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Recommendation Report SCT-3 IN REVIEW

Stem Cell Transplantation in Myelodysplastic Syndromes and Acute Myeloid Leukemia

C.T. Kouroukis, R.B. Rumble, I. Walker, C. Bredeson, and A. Schuh

Report Date: March 29, 2012

An assessment conducted in March 2018 placed Recommendation Report SCT-3 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Recommendation Report SCT-3 is comprised of 2 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/976

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

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Recommendation Report SCT-3: Section 1

Stem Cell Transplantation in Myelodysplastic Syndromes and Acute Myeloid Leukemia: Recommendations

C.T. Kouroukis, R.B. Rumble, I. Walker, C. Bredeson, and A. Schuh

Report Date: March 29, 2012

CLINICAL QUESTIONS

Myelodysplastic syndrome (MDS)

What is the role of stem cell transplantation (SCT) in the treatment of MDS?

Acute Myeloid Leukemia (AML)

What is the role of SCT in the treatment of AML?

TARGET POPULATION

All adult patients with MDS or AML being considered for treatment that includes either blood or bone marrow transplantation.

RECOMMENDATIONS AND SUPPORTING EVIDENCE

MYELODYSPLASTIC SYNDROME (MDS)
Allogeneic transplantation is an option for patients with MDS. This is the only potentially curative therapy for MDS.
Evidence • One systematic review comprising a total of 22 studies demonstrated a long-term curative outcome for related, unrelated, either or unspecified allogeneic SCT (alloSCT) (1).
Autologous stem cell transplantation is not recommended for patients with MDS.
Evidence • One systematic review comprising a total of 22 studies did not detect any benefit associated with autologous SCT (ASCT), and does not recommend it outside of a clinical trial (1).

ACUTE MYELOID LEUKEMIA (AML)
First complete remission
Allogeneic transplantation is a treatment option for patients with AML in first complete remission (CR1), with high-risk features including intermediate or high-risk cytogenetic or molecular phenotypes, high-risk clinical features at presentation, and secondary or treatment-related AML.

Evidence

- One systematic review (2), comprising 24 clinical studies involving 6,007 patients with AML in CR1 comparing alloSCT, ASCT, chemotherapy (CT), or any combination of the three, found a significant RFS and OS benefit associated with allogeneic SCT. That review performed subgroup analyses for both recurrence or relapse-free survival (RFS) and overall survival (OS) according to patient risk (good, intermediate, or poor risk). Significant benefits in favour of alloSCT for both intermediate and poor risk patients ($p<0.01$) were detected, but no difference was detected with good risk patients. The OS subgroup analysis also detected significant benefits in favour of alloSCT for intermediate and poor risk patients ($p<0.01$) but not for good risk patients.
- One meta-analysis (3), that pooled data from two trials (AML 96 and AML 02) that compared alloSCT with ASCT with CT, including a total of 708 patients, detected significant differences in favour of alloSCT for both OS and leukemia-free survival (LFS) at two years. In a multivariate analysis, factors associated with better OS and longer LFS were being younger ($p=0.008$) and receiving an allogeneic transplant.
- One prospective cohort study (4) found significant benefits in favour of alloSCT compared with ASCT in the relative risk for eight-year disease-free survival (DFS).

ASCT is not recommended for patients with AML in first complete remission.

Evidence

- While associated with more favourable treatment-related mortality (TRM) rates, if long-term survival is the primary outcome of interest, then there is no evidence to support the use of ASCT in first complete remission.

Beyond first complete remission

Allogeneic transplantation is the recommended option for patients with AML who achieve a second or subsequent remission.

Evidence

- Evidence from one clinical practice guideline (5) demonstrated that if CR only occurs after a second course of induction therapy, myeloablative alloSCT from a fully-matched sibling donor is recommended, regardless of the risk, if the patient is under 55 years of age and has no other co-morbidities

There is insufficient evidence to support the use of ASCT for patients with AML in second or subsequent remission.

Evidence

- If long-term survival is the primary outcome of interest, then there is no evidence to support the use of ASCT in second or subsequent remission.

Autologous transplantation is recommended for acute promyelocytic leukemia (APL) in a molecularly-negative second remission.

Evidence

- No evidence was obtained in this update of the 2009 report (6), and the Expert Panel continues to support this recommendation.

Select patients with AML not in remission may derive benefit from allogeneic transplant.

Evidence

- Evidence from one clinical practice guideline (7) demonstrated that, when a patient does not experience a CR, then that patient should be offered entry into a clinical trial, or reduced intensity alloSCT within a clinical trial setting, or best supportive care (BSC).

[1] 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] (6).

QUALIFYING STATEMENT

The patient selection process and the ultimate decision to perform an SCT should take into account not only disease-related characteristics, but also co-morbidities and patient preferences. Patients with MDS or AML should be referred to a transplant centre for transplant assessment.

FUTURE RESEARCH

Ongoing studies in MDS and AML testing newer agents may or may not impact on the number of patients potentially requiring SCT. Reduced intensity transplant and newer methods of preventing or treating graft versus host disease may expand the eligible transplant population. In addition, stem cell procurement from alternative donors such as cord blood and haploidentical donors may also allow SCT to be an option for a greater number of patients.

IMPLICATIONS FOR POLICY

Given the potential increase in the numbers of patients with MDS and AML over time, and the possibility of new transplant methodologies resulting in better outcomes and more donors available thru newer sources, the number of patients eligible for SCT will likely increase.

RELATED PROGRAM IN EVIDENCE-BASED CARE REPORTS

- Imrie K, Rumble RB, Crump M; Advisory Panel on Bone Marrow and Stem Cell Transplantation; Hematology Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Stem Cell Transplantation in Adults, [Report Date: January 30, 2009]. Available from: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=35448

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Recommendation Report SCT-3: Section 2

Stem Cell Transplantation in Myelodysplastic Syndromes and Acute Myeloid Leukemia: Summary of Methods and Evidence

C.T. Kouroukis, R.B. Rumble, I. Walker, C. Bredeson, and A. Schuh

Report Date: March 29, 2012

QUESTIONS

Myelodysplastic syndrome (MDS)

What is the role of stem cell transplantation (SCT) in the treatment of MDS?

Acute Myeloid Leukemia (AML)

What is the role of SCT in the treatment of AML?

INTRODUCTION

MDS and AML are both cancers affecting hematopoietic stem cells in one or more cell lines, eventually leading to bone marrow failure if left untreated (1). MDS is an age-related cancer, with 86% of all new cases occurring in patients older than 60 (median age, 76) (1). Symptoms associated with MDS include anemia, bleeding, infection, and ultimately, multi-organ failure (1). MDS has various presentations, with some patients experiencing chronic malaise, while others present with aggressive, high-risk disease that is associated with median survivals of six months (1,2). MDS can be primary or secondary to past treatment with chemotherapy agents, especially prior autologous stem cell transplantation (ASCT) for non-Hodgkin lymphoma (2). Patients developing secondary MDS experience poorer outcomes than those with primary MDS, possibly due to the previous exposure to DNA-damaging agents (2). Currently, allogeneic stem cell transplantation (alloSCT) is the only potentially curative treatment option for either MDS (2) or AML patients (3). Despite the availability of ASCT as a curative treatment option, there are a proportion of MDS patients who would benefit from observation until clear symptoms of anemia or other cytopenias appear due to age, performance status, or co-morbidities (2).

In order to compare new therapies with existing treatment options, a systematic review of the available evidence is warranted.

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

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

METHODS: MDS

The MEDLINE (OVID) database (1996 through October (week two) 2010) was systematically searched for evidence on October 21, 2010 using the strategy that appears in Appendix A. A total of 89 hits were obtained, and after excluding irrelevant papers according to a title and abstract review, 21 were ordered for full-text review. Of these 21, only four met the inclusion criteria and were retained.

