst the published papers that allogeneic SCT is an option for patients felt to be unlikely to respond to tyrosine kinase inhibitors as well as those who have failed or are intolerant of such therapy. The Panel was in agreement with this opinion.

Hodgkin's Lymphoma

The Panel considered the evidence evaluating the role of SCT in HL to be of good quality, based on a limited number of controlled clinical trials. All identified publications consider autologous SCT to be an option or the recommended option for patients with relapsed HL. The Panel considered autologous SCT to be the recommended treatment option for patients

with relapsed or refractory HL, weighing the more recent EBMT report more heavily than the older papers. The DSG noted that autologous SCT has been reported to improve survival compared to conventional chemotherapy in this setting. The panel noted that none of the papers report an established role for allogeneic BMT in this disease but considered that allogeneic transplantation is an option in the rare situation of an identical twin (Syngeneic transplant) or in selected patients who relapse after autologous transplantation.

Multiple Myeloma

The Panel noted that a greater body of evidence exists addressing the role of SCT in MM than in any other disease. These include published practice guidelines, including a CCO guideline and systematic reviews. All of the published reports identify a role for SCT, with the majority recommending it as the preferred treatment option for younger patients. There is some variability in the recommended upper age limit, ranging from 55 to 75 years, with age 65-70 being the most commonly reported cut-off. Some variability exists in the recommendations regarding the role of double or tandem autologous SCT, with some recent reports suggesting that it is an option for patients who fail to obtain a complete response with a single transplant. The Panel recommends autologous SCT as the optimal treatment for eligible patients up to age 65-70 years of age and recommends tandem transplantation as an option in cases in which a complete response is not obtained. The Panel noted that few published reports suggest a role for allogeneic SCT but did consider it should be an option for highly selected patients with poor-risk cytogenetics or who fail primary therapy. The role of SCT in myeloma will need to be revisited periodically, with the emergence of new agents with activity in this disease.

Myelodysplastic Syndrome

The available evidence on the role of SCT in MDS is limited to small uncontrolled series. The retrieved documents consistently recommend that allogeneic SCT is an option, given its curative potential, but that autologous SCT is not recommended. The Panel agreed with these recommendations but noted that allogeneic SCT would be an option only for a selected number of such patients given the median age of presentation of this disease.

Non-Hodgkin's Lymphoma

The Panel noted that assessing the role of SCT in NHL is complicated by the many subtypes of this disease and the changes in available lymphoma therapy that have occurred in recent years. The Panel considered the role of SCT to be best established in the aggressive lymphomas, including diffuse large B-cell lymphoma (DLBCL). The role of SCT as a component of primary therapy has been extensively studied without consistent evidence of a benefit and is not recommended by any of the identified papers. This question remains the subject of ongoing trials. In contrast, SCT is recommended in all of the identified papers as the preferred treatment for patients with relapsed or refractory disease. Autologous SCT is preferred over allogeneic SCT in this setting, but the Panel notes that not all patients are able to undergo autologous transplantation and recommend that allogeneic SCT be an option for such patients as well as those with an identical twin (syngeneic) donor.

The role of SCT in follicular lymphoma is not as clear. Allogeneic SCT offers the potential for cure in this disease, and autologous SCT has been reported to be associated with improved disease control when compared to conventional chemotherapy in a limited number of controlled trials. Many patients can be expected to do well with conventional chemotherapy, particularly when combined with rituximab. For this reason, the Panel recommends that SCT (autologous or allogeneic) be reserved as an option for selected

patients who have failed second-line therapy. It would be reasonable to extrapolate this strategy to the other indolent B-cell non-Hodgkin lymphomas.

The Panel gave careful consideration to the role of SCT in mantle cell lymphoma. It noted that the evidence for SCT in this indication is scant, with only the only publication identified in our systematic review recommending SCT as a treatment option. The Panel noted that the outcome of this subtype of lymphoma with conventional treatment, including rituximab-containing regimens, is poor, and one randomized trial has reported improved progression-free survival with autologous SCT. The Panel also noted that the NCCN recommends autologous SCT in first remission. It is the perception of the Panel that autologous SCT is currently viewed as a component of standard first-line therapy in mantle cell lymphoma in many Ontario centres. The Panel debated whether SCT should be considered "an option" or the "recommended option" for eligible patients with mantle cell lymphoma and endorsed a recommendation that it should be an option.

The Panel considered the role of SCT in lymphoblastic and Burkitt's lymphoma. While these diseases are aggressive, many can be treated effectively with conventional chemotherapy. The Panel recommended that SCT be reserved for use in patients who fail to achieve a remission or relapse after primary therapy.

The Panel reviewed the limited data available for other lymphoma subtypes and was unable to make recommendations regarding the role of SCT in these settings.