METHODS: AML

The MEDLINE (OVID) database (1996 through October (week one) 2010) was systematically searched for evidence on October 21, 2010 using the strategy that appears in Appendix B. A total of 211 hits were obtained, and after excluding irrelevant papers according to a title and abstract review, 64 were ordered for full-text review. Of these 64, only 17 met the inclusion criteria and were retained.

Study Selection Criteria

Inclusion Criteria: MDS

Articles were selected if they were the following:

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

Inclusion Criteria: AML

Articles were selected if they were the following:

1. SRs with or without meta-analysis or clinical practice guidelines if evidence was obtained with an SR.
2. Fully published RCTs on patients with AML who received SCT that reported on survival outcomes and/or QoL.
3. Fully published non-randomized studies on patients with AML who received SCT that had an appropriate comparison group that reported on survival outcomes or QoL.
4. Reports published in English only.

Synthesizing the Evidence

While no pooling was planned, it would be considered if data allow.

Assessment of study quality

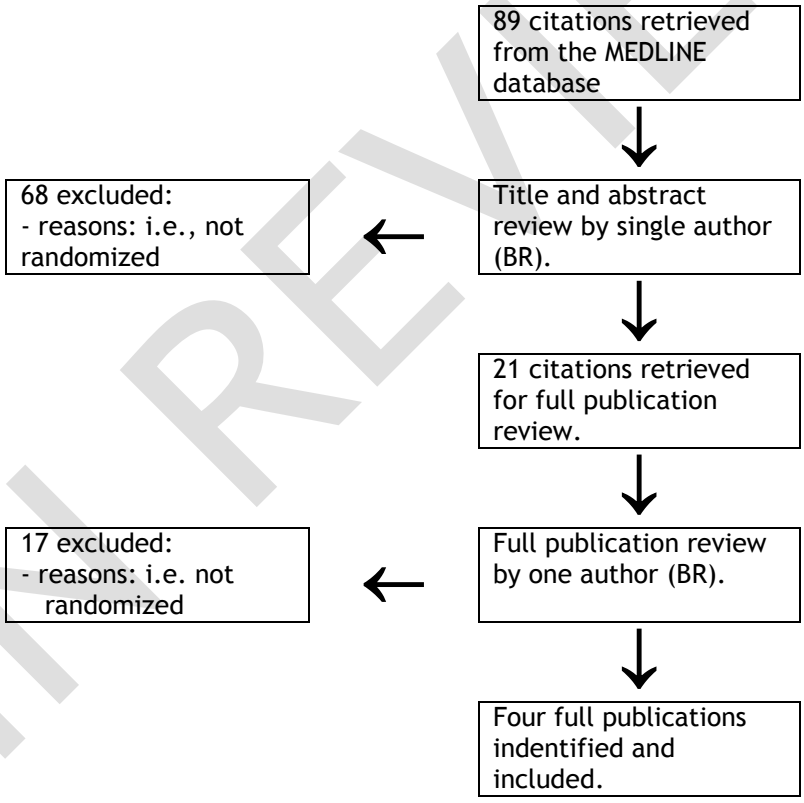
The quality of the included evidence was assessed as follows. For systematic reviews that would be used as the sole evidence base for our recommendations, or where solely an SR supported any specific recommendation, the Assessment of Multiple Systematic Reviews (AMSTAR) tool would be used to assess quality. For CPGs, the Appraisal of Guidelines for Research and Evaluation (AGREE) II Instrument would be used, but only if an adaptation of the recommendations was being considered.

Where recommendations from CPGs were not adapted, the evidence base in those CPGs would be informally assessed for completeness, and any relevant evidence within would be considered as a basis for recommendations in this report. Any meta-analysis would be assessed for quality using criteria similar to that used for RCTs, where appropriate. RCTs would be assessed for quality by examining the following seven criteria: the method of randomization, reporting of blinding, the power and sample size calculation, length of follow-up, reporting on details of the statistical analysis, reporting on withdrawals to treatment and other losses to follow-up, and reporting on the sources of funding for the research. Comparative, but non-randomized, evidence would be assessed according to the full reporting of the patient selection criteria, the interventions each patient received, and all relevant outcomes.

RESULTS: Literature Search and Quality of Evidence: MDS

An SR reported by Olianksy et al (4), a National Comprehensive Cancer Network (NCCN) CPG reported by Greenberg et al (5), and two retrospective cohort studies that reported on the use of SCT in the treatment of MDS and secondary AML were obtained.

Figure 1. Selection of studies investigating SCT in MDS from the MEDLINE search results.



Quality of Included Studies: MDS

Systematic Review

Although the SR reported by Olianksy et al (4) was not suitable for replacing the evidence base upon which to form recommendations, a formal assessment of quality was performed using the AMSTAR instrument. Details of the assessment can be

found in Appendix D. Overall, the SR was of high quality and was deemed a suitable source of evidence upon which to base recommendations.

Clinical Practice Guideline

As the CPG reported by Greenberg et al (5) was not suitable for adapting, no formal assessment of quality was performed, but recommendations appear in the Results section.

Retrospective Cohort Studies

The two retrospective studies were assessed for quality according to the following criteria: reporting differences in patient selection criteria, fully describing the interventions each patient received, and fully reporting all relevant outcomes. The retrospective cohort study reported by Martino et al (6) analyzed the data from 993 patients from 128 centres that had been registered in the European Group for Blood And Marrow Transplantation (EBMT) with a primary diagnosis of MDS or AML secondary to MDS between the years 1997 and 2001. Differences between the baseline characteristics of the standard myeloablative conditioning (SMC) group and the reduced-intensity conditioning (RIC) group were detected for median age (younger in SMC group; $p<0.001$), CMV risk (lower risk in SMC group; $p<0.005$); last French-English-British (FAB) disease classification (more refractory anemia with excess of myeloblasts in RIC and more refractory anemia with excess of myeloblasts in transformation; $p<0.05$); response to CT at transplantation (more untreated in RIC; more SMC in CR1; more than 10% myeloblasts in BM at transplant; more in RIC; $p=0.04$); prior autologous hematopoietic SCT (HSCT) (more in RIC group; $p<0.01$); stem cell source (bone marrow (BM) used more in SMC group; peripheral blood stem cells (PBSC) used more in RIC group; $p<0.001$); and median follow-up in survivors (longer in stem cell media (SMC); $p<0.05$). As the source of the data in this study was a registry database, the interventions that each patient received were well documented. The outcomes of graft-versus-host disease (GVHD) and OS were also well reported.

The retrospective cohort study reported by Al-Ali et al (7) analyzed the data from 593 consecutive patients with either MDS or secondary AML that received either an ASCT or alloSCT from a matched unrelated donor between the years 1991 and 2003. Differences in baseline characteristics were reported for age only (patients that received ASCT were older than those that received alloSCT; $p<0.001$). As the source of the data in this study was a registry database, the interventions that each patient received were well documented. The outcomes of OS, median survival, DFS, and TRM were also well reported.

RESULTS: Clinical Evidence: MDS

Four papers were obtained reporting on the use of SCT in the treatment of MDS, a systematic review (4), a CPG (5), and two retrospective studies (6,7).

Systematic Review

One systematic review by Oliansky et al (4), sponsored by the American Society for Blood and Marrow Transplantation (ASBMT), was retained. In this systematic review, the PubMed and MEDLINE databases, along with websites developed by the National Centre of Biotechnology Information were searched in January 2007 and updated in April 2008. Exclusion criteria included the following: published prior to 1990, fewer than 25 patients, not peer-reviewed, and non-comparative, as well as

letters to the editor, editorials, and CPGs. A total of 22 studies were included in this SR and were graded for quality according to the methods of Harbour & Miller.

Recommendations from that SR were as follows:

- There are sufficient data demonstrating a long-term curative outcome for related, unrelated, either or unspecified alloSCT.
- If a human leukocyte antigen (HLA)-matched allogeneic donor (sibling, other family member, unrelated individual, or cord blood) is available, then alloSCT is recommended. If an HLA-matched donor is not available, and induction therapy has achieved CR, ASCT can be considered, but only in the context of a clinical trial.
- Allogeneic PBSCT and BMT from related donors have similar outcomes in low-risk disease. Patients with high-risk disease may have a survival advantage with related-donor allogeneic PBSCT.

Clinical Practice Guideline

In the CPG reported by Greenberg et al (5), for the NCCN, recommendations were provided for supportive care, low-intensity therapy, hypo-methylating agents, immunosuppressive therapy, high-intensity therapy, therapy for lower-risk patients, therapy for high-risk patients, intensive CT, non-intensive CT, and intensive therapy using alloSCT. The recommendations on alloSCT were as follows:

- AlloSCT is an option if a suitable donor is available (either HLA-matched sibling or matched unrelated donor (MUD)) and the patient's marrow blast count is low enough (typically <10-20%), and in consideration of other factors such as patient age, performance status (PS), major co-morbidities, patient preferences, psychosocial status, and International Prognostic Scoring System (IPSS) status).
- HLA-matched sibling donor is preferred over MUD, but in selected patients the results are similar.
- Prior to transplantation, MAC is recommended in younger patients and RIC or non-myeloablative conditioning in older patients.

Retrospective Cohort Studies

The first retrospective cohort study, reported by Martino et al (6) and funded by the EBMT, included 836 patients who received SCT with an HLA-identical sibling donor allocated to either RIC or SMC. Results found a significant benefit with SMC in three-year relapse rate (HR, 1.64; $p<0.001$) but a benefit associated with RIC in three-year non-relapse mortality (HR, 0.61; $p=0.15$). No significant differences were found between RIC and SMC for OS or PFS.

The second retrospective cohort study, reported by Al-Ali et al (7), included 593 patients who received either HSCT from a MUD without prior chemotherapy (MUD-U), ASCT in first complete remission (auto-CR1), or HSCT from an MUD in first complete response (MUD-CR1). Results found significant benefits with MUD-U compared with auto-CR1 for the three-year OS (auto-CR1 HR: 1; MUD-U HR: 2.3; $p<0.001$) but no difference was detected between auto-CR1 and MUD-CR1. No differences were detected between the groups in median survival or DFS. Significant differences were detected between the groups for TRM, with the allogeneic transplants being associated with significantly higher risk for death compared with the autologous transplant (auto-CR1 HR: 1; MUD-U HR: 7.4; MUD-CR1 HR: 3.7; $p<0.001$). This study

was performed by the Chronic Leukemia Working Party (CLWP) of the EBMT, and the results appear in Table 1.

Table 1. MDS: three-year OS, median survival, three-year DFS, three-year TRM, and aGVHD.

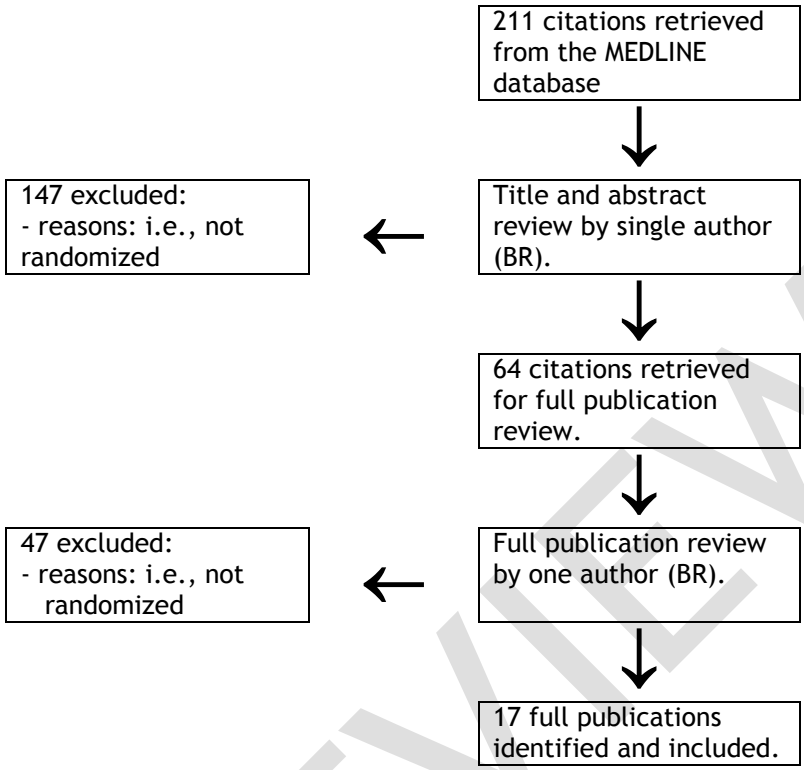
Authors, year	**Arm 1 (N)**	**Arm 2 (N)**	**Arm 3 (N)**	**Three-year overall survival % (95%CI)**	**Median survival [Months] (95%CI)**	**Three-year DFS % (95%CI)**	**aGVHD % (95%CI)**
Martino R et al, 2006 (6)	RIC (215)	SMC (621)	-	RIC: 41 SMC: 45 p=0.8	NR	NR	RIC: 43 SMC: 58 p<0.001
Authors, year	Arm 1 (N)	Arm 2 (N)	Arm 3 (N)	Three-year overall survival Hazard Rate [HR] (95%CI)	Median survival [Months] (95%CI)	Three-year DFS % (95%CI)	Three-year TRM % (95%CI)
Al-Ali HK et al, 2007 (7)	AutoCR1 (290)	MUD-U (167)	MUD-CR1 (136)	AutoCR1: 1 MUD-U: 2.3 (1.6-3.3) MUD-CR1: 1.2 (0.8-1.7) [p<0.001 for all compared with AutoCR1]	AutoCR1: 22 (13-32) MUD-U: 9 (4-15) MUD-CR1: 33 (0-81)	AutoCR1: 1 MUD-U: 1.4 (1.0-2.0) MUD-CR1: 0.8 (0.6-1.1) [p<0.01 for all compared with AutoCR1]	AutoCR1: 1 MUD-U: 7.4 (4.3-12.8) MUD-CR1: 3.7 (2.2-6.2) [p<0.001 for all compared with AutoCR1]

Note: DFS, disease-free survival; TRM, treatment-related mortality; AutoCR1, Autologous hematopoietic cell transplantation in first complete remission; MUD-U, Allogeneic hematopoietic cell transplantation from a matched unrelated donor without prior chemotherapy; MUD-CR1, Allogeneic hematopoietic cell transplantation in first complete remission; aGVHD, acute graft-versus-host disease.

RESULTS: Literature search and quality of evidence: AML

Seventeen papers reporting on the results of SCT in AML were obtained (8-24), comprising three SRs (11,15,20), three CPGs (12,18,19), three meta-analyses (9,10,14), one prospective cohort study (22), and seven retrospective cohort studies (8,13,16,17,21,23,24).

Figure 2. Selection of studies investigating stem cell transplantation in AML from the MEDLINE search results.



Quality of Included Studies: AML

Systematic Reviews

None of the three SRs obtained (11,15,20) were suitable for forming the evidence base upon which to make our recommendations. However, one of the SRs (15) was the sole source of evidence supporting a recommendation, and for this SR, quality was assessed using the AMSTAR instrument. Details of the assessment can be found in Appendix D. Overall, the SR was of high quality and was deemed a suitable source of evidence upon which to base recommendations.

Clinical Practice Guidelines

As none of the three CPGs obtained (12,18,19) were suitable for adapting the recommendations, no formal assessment of quality was performed, but a description of the evidence included in each CPG is described in the Results section. A summary of the recommendations along with the type of supporting evidence appears in Appendix D.