Solid Tumours

The Panel is aware that SCT has a role in the management of pediatric cancers such as neuroblastoma and Ewings sarcoma but notes that pediatric cancers lie outside the scope of this document. Two publications, including the recent one by the EBMT, report a role for autologous SCT in patients with germ cell tumours that are refractory to or have relapsed after cisplatin-based chemotherapy, and the Panel supports this recommendation.

There is no evidence to support the use of SCT in the treatment of breast, ovarian, or lung cancer.

Non-Malignant Indications

The Panel is aware that SCT is performed in adults for non-malignant indications such as myleoproliferative disorders, immune deficiency syndromes, and hemoglobinopathies. Such indications account for a very small proportion of transplants performed in Ontario, and as the retrieved publications did not specifically address these indications, the Panel is unable to make recommendations regarding the role of SCT for these indications at this time.

RECOMMENDATIONS DEVELOPMENT

Initial Draft Recommendations and Panel Review

The initial recommendations were drafted by two clinical experts designated by the Panel and the Hematology DSG as the lead clinicians for the project. They were drafted to be evidence-based to the greatest extent feasible, given the evidence review.

The Panel then reviewed the draft recommendations and the evidence review and provided feedback. This discussion and the Panel's evaluation of the evidence and recommendations is summarized above in the "Discussion of Evidence Review" section.

Advisory Panel on Bone Marrow and Stem Cell Transplantation Consensus

Following presentation of the draft recommendations to the Advisory Panel at the third and final meeting, the entire Panel was polled once more for any additional comments before the document went on to completion. All Panel members approved the recommendations as drafted, with the following exceptions forwarded by two members on three of the included indications, along with some additional commentary of a more general nature.

For the recommendations on AML, one member considered that allogeneic SCT should be an option for patients in first complete remission that were intermediate risk (rather than being restricted to high risk). The Panel considered the evidence for a role for allogeneic SCT in intermediate risk to be insufficient for a recommendation. The role of SCT in patients not in remission was also discussed, and the Panel recommended that SCT not be recommended for such patients.

For the multiple myeloma recommendations, one member questioned the source of the supporting evidence in favour of tandem autologous transplantation. The Panel noted that the evidence regarding the role of tandem transplantation is conflicting and in evolution. The Panel noted that the Hematology DSG has authored a practice guideline on the role of transplantation in MM and left the recommendation regarding tandem transplantation unchanged until the review by the DSG. The data regarding the role of tandem transplantation is summarized on page 23 of Section 2 of this Recommendation Report.

For the recommendations on CML, one member stated that allogeneic SCT is standard treatment for all CML patients beyond first complete response and that it is offered to patients who do not want life-long medical management of their disease.

One member also noted that there was nothing in the document providing any guidance on the use of allografting for congenital marrow failure such as immunodeficiency syndromes, myeloproliferative disorders, and other hemoglobin disorders, some of which do not manifest until adulthood. In response, a paragraph detailing why no recommendations were made regarding these indications was included in the Discussion.

No other Panel members submitted comments, agreeing with the recommendations as worded.

Hematology Disease Site Group Consensus

In order that this document be fully completed and made available to the clinical community of Ontario, a decision was made by the Panel and the Director of the PEBC that the document become the responsibility of the Hematology DSG upon completion of the Panel's mandate. The Hematology DSG agreed to take on this responsibility, and the draft document created by the Panel was presented to the Hematology DSG. The Hematology DSG was provided with the full document, including the evidence review and the draft recommendations developed by the Panel. Given the wide variability in the evidence base, and the heavy reliance upon consensus for some indications, the co-chairs of the DSG decided that a formal vote be taken for each of the recommended indications. For each of the indications, an electronic voting

system was used to compile DSG responses. All members were asked to approve the draft recommendations as stated or to ask for revisions. The option to decline a vote was offered if some felt they were not qualified to make a decision, which explains the variation in response rates.

The DSG recognized the importance of this document as a means of facilitating equitable access to transplant services across the province but expressed some discomfort with the highly variable nature of the evidence available to inform the recommendations. The DSG noted that, for some indications, recommendations were entirely based on expert opinion, with no available controlled trials. The DSG requested that the quality of evidence supporting the individual recommendations be included in the document. This systematic review is of guidelines and of systematic reviews rather than of the primary studies. A listing of the RCTs that informed the guidelines has been included in Appendix 6.

Changes were made as described in the following sections:

Acute Lymphoblastic Leukemia

For ALL, 10 members voted, with nine in favour of the recommendations as drafted (90%), and one not in favour (10%). For the recommendations regarding first complete remission, one member thought that the recommendation should include some guidance on the role of imatinib and requested a qualifying statement be added describing this. The DSG endorsed this request. For the recommendations regarding SCT beyond first complete remission, one member requested that, because the evidence was weak, instead of stating SCT was "an option," it would be more prudent to state "there is insufficient evidence to support or refute" its use. This same member also suggested that the term "beyond first remission" be changed to "who achieve a second remission." The DSG agreed to these modifications, and the recommendations were changed to reflect them.