Meta-analyses

Two meta-analyses were obtained in this review (9,10). The first meta-analysis, reported by Cornelissen et al (10), pooled data from three HOVON-SAKK trials and then pooled those results with the results from three other trials (MRC, EORTC, and BGMT). The main outcomes of interest in this meta-analysis were OS and DFS, both measured starting from the date consolidation treatment began. Individual patient data were not available. OS was calculated as death from any cause, with patients censored from their date of last contact. The event for DFS was death in the

first CR (considered TRM) or relapse. Relapse and TRM were considered competing risks. Outcomes (OS, DFS, TRM, and relapse) were calculated based on the intent-to-treat (ITT) principle, using a multivariate Cox regression analysis comparing ASCT with alloSCT and expressed using HRs. Treatment group comparisons were made using the log-likelihood ratio test. This meta-analysis was of acceptable quality, with appropriate analyses for the comparisons and with all the relevant outcomes reported. The Queen Wilhelmina Fund (KWF), Kankerbestrijding, provided funding for this research.

The second meta-analysis, reported by Basara et al (9), pooled data from two East German Study Group (OSHO) trials (AML 96 and AML 02). The main outcomes of interest were OS and LFS, both measured from the date of the first CR estimated using the ITT principle and the Kaplan-Meier method compared between treatment groups using the log-rank test. Individual patient data were not available. The event for OS was death from any cause, censored from the date of last contact. Risk factors for death were examined using a proportional hazards regression model, with acute GvHD, rejection and relapse being considered competing events. Various patient and treatment factors were examined using a step-wise multivariate analysis, which was reported using two-sided p-values. This meta-analysis was of acceptable quality, with appropriate analyses for the comparisons and with all the relevant outcomes reported. The funding source for the meta-analysis was not reported.

Prospective Cohort Study

The prospective study was assessed for quality according to the following criteria: reporting differences in patient selection criteria, fully describing the interventions each patient received, and fully reporting all the relevant outcomes. In the prospective study reported by Sakamaki et al (22), patients were allocated into either a donor or no-donor treatment group. These groups were comparable, with no significant differences being reported. As this was a prospective study following a protocol (JALSG AML97), the interventions were both well described and well reported. The outcomes OS, DFS, and TRM were calculated according to the ITT principle, using the Kaplan-Meier method for time-to-event outcomes and with comparisons between groups being made using a log-rank test.

Retrospective Cohort Studies

The retrospective studies were assessed for quality according to the following criteria: reporting differences in patient selection criteria, fully describing the interventions each patient received, and fully reporting all relevant outcomes.

The study reported by Lazarus et al (16) compared autoSCT with unrelated donor (URD) SCT in patients with AML. Differences in patient characteristics between the two groups were reported in age (with autologous patients more likely to be younger than 10 years old), and patients who received URD SCT were more likely to be male, to have a PS < 90%, to have poor cytogenetics, to require more than eight weeks of treatment to achieve CR1, to have received total body irradiation for pretransplant conditioning, and to have been transplanted recently. The interventions each patient received were reported as entered into the Centre for International Blood & Marrow Transplant Research (CIBMTR). The outcomes TRM, clinical leukemia relapse, LFS, and OS were calculated using the Kaplan-Meier method and compared between groups using the log-rank test.

The study reported by Herr et al (13) compared RIC followed by HLA-identical allogeneic PBSCT with autologous PBSCT in patients with AML. Differences in patient

characteristics between groups were reported in sex (more males in RIC group, p=0.001), proportion of patients with advanced disease (more in RIC group, p<0.0001), time from diagnosis to transplantation (longer in RIC group, p<0.001), and cytogenetics (poorer in RIC group, p<0.05). The intervention each patient received was reported as entered into the EBMT registry database after being checked for compliance and for duplicate and/or overlapping reports. The outcomes OS, non-relapse mortality (NRM), relapse incidence (RI), and LFS were calculated using the Kaplan-Meier method and compared between groups using the log-rank test.

The study reported by Loh et al (17) compared alloSCT with ASCT in Asian patients less than 46 years of age. No differences were reported in patient characteristics, except that there were more alloSCT recipients with unknown karyotype results compared with ASCT patients (34.6% versus (vs.) 10.3; p=0.017). The intervention each patient received was reported as entered into the single institution's records. The OS and DFS outcomes were calculated using the Kaplan-Meier method and compared between groups using the log-rank test. Time-to-event outcomes with competing risks (i.e., NRM, RI, and GVHD) were calculated using cumulative-incidence curves.

The study reported by Schlenk et al (23) compared HLA-matched sibling SCT with CT alone in patients with t(8;21) AML. The only difference in patient characteristics reported was in age, with alloSCT patients being younger than CT patients (32 vs. 42 years of age; p<0.001). The intervention each patient received was as entered in the CIBMTR. Time-to-event outcomes were calculated using the Kaplan-Meier method, but the method of comparison between the two groups was not reported. In order to minimize the potential bias in survival outcomes of the transplanted group (transplant recipients have to survive long enough to receive the transplant), left-truncated Cox regression models and left-truncated cumulative incidence estimates were used.

The study reported by Atska et al (8) compared unrelated cord blood (CB) with unrelated BM, both following myeloablative conditioning (MAC) in patients with AML. Differences in patient characteristics were reported for gender (female/male ratio dissimilar compared to treatment received, CB vs. BM, 54% vs. 38%; p<0.001), and for donor-patient sex-match rate (CB vs. BM, 48% vs. BM, 48% vs. 69%; p<0.001). CB recipients were also more likely to have advanced disease at the time of transplantation (relapse or induction failure, CB vs. BM, 47% vs. 31%; p=0.003). The intervention each patient received was as entered in the Japan Cord Blood Bank Network (JCBBN) and the Japan Marrow Donor Program (JMDP) databases. While this study did include both AML and ALL patients, separate analyses were performed for each. The outcomes OS and LFS were calculated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis was performed to investigate the influences of the patient and treatment characteristics in a Cox proportional hazards regression model.

The study reported by Ringdén et al (21) compared RIC with MAC in AML patients that received unrelated alloSCT. Differences in patient characteristics between the groups were reported for age (RIC patient were older; p<0.05) and time from diagnosis to transplant in CR (longer interval for RIC patients; p<0.05). The intervention each patient received was as entered into the Acute Leukemia Working Party (ALWP) of the EBMT database. For the time-to-event outcome of LFS, Kaplan-Meier curves were calculated and compared using the log-rank test. Multivariate analysis using patient and transplant variables were done using the Cox proportional hazards model.

The study reported by Shin et al (24) compared alloSCT with high-dose CT after CR1 in patients with AML. Differences in patient characteristics were reported in sex (more males in alloSCT group, 68% vs. 32%; p0.004), median lactate dehydrogenase (LDH) (higher in alloSCT group, 968.5 vs. 702; p=0.034). The intervention as received by each patient was obtained from questionnaires distributed to each of the 18 participating hospitals. The time-to-event outcomes of OS and DFS were calculated using the Kaplan-Meier method and compared using the log-rank test. The potential bias arising from the time to post-remission treatment in the transplant group was investigated with a semi-landmark analysis. A multivariate survival analysis using patient characteristics as variables was carried out using the Cox proportional hazards model.

RESULTS: Clinical Evidence: AML

Sixteen papers reporting on the results of SCT in AML were obtained (8-24), including three SRs (11,15,20), three CPGs (12,18,19), two meta-analyses (9,10), one prospective cohort study (22) and seven retrospective cohort studies (8,13,16,17,21,23,24).

Systematic Reviews

Three SRs were retained (11,15,20). The first, by Efficace et al (11), reported on the Health-related Quality of Life (HRQoL) results of two RCTs in AML that included a total of 636 patients. The first RCT (155 patients) compared alloSCT versus ASCT versus CT, and results were significantly poorer outcomes associated with SCT (CT was superior to alloSCT, which was superior to ASCT) in both general and specific HRQoL domains ($p<0.05$). The second RCT (481) compared ASCT versus CT alone, and results were significantly different in favour of CT for mouth dryness only ($p<0.05$).

The second, by Oliansky et al (20), was a systematic review of the evidence available on SCT combined with CT for the treatment of AML. Findings appear in Appendix D.

The third, by Koreth et al (15), was an SR of the evidence for AML in CR1, where patients received alloSCT, ASCT, CT, or any combination of the three. Outcomes of interest were OS and RFS. Evidence was obtained from 24 trials with a total of 6,007 patients. The SR found a significant RFS benefit associated with alloSCT, based on pooling data from 18 trials (HR, 0.80; 95%CI, 0.74 to 0.86; $p<0.01$), and a significant OS benefit associated with alloSCT, based on pooling data from 15 trials (HR, 0.90; 95%CI, 0.82-0.97; $p<0.01$).

Subgroup analyses were performed for both RFS and OS according to patient risk (either good, intermediate, or poor risk). The RFS subgroup analysis continued to detect significant benefits in favour of alloSCT for both intermediate and poor risk patients ($p<0.01$), but no difference was detected with good risk patients. The OS subgroup analysis also detected significant benefits in favour of alloSCT for intermediate and poor risk patients ($p<0.01$), but not for good risk patients.

Clinical Practice Guidelines

Three CPGs were obtained (12,18,19), sponsored by ESMO (12), the Italian Society of Hematology and affiliated societies (SIES and GITMO) (18), and the NCCN (19), respectively. Summaries of the recommendations made for each of these CPGs appear in Appendix D.

The first CPG, reported by Fey et al (12), provided treatment recommendations for adults with AML for both the induction CT phase and the consolidation therapy

phase. That CPG made recommendations based on evidence that ranged from single well-designed RCTs to expert consensus, but no description of the methods used to obtain the included evidence was described.

The second CPG, reported by Morra et al (18), provided recommendations for patients with a diagnosis of de novo AML. In that CPG, the body of evidence that informed the recommendations ranged from meta-analyses to expert consensus. An SR methodology was used to obtain the evidence in this CPG. The PubMed database, the Cochrane library, and the major hematology, oncology, and general medicine journals were searched for evidence from 1995 through to 2008. Evidence was graded according to the Scottish Intercollegiate Guidelines Network (SIGN) criteria.

The third CPG, reported by O'Donnell et al (19), provided comprehensive recommendations for all AML patients. The evidence supporting the recommendations in that CPG was comprised of well-designed RCTs. No description of the methods used to obtain the included evidence was described.

Meta-analyses

Two meta-analyses were obtained (9,10). The first, by Cornelissen et al (10), pooled data from three HOVON-SAKK trials (AML 4, AML 29 and AML 42) and then pooled those results with those from three other trials (an MRC, EORTC, and BGMT trial) that compared alloSCT with ASCT, which ran from 1987 through 2004 and accrued a total of 2,287 patients. The outcomes of interest were OS, DFS, and TRM. Significant differences were found in favour of ASCT for both four-year DFS (64% vs. 52%, $p<0.001$) and four-year TRM (4.5% vs. 21%; $p<0.001$). No differences were detected for OS. A subgroup analysis by risk found no differences for good risk patients, but, for intermediate and poor risk patients, significant benefits were associated with alloSCT for DFS ($p<0.05$) and with ASCT for TRM ($p<0.05$). Another subgroup analysis done by age found significant benefits associated with alloSCT in OS and DFS ($p<0.05$), but significant benefits associated with ASCT for TRM ($p<0.05$) for patients younger than 40 years of age. For patients older than 40 years of age, the only significant difference detected was in TRM, with a benefit being associated with ASCT ($p<0.05$).

The second meta-analysis, by Basara et al (9), pooled data from two East German Study Group (OSHO) trials (AML 96 and AML 02) that compared alloSCT with ASCT + CT and that ran from 1996 through 2002, accruing a total of 708 patients. Outcomes of interest were OS and LFS. Significant differences were detected in favour of alloSCT for both OS ($p=0.005$) and LFS ($p=0.009$) at two years. In a multivariate analysis, the factors associated with a better OS and longer LFS were those of being younger ($p=0.008$) and of receiving an allogeneic transplant.

Table 2. Meta-analyses results for SCT in AML.

Authors, year	Patient population	Treatments	OS %	LFS/DFS %	TRM %
Cornelissen JJ et al, 2007 (10) Pooled analysis of three trials (HOVON/SAKK)	Children and adults 50 years of age and younger that had experienced a CR after two rounds of induction CT	ASCT (599)	4 year OS: 54	4 year DFS: 64	4.5
		AlloSCT (326)	48	52	21
		p-value	p=0.09	**p<0.001**	**p<0.001**
Basara N et al,	Children and		2 year OS:	2 year LFS:	-

2009 (9) Reanalysis of AML 96 and AML 02 trials	adults with de novo and secondary AML	CT+ASCT (30)	24 (16-32)	19 (11-27)	
		AlloSCT (47)	52 (43-61)	42 (34-50)	-
		p-value	**p=0.005**	**p=0.009**	-

Note: CR, complete response; CT, chemotherapy; ASCT, autologous stem cell transplantation; alloSCT, allogeneic stem cell transplantation; OS, overall survival; LFS, leukemia-free survival; DFS, disease-free survival; TRM, treatment-related mortality; AML, acute myeloid leukemia.

Prospective Cohort Study

Sakamaki et al (22) found significant benefits in favour of alloSCT compared with ASCT in the relative risk for eight-year DFS (39% vs. 19%; p=0.016).

Table 3. Prospective cohort study results for SCT in AML.

Authors, year	**Patient population**	**Treatments**	**OS %**	**LFS/DFS %**	**TRM %**
Sakamaki H et al, 2010 (22) JALSG AML97 study	Children and adults with de novo AML	ASCT (92)	RR±SE 8 year OS: 29 (23-35)	RR±SE 8 year DFS: 19 (15-23)	RR±SE 8 year TRM: 17 (10-24)
		AlloSCT (73) matched sibling donor (PBSCT or BMT)	46 (39-53)	39 (33-45)	16 (10-22)
		p-value	p=0.088	**p=0.016**	p=0.959

Note: OS, overall survival; LFS, leukemia free survival; DFS, disease free survival; TRM, treatment related mortality; AML, acute myeloid leukemia; ASCT, autologous stem cell transplant; RR, relative risk ratio; SE, standard error of the estimate; alloSCT, allogeneic stem cell transplantation; PBSCT, peripheral blood stem cell transplantation; BMT bone marrow transplantation.

Retrospective Cohort Studies

Seven retrospective cohort studies were obtained (8,13,16,17,21,23,24), and the details appear in Table 4. Six of the seven reported on OS (8,13,16,17,23,24), all reported on either LFS or DFS, and four reported on TRM (8,16,17,23). Significant differences were found in three of the six studies that reported on OS, (8,16,23). Lazarus et al (16) reported a five-year OS benefit associated with ASCT over unrelated alloSCT (p<0.001), Schlenk et al (23) reported an OS benefit associated with either alloBMT or alloPBSCT over CT alone in AML patients who did not experience the loss of a sex chromosome, and Atsuka et al (8) reported a one-year OS benefit associated with BMT over CB (p<0.001).

Significant differences were found in two of the seven studies that reported on either LFS or DFS (16,21). Lazarus et al (16) reported a five-year LFS benefit associated with ASCT over unrelated alloSCT (p<0.001). Ringdén (21) reported two-year LFS benefits associated with MAC followed by alloSCT over RIC followed by alloSCT (p=0.03).

Significant differences were found in three of the four studies that reported on TRM (8,16,23). Lazarus et al (16) reported a 100-day TRM benefit associated with ASCT over unrelated alloSCT (p<0.001), Schlenk et al (23) reported a TRM benefit associated with CT alone compared with either alloBMT or alloPBSCT (p<0.001), and Atsuka et al (8) reported a benefit in TRM associated with BMT compared with CB transplants (p<0.004).

Table 4. Retrospective cohort study results in AML.