Acute Myeloid Leukemia

For AML, 16 members voted, with 12 in favour of the recommendations as drafted (75%) and four not in favour (25%). For the first recommendation under first complete remission, two members suggested a qualifying statement be added noting that allogeneic SCT is not typically performed beyond an upper age threshold as toxicity and treatment-related mortality increase with age. The DSG did not consider this to be relevant to AML specifically and therefore added a qualifying statement regarding age being a surrogate for co-morbidities and a factor in the decision regarding transplantation. For the recommendations covering SCT beyond first remission, two members suggested the second bullet be reworded from "not recommended" to "there is no evidence to support or refute." The DSG agreed to the change in wording.

Acute Promyelocytic Leukemia

The members of the DSG noted that the recommendations regarding SCT in APL were based on a single publication consisting of expert consensus. While the members expressed the sentiment that SCT was appropriate for selected patients with APL, the consensus was to change the wording from stating that SCT was "an option" to "There is insufficient evidence to support or refute the use of stem cell transplantation for patients with APL in the second or subsequent remission." A qualifying statement was added to the overall document stating "the choice of whether to use an autologous or allogeneic procedure must be made by the patient in consultation with his/her clinician in consideration of the expected benefits and harms associated with each procedure in this disease setting." The DSG agreed unanimously to these changes.

Aplastic Anemia
For AA, 19 members voted, with 18 in favour of the recommendations as drafted (95%) and one (5%) not in favour. The single member not in favour suggested that a qualifying statement be added stating that for patients not considered candidates for SCT, immunosuppressive therapy with antithymocyte globulin (ATG) should be considered. The DSG agreed to this modification.

Chronic Lymphocytic Leukemia
For CLL, 14 members voted, with 12 in favour of the recommendations as drafted (86%) and two not in favour (14%). The two members not in favour both wanted a qualifying statement added following the recommendations indicating that there are numerous other treatment options for treating CLL, including targeted therapies such as rituximab and alemtuzumab. The DSG agreed to this modification.

Chronic Myeloid Leukemia
For CML, 14 members voted, with 100% in favour of the recommendations as drafted, but a qualifying statement was suggested by one member clarifying that allogeneic SCT should still be considered a treatment option for patients with accelerated blast crisis undergoing treatment with imatinib who are currently in remission.

Hodgkin's Lymphoma
For HL, 15 members voted, with 100% being in favour of the recommendations as worded, with no changes.

Multiple Myeloma
For MM, 14 members voted, with eight in favour of the recommendations as drafted (57%) and six not in favour (43%). The members stated that a great deal of new evidence is available that would inform decisions regarding transplantation for myeloma, addressing in particular the role of tandem transplantation and maintenance thalidomide. The DSG noted that the CCO guideline addressing transplantation in myeloma (EBS #6-6) has not been updated since October 2003 and should be a high priority for updating. DSG members were aware of new data that is relevant to the recommendations but was not cited in the retrieved documents or in EBS #6-6. The DSG recommended that a qualifying statement about referring to EBS #6-6 be inserted. A strong consensus emerged from the discussion that tandem transplantation should be considered an option rather than the "recommended option."

Myelodysplastic Syndrome
For MDS, 14 members voted, with 13 in favour of the recommendations as drafted (93%) and one not in favour (7%). No suggestions were offered by the single dissenting vote, and the recommendations remain as drafted.

Aggressive Histology Non-Hodgkin's Lymphoma
For AH-NHL, 14 members voted, with 11 in favour of the recommendations as drafted (79%) and three not in favour (21%). One member suggested rewording the first recommendation from "for eligible patients" to "for eligible chemosensitive patients." The DSG approved this change. No additional suggestions were proposed.

Follicular Lymphoma
For FL, 14 members voted, with ten members in favour of the recommendations as drafted (71%) and four not in favour (29%). One member suggested rewording the first bullet to

include patients with poor prognosis in the group of "selected" patients. Two members also suggested not excluding SCT as primary treatment for selected patients.

Burkitt's Lymphoma
For BL, 10 members voted, with nine members in favour of the recommendations as drafted (90%) and one not in favour (10%). No suggestions for change were offered, and the recommendations remain as drafted.

Mantle Cell Lymphoma
For MCL, 12 members voted, with 10 members in favour of the recommendations as drafted (82%) and two not in favour (18%). No suggestions for change were offered, and the recommendations remain as drafted.

Solid Tumours
For solid tumours, 17 members voted, with 100% being in favour of the recommendations as drafted. No changes to the drafted recommendations were made.

Other Indications
A number of members of both the Panel and the DSG noted that transplantation is also performed for a number of rare indications for which little data are available. These include rare cases of transplantation in adults with hemoglobinopathies or immune deficiency states as well as myeloproliferative disorders. Given that no publications addressing these indications were identified in the systematic review, recommendations regarding them would not be developed in this document. The DSG noted that this should not be taken to indicate that transplantation is inappropriate for such indications but rather that these rare circumstances should be evaluated on an individual patient basis.

Measures to Assess Transplant Outcomes
One member recommended that "second cancers" be removed from the final bullet and to be added into the list of discrete outcomes as a bullet on its own. No other changes were made.

FINAL RECOMMENDATIONS
The final recommendations resulting from the evidence review and development process described above can be found in Section 1 of this report.

CONFLICT OF INTEREST
None declared (by KI, BR).

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Appendix 1. Members of the Quality Group of the Advisory Panel on Bone Marrow and Stem Cell Transplantation.

Dr. Jose Chang, MD

Dr. Michael Crump, MD (Clinical lead)

Ms. Sherrie Hertz, BScPhm

Dr. Kang Housen-Jan, MD

Dr. Kevin Imrie, MD (Chair)

Dr. Janet MacEachern, MD

Dr. Sheila McNair, PhD

Mr. R. Bryan Rumble, BSc (Research Coordinator)

Dr. Carol Sawka, MD

Dr. Irwin Walker, MD

Appendix 2: MEDLINE search.

Database: Ovid MEDLINE(R) <1996 to February Week 4 2008>
Search Strategy:
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1 exp Bone Marrow Transplantation/ (14352)
2 exp Stem Cell Transplantation/ (23028)
3 1 or 2 (35127)
4 exp transplantation, homologous/ or exp transplantation, autologous/ (28897)
5 3 or 4 (52525)
6 exp Leukemia, Myeloid/ or exp Leukemia, Myelocytic, Acute/ (23058)
7 exp Leukemia, Lymphocytic, Acute/ or exp Leukemia, Lymphocytic, Acute, L1/ or exp Leukemia, Lymphocytic, Acute, L2/ (9965)
8 exp Leukemia, Myeloid, Chronic/ (6392)
9 exp Myelodysplastic Syndromes/ (10893)
10 exp Lymphoma, Non-Hodgkin/ (28497)
11 exp Leukemia, Lymphocytic, Chronic/ (4494)
12 exp Hodgkin Disease/ (5669)
13 exp Multiple Myeloma/ (8492)
14 exp Neoplasms/ (749715)
15 exp Anemia, Aplastic/ (2978)
16 or/6-15 (754895)
17 5 and 16 (16816)
18 limit 17 to (humans and english language and yr="1999 - 2007") (11350)
19 guideline:.mp. (110920)
20 technology assessment.mp. or exp Technology Assessment, Biomedical/ (4222)
21 evidence-based medicine.mp. or exp Evidence-Based Medicine/ (27072)
22 exp Practice Guidelines/ or exp Benchmarking/ or best practice.mp. (45185)
23 practice parameter.mp. (180)
24 position paper.mp. (605)
25 exp "Practice Guideline [Publication Type]"/ (9108)
26 exp "government publications [publication type]"/ (18)
27 or/19-26 (140693)
28 18 and 27 (168)
29 from 28 keep 1-168 (168)

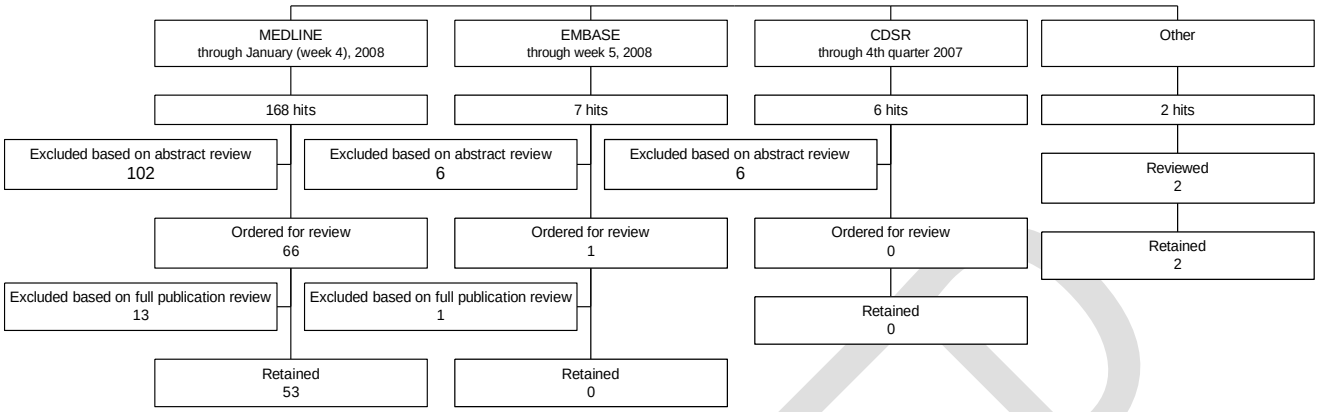
Appendix 3: EMBASE search.