Authors, year	Patient population	Treatments	OS %		LFS/DFS %	TRM %
Lazarus, HM et al, 2006 (16)	Children and adults with AML in CR1 or CR2	ASCT (668)	5 year OS: 51 (47-55)		5 year LFS: 46 (42-50)	100 d TRM: 6 (5-8)
		AlloSCT (unrelated) (476)	36 (31-40)		34 (29-38)	31 (26-35)
		p-value	**p<0.001**		**p<0.001**	**p<0.001**
Herr AL et al, 2007 (13)	Adult patients 50 years or older with *de novo* AML	AutoPBSCT (1369)	2 year OS: 50 (48-52)		2 year LFS: 39 (37-41)	-
		AlloPBSCT (361)	54 (51-57)		42 (39-45)	-
		p-value	p=0.86		p=0.99	-
Loh Y et al, 2007 (17)	Children and adults with AML 45 years or younger in CR1	ASCT (29)	15 year OS: 51 (32-70)		15 year DFS: 43 (24-62)	48.2
		AlloSCT (52)	55 (42-69)		54 (41-68)	44.2
		p-value	p=0.92		p=0.56	p=NR
Schlenk RF et al, 2008 (23)	Children and adults with t(8:21) AML in CR1		No LOS	LOS	RFS RR:	TRM RR:
		CT alone (132)	OS RR: 1.00	OS RR: 1.00	1.00	1.00
		AlloBMT (104) AlloPBSCT (14)	3.05 (1.51-6.15)	0.90 (0.47-1.70)	1.29 (0.84-1.98)	6.76 (2.95-15.45)
		p-value	**p=0.002**	p=0.74	p=0.24	**p<0.001**
Atsuta Y et al, 2009 (8)	Children and adults with AML eligible for SCT with unrelated donor cord blood (CB) or BMT	CB (173)	1 year OS: 51		1 year LFS: 27	1 year TRM: 30
		BMT (311)	69		20	19
		p-value	**p<0.001**		p=0.067	**p=0.004**
Ringdén O et al, 2009 (21)	Children and adults with AML	AlloRIC (149)	-		2 year LFS: 37 (32-42)	-
		AlloMAC (972)	-		43 (41-45)	-
		p-value	-		**p=0.03**	-
Shin HJ et al, 2010 (24)	Children and adults with AML in CR1	CT (78)	5 year OS: 66.2 (59.8-72.6)		5 year DFS: 59.4 (53.2-65.6)	-
		AlloSCT (60)	69.6 (62.4-76.8)		72.6 (66.7-78.5)	-
		p-value	p>0.05		p>0.05	-

Note: OS, overall survival; LFS, leukemia free survival; DFS, disease free survival; TRM, treatment-free survival; AML, acute myeloid leukemia, CR1, first complete response; CR2, second complete response; ASCT, autologous stem cell transplant; alloSCT, allogeneic stem cell transplant; PBSCT, peripheral blood stem cell transplantation; LOS, loss of a sex chromosome; RR, relative risk ratio; RIC, reduced intensity chemotherapy; MAC, myeloablative conditioning.

DISCUSSION

The SCT Steering Committee developed the current recommendations based on those in the 2009 report (25), along with the updated data presented in this report and consensus discussion.

The terms 'selected' or 'eligible' were removed from the current set of recommendations for both MDS and AML. To define a priori what selection or eligibility criteria clinicians could use to determine transplant eligibility was no longer felt to be appropriate or possible. Instead, it was strongly felt that patients with MDS or AML be sent for consultation to a regional transplant centre to determine whether a transplant would be appropriate, based on a review of the clinical circumstances, co-morbidities, and patient preferences.

The SCT Steering Committee acknowledges the difficult decision-making process around SCT in MDS and AML. In MDS, in particular, the timing of the transplant may be problematic. The decision analysis by Cutler et al (26) has found that in lower risk MDS (low or INT-1 risk groups), the maximal benefits are seen when the transplantation is performed after diagnosis but prior to leukemic transformation. For higher risk MDS (INT-2 or higher) a transplantation at diagnosis is associated with maximal survival benefits. In these recommendations we do not offer specific guidance regarding the timing of a transplant in MDS; rather, that timing is best decided in consultation with the transplant service. Despite the availability of 5-azacytidine, it was acknowledged that an allogeneic transplant in MDS is the only potentially curative therapy.

Regarding allogeneic transplant in AML in either first remission with high or intermediate risk features or in second or subsequent remission, the committee supported the standard indication for transplantation in those patients. Patients with those features should be referred as soon as possible for assessment to a centre that performs allogeneic transplants.

There was more discussion regarding allogeneic transplantation for patients with AML who are not in remission. The number of such potential patients is not trivial, given the less than ideal results of current CT in the treatment of AML. The current practice of transplanting those patients varies across the Province of Ontario. The SCT Steering Committee reviewed two recent publications, one by Duval et al (27) and the other by Craddock et al (28). In the Duval et al publication, the CIBMTR database was analyzed from 1995 to 2004 for patients with acute leukemia not in remission that were treated with an allogeneic transplant. In patients with AML, the following five risk factors were found to influence OS: first CR duration of less than six months; circulating blasts; non-HLA identical sibling; Karnofsky performance score <90, and poor risk cytogenetics. Three-year OS varied from 6% in those with at least three factors to 42% in those with no risk factors. In the paper by Craddock et al, 168 patients were reviewed from the EBMT registry that had received a matched unrelated transplant for refractory AML. In this study, the following three risk factors were prognostic on multivariate analysis: greater than two induction courses, pre-transplant bone marrow blasts of more than 38.5% (the median in this study), and negative patient CMV serology. The five-year OS was between 44% for those with no risk factors to 0% for those with three risk factors. Based on such data, the SCT Steering Committee agreed that there are selected patients with refractory AML who may derive benefit from an allogeneic transplant, and that, given the complexity of the risks versus benefits, these patients should also be reviewed in a transplant centre as soon as possible.

As the use of alternative donors or sources of stem cells is a rapidly changing area in transplantation, it was not possible to provide definitive comments about the applicability of specific donor sources at this time. However, the committee did acknowledge the increasing potential use of haploidentical donors and CB products for AML and MDS transplants.

CONCLUSIONS

Patients with MDS or AML should be reviewed at a regional transplant centre to determine their transplant eligibility. Our current recommendations have not substantially changed compared to the previous report. In summary, alloSCT is a recommended option for patients with MDS, as it represents the only potentially curative therapy. For patients with AML, the committee was unanimous in supporting the recommendation for allogeneic transplant in those AML patients with intermediate or high-risk features in first remission, or patients in second or greater remission. Autologous transplantation was only recommended for APL in a molecularly negative second remission. The committee felt that a number of patients having AML not in remission might benefit from allogeneic transplantation, depending on their clinical and laboratory features, but being able to set predetermined criteria was difficult. Given the high-risk nature of their disease, particularly when not in remission, timely referral to a transplant centre is particularly important.

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

Protocol ID	Title, details
NCT00342316	Reduced Intensity Conditioning Transplantation Versus Standard of Care in Acute Myeloid Leukemia Study ID: TRALG1/02 Status: recruiting Updated: August 3, 2010
NCT01246752	Haematopoietic Stem Cell Transplantation (HSCT) in Comparison to Conventional Consolidation Therapy for Patients With Acute Myeloid Leukemia (AML) (Intermediate Risk) <= 60y. After First CR Study ID: TUD-ETAL-1-045 Status: recruiting Updated: April 19, 2011
NCT00630565	Stem Cell Transplant in Treating Patients With Acute Myeloid Leukemia Study ID: MT2006-13, 0607M89052 Status: recruiting Updated: June 20, 2011
NCT00266136	Biology and Treatment Strategy of AML in Its Subgroups: Multicenter Randomized Trial by the German Acute Myeloid Leukemia Cooperative Group (AMLCG) Study ID: AMLCG 99, BMBF 01 GI 02070 Status: recruiting Updated: January 14, 2010
NCT00454480	Combination Chemotherapy With or Without Gemtuzumab Ozogamicin or Tipifarnib in Treating Patients With Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndromes Study ID: CDR0000526121, UHW-AML16, EU-20677, ISRCTN11036523, EUDRACT-2005-002846-14, MREC-CU106 Status: recruiting Updated: August 5, 2011
NCT01339910	Reduced Intensity Conditioning Versus Myeloablative Conditioning for Acute Myeloid Leukemia or Myelodysplastic Syndrome (BMT CTN 0901) Study ID: 709, U01HL069294-05, 0901 Status: recruiting Updated: April 20, 2011