Ovid Technologies, Inc. Email Service

Database: EMBASE <1996 to 2008 Week 5>
Search Strategy:

1 exp Bone Marrow Transplantation/ (18338)
2 exp Stem Cell Transplantation/ (25092)
3 1 or 2 (40102)
4 exp transplantation, homologous/ or exp transplantation, autologous/ (6200)
5 3 or 4 (44102)
6 exp Leukemia, Myeloid/ or exp Leukemia, Myelocytic, Acute/ (27711)
7 exp Leukemia, Lymphocytic, Acute/ or exp Leukemia, Lymphocytic, Acute, L1/ or exp Leukemia, Lymphocytic, Acute, L2/ (2404)
8 exp Leukemia, Myeloid, Chronic/ (9547)
9 exp Myelodysplastic Syndromes/ (6833)
10 exp Lymphoma, Non-Hodgkin/ (34344)
11 exp Leukemia, Lymphocytic, Chronic/ (6233)
12 exp Hodgkin Disease/ (8776)
13 exp Multiple Myeloma/ (10520)
14 exp Neoplasms/ (822732)
15 exp Anemia, Aplastic/ (8106)
16 or/6-15 (829141)
17 5 and 16 (22227)
18 limit 17 to (humans and english language and yr="1999 - 2007") (16495)
19 guideline:.mp. (115460)
20 technology assessment.mp. or exp Technology Assessment, Biomedical/ (5478)
21 evidence-based medicine.mp. or exp Evidence-Based Medicine/ (238817)
22 exp Practice Guidelines/ or exp Benchmarking/ or best practice.mp. (215138)
23 practice parameter.mp. (193)
24 position paper.mp. (492)
25 exp "Practice Guideline [Publication Type]"/ (0)
26 exp "government publications [publication type]"/ (0)
27 or/19-26 (452535)
28 18 and 27 (2118)
29 28 not [medline results] (151)
30 from 29 keep 1,22,47,66,70,83,99 (7)
31 from 29 keep 1-7 (7)

Appendix 4: Flow diagram of literature search & excluded papers listing.



Total: Medline (53) + Other (2) = 55

Excluded papers (MEDLINE)

Citation	Reason for exclusion
High-dose chemotherapy with autologous stem cell support in the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma. Tecnologica MAP Suppl 2000 Jan;17-9.	No outcomes of interest reported on.
Nonmyeloablative allogeneic stem-cell transplantation for malignancy. Tecnologica MAP Suppl 2001 Apr 13;14-7.	No outcomes of interest reported on.
Barosi G, Carella A, Lazzarino M, Marchetti M, Martelli M, Rambaldi A, et al. Management of nodal indolent (non marginal-zone) non-Hodgkin's lymphomas: practice guidelines from the Italian Society of Hematology, Italian Society of Experimental Hematology and Italian Group for Bone Marrow Transplantation. Haematologica 2005 Sep;90(9):1236-57.	No outcomes of interest reported on.
Brandt L, Kimby E, Nygren P, Glimelius B, SBU-group. Swedish Council of Technology Assessment in Health Care., Brandt L, et al. A systematic overview of chemotherapy effects in Hodgkin's disease. [Review] [116 refs]. Acta Oncol 2001;40(2-3):185-97.	No outcomes of interest reported on.
Cunningham R, Cunningham R. Perspectives. Indefinite results in ABMT (autologous bone marrow transplantation) trials add to challenges for practice standards, quality assurance in cancer care. Med Health 1999 Apr;53(16):suppl-4.	Not EBM report.
Firshein J, Firshein J. ABMT and breast cancer. Healthplan 1935 Jul 9;40(4):30-3.	No outcomes of interest reported on.
Gertz M, Gertz M. Transplantation for multiple myeloma. Pertinent Questions. Blood 2003 Nov 15;102(10):3472-5.	Not EBM report.
Hiddemann W, European Society for Medical Oncology. ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of newly diagnosed follicular lymphoma. Ann Oncol 2003 Aug;14(8):1163-4.	No outcomes of interest reported on.
Lyman GH, Kuderer NM, Lyman GH, Kuderer NM. Cost effectiveness of myeloid growth factors in cancer chemotherapy. [Review] [71 refs]. Curr Hematol Rep 2003 Nov;2(6):471-9.	No outcomes of interest reported on.
O'Brien S, Berman E, Bhalla K, Copelan EA, Devetten MP, Emanuel PD, et al. Chronic myelogenous leukemia. J 2007 May;5(5):474-96.	No outcomes of interest reported on.

Stone R, Potting CM, Clare S, Uhlenhopp M, Davies M, Mank A, et al. Management of oral mucositis at European transplantation centres. EUR J ONCOL NURS 2007;11 Suppl 1:S3-S9.	No data on BMT/SCT.
Whittaker SJ, Marsden JR, Spittle M, Russell JR, British Association of Dermatologists, Cutaneous Lymphoma Group UK, et al. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. Br J Dermatol 2003 Dec;149(6):1095-107.	No data on BMT/SCT.
Wolf SM, Kahn JP, Wagner JE, Wolf SM, Kahn JP, Wagner JE. Using preimplantation genetic diagnosis to create a stem cell donor: issues, guidelines & limits. J Law Med Ethics 2003;31(3):327-39.	No data reported on adults.