NCT00568633	Allogeneic HCT Using Nonmyeloablative Host Conditioning With TLI & ATG vs. SOC in AML Study ID: SU-11122007-874, 97843, BMT190 Status: recruiting Updated: April 23, 2011
NCT00822393	Clinical Phase III Trial Treosulfan-based Conditioning Versus Reduced-intensity Conditioning (RIC) Study ID: MC-FludT.14/L, EudraCT-No.: 2008-002356-18 Status: recruiting Updated: June 9, 2011
NCT01203228	Dose-reduced Versus Standard Conditioning in MDS/sAML (RICMAC) Study ID: 2005-002011-24, EBMT 42205525 Status: recruiting Updated: August 4, 2011
NCT00682396	Dose-Reduced Versus Standard Conditioning Prior Allo SCT for MDS/sAML Patients Study ID: RICMAC, EBMT 42205525 Status: recruiting Updated: April 5, 2009
NCT00766779	HCT Versus CT in Elderly AML Study ID: 2007-003514-34, EBMT-ALWP01/2008 Status: recruiting Updated: August 15, 2011

CONFLICT OF INTEREST

The authors of this recommendation report disclosed potential conflicts of interest relating to the topic of this special advice report. Three of the authors reported no conflicts (TK, RBR, CB). One author reported being a PI on a related trial (IW), and another reported attending an out-of-country request hearing as a patient advocate (AS).

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UPDATING

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

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Appendix A. MDS literature search strategy.

1 exp Myelodysplastic Syndromes/
2 myelodysplasia.mp.
3 MDS.mp.
4 exp Preleukemia/
5 or/1-4
6 exp Bone Marrow Transplantation/
7 exp Stem Cell Transplantation/
8 exp Peripheral Blood Stem Cell Transplantation/
9 or/6-8
10 5 and 9
11 letter.pt.
12 comment.pt.
13 editorial.pt.
14 or/11-13
15 exp Randomized Controlled Trial/
16 randomised controlled trial.mp.
17 exp Clinical Trial/
18 Comparative Study/
19 or/15-18
20 pooling.mp.
21 pooled analysis.mp.
22 exp Meta-Analysis/
23 meta-analyses.mp.
24 systematic review.mp.
25 health technology assessment.mp.
26 exp Evidence-Based Medicine/
27 clinical practice guideline.mp. or exp Practice Guideline/
28 or/20-27
29 19 or 28
30 29 not 14
31 10 and 30
32 limit 31 to (english language and humans and yr="2006 -Current") (87)

Appendix B. AML literature search strategy.

1 exp Leukemia, Myeloid, Acute/
2 acute myeloid leukemia.mp.
3 acute myelogenous leukemia.mp.
4 AML.mp.
5 or/1-4
6 exp Bone Marrow Transplantation/
7 exp Stem Cell Transplantation/
8 exp Peripheral Blood Stem Cell Transplantation/
9 or/6-8
10 5 and 9
11 letter.pt.
12 comment.pt.
13 editorial.pt.
14 or/11-13
15 exp Randomized Controlled Trial/
16 randomised controlled trial.mp.
17 exp Clinical Trial/
18 Comparative Study/
19 or/15-18
20 pooling.mp.
21 pooled analysis.mp.
22 exp Meta-Analysis/
23 meta-analyses.mp.
24 systematic review.mp.
25 health technology assessment.mp.
26 exp Evidence-Based Medicine/
27 clinical practice guideline.mp. or exp Practice Guideline/
28 or/20-27
29 19 or 28
30 29 not 14
31 10 and 30
32 limit 31 to (english language and humans and yr="2007 -Current") (151)

Appendix C. Development & review

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

TENTATIVE RECOMMENDATIONS: MYELODYSPLASTIC SYNDROME (MDS)[1]
[Replaced with Definitive Recommendations (see below)]

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

TENTATIVE RECOMMENDATIONS: ACUTE MYELOID LEUKEMIA (AML)[1]
[Replaced with Definitive Recommendations (see below)]

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.

[1]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].

DEFINITIVE RECOMMENDATIONS AND SUPPORTING EVIDENCE

MYELODYSPLASTIC SYNDROME (MDS)
Allogeneic transplantation is an option for patients with MDS. This is the only potentially curative therapy for MDS.
Evidence: • One systematic review comprising a total of 22 studies demonstrated a long-term curative outcome for related, unrelated, either or unspecified allogeneic SCT (1).
Autologous stem cell transplantation is not recommended for patients with MDS.
Evidence: • One systematic review comprising a total of 22 studies did not detect any benefit associated with autologous SCT, and does not recommend it outside of a clinical trial (1).

ACUTE MYELOID LEUKEMIA (AML)
First complete remission:
Allogeneic transplantation is a treatment option for patients with AML in first complete remission (CR1) with high-risk features including intermediate or high-risk cytogenetic or molecular phenotypes, high-risk clinical features at presentation, and secondary or treatment-related AML.

Evidence:

- One systematic review (2), comprising 24 clinical studies involving 6,007 patients with AML in CR1 comparing allogeneic SCT, autologous SCT, chemotherapy (CT), or any combination of the three found a significant RFS and OS benefit associated with allogeneic SCT. That review performed subgroup analyses for both RFS and OS according to patient risk (either good, intermediate, or poor risk) and significant benefits in favour of allogeneic SCT for both intermediate and poor risk patients ($p<0.01$) were detected, but no difference was detected with good risk patients. The OS subgroup analysis also detected significant benefits in favour of allogeneic SCT for intermediate and poor risk patients ($p<0.01$), but not for good risk patients.
- One meta-analysis (3), that pooled data from two trials (AML 96, AML 02) that compared allogeneic SCT with autologous SCT with CT including a total of 708 patients detected significant differences in favour of allogeneic SCT for both OS and LFS at two years. In a multivariate analysis, factors associated with better OS and longer LFS were being younger ($p=0.008$), and receiving an allogeneic transplant.
- One prospective cohort study (4) found significant benefits in favour of allogeneic SCT compared with autologous SCT in the relative risk for eight year DFS.

Autologous stem cell transplantation is not recommended for patients with AML in first complete remission.

Evidence:

- While associated with more favourable TRM rates, if long-term survival is the primary outcome of interest then there is no evidence to support the use of autologous SCT in first complete remission.

Beyond first complete remission:

Allogeneic transplantation is the recommended option for patients with AML who achieve a second or subsequent remission.

Evidence:

- One Clinical Practice Guideline (5) recommended that if CR only occurs after a second course of induction therapy myeloablative allogeneic SCT from a fully-matched sibling donor is recommended regardless of risk if the patient is under 55 years of age and has no other co-morbidities

There is insufficient evidence to support the use of autologous stem cell transplantation for patients with AML in second or subsequent remission.

Evidence:

- If long-term survival is the primary outcome of interest then there is no evidence to support the use of autologous SCT in second or subsequent remission.

Autologous transplantation is recommended for acute promyelocytic leukemia (APL) in a molecularly-negative second remission.

Evidence:

- No evidence was obtained in this update of the 2009 report (6), and the Expert Panel continues to support this recommendation.

Select patients with AML not in remission may derive benefit from allogeneic transplant.

Evidence:

- One Clinical Practice Guideline (7) recommended that when a patient does not experience a CR, then that patient should be offered entry into a clinical trial, or reduced intensity allogeneic SCT within a clinical trial setting, or Best Supportive Care (BSC).

[1]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] (6).

Appendix D. Summary of the findings from systematic reviews and recommendations from clinical practice guidelines.

Systematic review findings from Oliansky et al (2008).