Excluded papers (EMBASE)

Citation	Reason for exclusion
Einsele H, Bertz H, Beyer J, Kiehl MG, Runde V, Kolb H-J, et al. Infectious complications after allogeneic stem cell transplantation: Epidemiology and interventional therapy strategies - Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Annals of Hematology 82(SUPPL 2)()(pp S175-S185), 2003;(SUPPL. 2):S175-S185.	No outcomes of interest reported on.

Appendix 5: Organizations searched in targeted environmental scan.

Organization
BC Cancer Agency
Albert Cancer Board
Saskatchewan Cancer Agency
Cancer Care Manitoba
Cancer Care nova Scotia
N Z Cancer Control Strategy
N Z Cancer Control Trust
Regional Cancer Centre, Waikato Hospital, Hamilton, NZ
The Cancer Council Australia
National Cancer Control Initiative (Australia)
The Collaboration for Cancer Outcomes Research and Evaluation (AU)
State Government of Victoria, Australia
Peter MacCallum Cancer Centre (Australia)
Medical Oncology Group of Australia
Cancer UK
Cancer Services Collaborative, Avon Somerset and Wiltshire (UK)
Cancer Services Collaborative NHS Modernisation Agency
NHS (UK)
AHRQ, USA
European Group for Blood and Marrow Transplantation (EBMT)
The Centre for International Blood and Marrow Transplant Research (CIBMTR)

Appendix 6: RCTs included in retrieved papers.

Acute lymphoblastic leukemia (References: (2,9,10))

No RCTs addressing transplant listed.

Acute myeloid leukemia (References: (2,9,11-17))

Burnett AK, Goldstone AH, Stevens RM, Hann IM, Rees JK, Gray RG, et al. Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial. UK Medical Research Council Adult and Children's Leukaemia Working Parties. Lancet. 1998;351(9104):700-8.

Grimwade D, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. Blood. 1998;92(7):2322-33.

Burnett AK, Wheatley K, Goldstone AH, Stevens RF, Hann IM, Rees JH, et al. The value of allogeneic bone marrow transplant in patients with acute myeloid leukaemia at differing risk of relapse: results of the UK MRC AML 12 trial. Br J Haemat 2002;118;385–400.

Cassileth PA, Harrington DP, Appelbaum FR, Lazarus HM, Rowe JM, Paietta E, et al. Chemotherapy compared with autologous or allogeneic transplantation in the management of acute myeloid leukaemia in first remission. N Engl J Med 1998;339:1649–56.

Harrousseau JL, Cahn JY, Pignon B, Witz F, Milpied N, Delain M, et al. Comparison of autologous bone marrow transplantation and intensive chemotherapy as post-remission therapy in adult acute myeloid leukemia. The Group Ouese Est Leucemies Aigues Myeloblastiques (GOELAM). Blood 1997;90:2978-86.

Suciu S, Mandelli F, de Witte T, Zittoun R, Gallo E, Labar B, et al. Allogeneic compared with autologous stem cell transplantation in the treatment of patients younger than 46 years with acute myeloid leukemia (AML) in first complete remission (CR1): an intention-to-treat analysis of the EORTC/GIMEMA AML-10 trial. Blood 2003;102:1232–40.

Zittoun R, Suciu S, Watson M, Solbu G, Muus P, Mandelli F, et al. Quality of life in patients with acute myelogenous leukaemia in prolonged first complete remission after bone marrow transplantation (allogeneic or autologous) or chemotherapy: a cross-sectional study of the EORTC-GIMEMA AML 8A trial. Bone Marrow Transplantation 1997;20:307–15.

Breems DA, Boogaerts MA, Dekker AW, Van Putten WL, Sonneveld P, and Huijgens PC. Autologous bone marrow transplantation as consolidation therapy in the treatment of adult patients under 60 years with acute myeloid leukemia in first complete remission: a prospective randomized Dutch-Belgian Haemato-Oncology Co-operative Group (HOVON) and Swiss Group for Clinical Cancer Research (SAKK) trial. Br J Haematol 2005;128:59-65.

Reiffers J, Gaspard MH, Maraninchi D, Michallet M, Marit G, and Stoppa AM. Comparison of allogeneic or autologous bone marrow transplantation and chemotherapy in patients with acute myeloid leukemia in first remission: a prospective controlled trial. Br J Haematol 1989;72:57-63.

Acute promyelocytic leukemia (References: (20))

No RCTs addressing transplant listed.

Aplastic anemia (References: (2,19,20))

No RCTs addressing transplant identified.

Chronic lympocytic leukemia (References: (2,21-25))

No RCTs addressing transplant identified.

Chronic myeloid leukemia (References: (2,21,26-34))

Clift RA, Buckner CD, Thomas ED, Bensinger WI, Bowden R, Bryant E, et al. Marrow transplantation for chronic myeloid leukemia: a randomized study comparing cyclophosphamide and total body irradiation with busulfan and cyclophosphamide. Blood. 1994;84(6):2036-43.

Schmitz N, Bacigalupo A, Hasenclever D, Nagler A, Gluckman E, Clark P, et al. Allogeneic bone marrow transplantation vs filgrastim-mobilised peripheral blood progenitor cell transplantation in patients with early leukaemia: first results of a randomised multicentre trial of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 1998;21(10):995-1003.

Clift RA, Radich J, Appelbaum FR, Martin P, Flowers ME, Deeg HJ, et al. Long-term follow-up of a randomized study comparing cyclophosphamide and total body irradiation with busulfan and cyclophosphamide for patients receiving allogenic marrow transplants during chronic phase of chronic myeloid leukemia. Blood 1999;94(11):3960-2.

Hodgkin's lymphoma (References: (2,9,21,32,35))

Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet. 1993;341(8852):1051-4.

Schmitz N, Sextro M, Pfistner B et al. High-dose therapy followed by hematopoietic stem cell transplantation for relapsed chemosensitive Hodgkin's disease: final results of a randomized GHSG and EBMT trial (HD-R1). Proc Am Soc Clin Oncol 1999;18:2a.

Diehl V, Franklin J, Hasenclever D, et al. BEACOPP, a new dose-escalated and accelerated regimen, is at least as effective as COPP:ABVD in patients with advanced-stage Hodgkin's lymphoma: interim report from a trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol 1998;16:3810–21. (C1:1200).

Diehl V, Sieber M, Franklin J, et al. Dose escalated BEACOPP chemotherapy for advanced Hodgkin's disease: Promising results of the fourth interim analysis of the HD9 trial. VII Int Conf Malign Lymph, Lugano, 1999;61 Abstr. (C3:1200).

Multiple myeloma (References: (2,21,37,39-45))

Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 1996;335(2):91-7.

Fermand JP, Ravaud P, Katsahian S, Divine M, Leblond V, Belanger C, et al. High dose therapy (HDT) and autologous blood stem cell (ABSC) transplantation versus conventional treatment in multiple myeloma (MM): results of a randomized trial in 190 patients 55 to 65 years of age. Blood 1999;94(Suppl 1):396a.

Harousseau JL, Attal M, Payen C, Facon T, Michaux JL, Guilhot F, et al. Bone marrow (BM) versus peripheral blood versus CD34_progenitors as the source of stem cell for autologous transplantation in multiple myeloma. Blood 1998;92:443a.

Harrousseau JL, Facon T, Moreau P, Michallet M, Guilhot F, Hulin C, et al. Comparison of high-dose melphalan 140 mg/m2 plus total body irradiation and high-dose melphalan 200mg/m2 as conditioning regimen for peripheral blood progenitor cell autotransplantation in patients with newly diagnosed multiple
myeloma. Preliminary results of the IFM 9502 randomized trial. Blood 1999;94:713a.

Attal M, Harousseau JL, Facon T, Michaux JL, Guilhot F, Fruchard C, et al. Single versus double transplant in myeloma: a randomized trial of the InterGroup Francais du Myelome (IFM). Blood 1999;94:714a.

Tosi P, Cavo M, Zamagni E, Ronconi S, Benni M, Tura S, et al. A multicentric randomized clinical trial comparing single versus double autologous peripheral blood stem cell transplantation for patients with newly diagnosed multiple myeloma: results of an interim analysis. Blood 1999;94:715a.

Fermand JP, Ravaud P, Chevret SK, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. Blood 1998;92:3131–6.

Stewart AK, Vescio R, Schiller G, et al., Purging of autologous peripheral-blood stem cells using CD34 selection does not improve overall or progression-free survival after high-dose chemotherapy for multiple myeloma: results of a multicenter randomized controlled trial. J Clin Oncol 2001;19:3771–9.

Vescio R, Schiller G, Stewart AK, et al., Multicenter phase III trial to evaluate CD34(+) selected versus unselected autologous peripheral blood progenitor cell transplantation in multiple myeloma. Blood 1999;93:1858–68.

Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m2 melphalan and 8 Gy total body irradiation plus 140 mg/m2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9505 randomized trial. Blood. 2002;99:731–5.

Attal M, Harousseau JL, Facon T, et al. Double autologous transplantation improves survival of multiple myeloma patients: final analysis of a prospective randomized study of the Intergroupe Francophone du Myelome (IFM 94). Blood 2002;100:5a.

Segeren CM, Sonneveld P, Van der Holt B, et al. Myeloablative treatment following intensified chemotherapy in untreated multiple myeloma: a prospective, randomized phase III study. Blood 2001;98:815a.