Indication	Recommendation
ASCT versus CT in CR1	No recommendation could be made based on the evidence reviewed
AlloSCT versus CT in CR1	If survival is the main outcome of interest, alloSCT is recommended over CT for patients <55 years of age with high risk cytogenetics
SCT versus CT in CR2	AlloSCT and ASCT are both recommended over CT. If there is an available donor, alloSCT is recommended over ASCT
AlloSCT versus ASCT	HLA-matched related donor is preferred over ASCT. There are no data to recommend unmatched alloSCT over ASCT
ASCT: PBSCT versus BMT	PBSCT is recommended over BMT due to early mortality and safety differences, however long-term follow-up is required before recommendations can be made regarding survival outcomes
AlloSCT: related versus unrelated	HLA-matched related donor is preferred over ASCT, but HLA-matched unrelated donor SCT may provide equivalent outcomes

Note: ASCT, autologous stem cell transplantation; CT, chemotherapy; CR1, first complete response; alloSCT, allogeneic stem cell transplantation; CR2, second complete response; PBSCT, peripheral blood stem cell transplantation; BMT, bone marrow transplantation.

Guideline recommendations from Fey et al (2009).

Treatment phase	Recommendations
Induction chemotherapy	• Should include anthracycline and cytosine arabinoside (supported by at least one well-designed experimental study). • Patients that fail after one or two cycles of this are considered refractory (supported by at least one well-designed experimental study).
Consolidation therapy	• Patients that enter clinical and hematologic remission should receive at least one cycle of post-remission therapy (supported by at least one well-designed experimental study). • Patients deemed a good risk should receive CT only, with high-dose cytarabine (supported by expert opinion). • All other patients with HLA-identical sibling donors are candidates for alloSCT in 1st remission (supported by expert opinion). • A reduced-dose conditioning may be used in patients older than 40-45 years of age (supported by well-designed quasi-experimental studies such as non-randomized, controlled, single-group, pre-post, cohort, time, or matched case-control series). • Patients without a suitable donor and with poor risk features may be offered a transplant from a MUD (supported by well-designed quasi-experimental studies such as non-randomized, controlled, single-group, pre-post, cohort, time, or matched case-control series). • Where KIR mismatch exists, haploidentical transplants may be considered (supported by expert opinion). • The use of autoPBSCT is still under investigation, and cannot be recommended at this time (supported by expert opinion).

Note: alloSCT, allogeneic stem cell transplantation; autoPBSCT, autologous peripheral stem cell transplantation.

Guideline recommendations from Morra et al (2009).

Type of transplant	Recommendations
AlloSCT	• Myeloablative alloSCT from an HLA-matched sibling donor is recommended in CR1 for all children with intermediate to high-risk cytogenetics and for all adults deemed high-risk under the age of 55 with no severe co-morbidities (supported by at least one high-quality meta-analysis, SR of RCTs, or a single RCT with a low risk of bias). • Myeloablative alloSCT from a fully matched sibling donor is recommended in CR1 for adult patients deemed intermediate-risk, under 40, and with no comorbidities, except for NPM1 mutant and FLT3-ITD negative cases (supported by well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal). • If CR only occurs after second course of induction therapy myeloablative alloSCT from a fully-matched sibling donor is recommended regardless of risk if the patient is under 55 years of age and has no other comorbidities (supported by non-comparative studies and/or expert opinion). • Either PBSCT or BMT are acceptable choices (supported by non-comparative studies and/or expert opinion). • If a matched sibling donor is not available, unrelated donors can be considered for patients in CR1 that are under 30 years of age deemed high-risk or for those that achieved CR1 following the 2nd course of induction therapy (supported by non-comparative studies and/or expert opinion). • Unrelated donor alloSCT is not recommended for patients older than 50 that had a CR following induction therapy (supported by non-comparative studies and/or expert opinion). • RIC regimens should be considered for patients deemed high-risk 55 years of age or older or patients with severe comorbidities (supported by non-comparative studies and/or expert opinion).
ASCT	• Consolidation ASCT is recommended for patients eligible for high-dose CT that are not candidates for alloSCT from a fully HLA-matched donor (supported by at least one high-quality SR of case-control and/or cohort studies or high quality case-control or cohort studies with a low risk of confounding, bias, or chance and a high probability that the relationship is causal). • Transplants should be made within 6 months of CR1 (supported by non-comparative studies and/or expert opinion). • Patients with a CR1 that lasts longer than 6 months should not receive ASCT (supported by non-comparative studies and/or expert opinion). • SCT harvesting should be performed when the best 'in vivo' purging has been completed using PBSCT (supported by non-comparative studies and/or expert opinion).

Note: alloSCT, allogeneic stem cell transplantation; CR1, first complete response; CR, complete response; FLT3-ITD, Fms-like tyrosine kinase-gene internal tandem duplication; PBSCT, peripheral blood stem cell transplantation; BMT, bone marrow transplantation.

Guideline recommendations from O'Donnell et al (2011).

Treatment milieu	Recommendation
With antecedent hematologic disease or therapy-related AML, < 60 years of age	• CT or low-intensity therapy, or matched sibling or alternative donor alloSCT, or if neither of these options are available cytarabine/anthracycline-based CT (supported by lower-level evidence and uniform agreement within the expert panel).
Post-induction therapy after standard-dose cytarabine following induction failure, < 60 years of age	• Entry into a clinical trial, or matched sibling or alternative donor alloHST, or if neither of the above are available high-dose cytarabine with or without anthracycline, or BSC (supported by lower-level evidence and uniform agreement within the expert panel).
Post-induction therapy after high-dose cytarabine following induction failure, < 60 years of age	• Entry into a clinical trial, or matched sibling or alternative donor alloSCT, or BSC (supported by lower-level evidence and uniform agreement within the expert panel).
Intermediate-risk cytogenetics or molecular abnormalities, < 60 years of age	• Matched sibling or unrelated donor alloSCT, or 1-2 cycles of high-dose cytarabine-based consolidation followed by ASCT, or high-dose cytarabine 1.5-3g/m^3 over 3 hours every 12 hours on days 1,3,5 for 3-4 cycles, or entry into a clinical trial (supported by lower-level evidence and uniform agreement within the expert panel).
Treatment-related disease or poor-risk cytogenetics or molecular abnormalities, < 60 years of age	• Entry into a clinical trial, or matched sibling or alternative donor alloSCT, or 1-2 cycles of high-dose cytarabine-based consolidation therapy followed by ASCT if no allogeneic transplant option is available (supported by lower-level evidence and uniform agreement within the expert panel).
Post-induction therapy, ≥ 60 years of age	• Follow-up bone marrow 7-10 days after induction completed. If a significant cytoreduction with low % of residual blasts is found, then patient should receive additional standard-dose cytarabine with anthracycline (idarubicin or daunorubicin) or mitoxantrone, or reduced-intensity matched sibling or other donor alloSCT (if patient meets criteria for alloSCT), or await recovery (supported by lower-level evidence and uniform agreement within the expert panel).
Post-remission therapy, ≥ 60 years of age (Marrow to document remission status upon hematologic recovery at 4-6 weeks)	• If patient experiences a CR, then patient should be offered entry into a clinical trial, or RIC alloSCT, or standard-dose cytarabine with or without anthracycline, or high-dose cytarabine, or some other low-intensity regimen (supported by lower-level evidence and uniform agreement within the expert panel). • If patient did not experience a CR, then patient should be offered entry into a clinical trial, or reduced intensity alloSCT within a clinical trial setting, or BSC (supported by lower-level evidence and uniform agreement within the expert panel).

Note: CT, chemotherapy; alloSCT, allogeneic stem cell transplantation; BSC, best supportive care; ASCT, autologous stem cell transplantation.

Appendix E. AMSTAR results.

Criterion	Oliansky et al, 2009	Koreth et al, 2009
1. Was an a priori design provided? The research question and inclusion criteria should be established before the conduct of the review.	Unknown	Yes
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	Yes	Yes
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	Yes	Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	Yes	Unknown
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	No	No
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	Yes	Yes
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	Yes	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	Yes	Unknown
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	Unknown	Yes
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	No	Yes
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	Unknown	Yes