Blade J, Sureda A, Ribera AM, et al. High-dose therapy autotransplantation/intensification versus continued conventional chemotherapy in multiple myeloma patients responding to initial treatment chemotherapy. Results of a prospective randomized trial from the Spanish Cooperative Group PETHEMA. Blood 2001;98:815a.

Kropff M, Schneider P, Heyll A, Haas R, and Berdel WE. Randomized trial comparing an intensified therapy (HD-IMC) with a standard high-dose therapy (HD-M) for multiple myeloma [abstract]. Blood 2000;96:797a.

Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. New Engl J Med 2003:348:1875–83.

Cunningham D, Powles R, Malpas J, Raje N, Milan S, Viner C, et al. A randomized trial of maintenance interferon following high-dose chemotherapy in multiple myeloma: long-term follow-up results. Br J Haemat 1998;102:495–502.

Facon T, Mary J, Harousseau J, et al. Superiority of melphalanprednisone (MP) + thalidomide (THAL) over MP and autologous stem cell transplantation in the treatment of newly diagnosed elderly patients with multiple myeloma [abstract]. J Clin Oncol. 2006;24(suppl):1s. Abstract 1.

Fermand JP, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. Blood. 1998;92:3131-3136.

Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. J Clin Oncol. 2006 Feb 20;24:929-936. Epub 2006 Jan 23.

Blade J, Rosinol L, Sureda A, et al. Programa para el Estudio de la Terapeutica en Hemopatia Maligna (PETHEMA). High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. Blood 2005;106:3755-9.

Attal M, Harousseau JL, Facon T, et al. InterGroupe Francophone du Myelome. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med. 2003;349:2495-2502.

Cavo M, Cellini C, Zamagni E, et al. Superiority of double over single autologous stem cell transplantation as first-line therapy for multiple myeloma. Blood 2004;104:155a. Abstract 536.

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

Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood 2006;107:3474-80.

Myelodysplastic syndrome (References: (2,14,46-49))

No RCTs addressing transplant listed.

Non-Hodgkin's lymphoma (References: (2,9,36,50-56,61,62)

Hiddemann W, Unterhalt M, Wandt H, et al. Myeloablative radiochemotherapy followed by blood-stem cell-transplantation significantly prolongs the disease-free interval in patients with low-grade lymphomas as compared to standard maintenance with interferon alpha: results of a prospective randomized comparison by the German Low Grade Lymphoma Study Group (GLSG). Blood 1998;94(Suppl 1):610a (Abstr 2715).

Kanteti R, Miller KB, McCann JC, Roitman D, Morelli J, Hurley C, et al. Randomized trial of peripheral blood progenitor cells versus bone marrow as hematopoietic support for high-dose chemotherapy in patients with non-hodgkins lymphoma and hodgkins disease: a clinical and molecular analysis, Bone Marrow Transplantation 1999;24:473–81.

Schmitz N, Linch DC, Dreger P, Goldstone AH, Boogaerts MA, Ferrant A, et al. Randomised trial of filgratim mobilised peripheral blood progenitor cell transplantation versus autologous bone marrow transplantation in lymphoma patients. Lancet 1996;347:353–7.

Vellenga E, VanAgthoven M, Croockewit AJ, Verdonck LF, Wijermans PJ, Van Oers MHJ, et al. Autologous peripheral blood stem cell transplantation in patients with relapsed lymphoma results in accelerated haematopoietic reconstitution, improved quality of life and cost reduction compared with bone marrow transplantation: the Hovon 22 study, Br J Haemat 2001;114(2):319–26.

Vose JM, Sharp G, Wing C, Nicholls C, Loh K, Inwards D, et al. Autologous Transplantation for Aggressive Non-Hodgkin's Lymphoma: results of a randomised trial evaluating graft source and minimal residual disease. J Clin Oncol 2002;20(9):2344–52.

Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995;333(23):1540-45.

Philip T, Chauvin F, and Bron D et al on behalf of the PARMA protocol group. PARMA international protocol: pilot study on 50 patients and preliminary analysis of the ongoing randomized study (62 patients). Ann Oncol 1991;2(Suppl 1):57-64.

Gherlinzoni F, Martelli M, Tnra S. Early Autologous stem cell transplantation (ASCT) versus conventional first line chemotherapy in high-risk aggressive Non Hodgkin's lymphoma (NHL): an Italian multicenter randomized trial. Blood 2000;96(11):481 a.

Verdonck LF, van Putten WLJ, Ilagenbeek A, et al. Comparison of CHOP chemotherapy with autologous bone marrow transplantation for slowly responding patients with aggressive non-Hodgkin's lymphoma. N Engl J Med 1995;332:1045-1051.

Martelli M, Gherlinzoni F, and Ziuzani PL et al on behalf of the Italian Cooperative Study Group. Early autologous stem cell transplantation as first-line therapy in poor prognosis non-Hodgkin's lymphoma (NHL): an Italian randomized trial. Ann Oncol 1999;10(suppl 3):78.

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