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Recommendation Report SCT-6 REQUIRES UPDATING

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Stem Cell Transplantation in the Treatment of Acute Lymphoblastic Leukemia

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An assessment conducted in February 2020 indicated that Recommendation Report SCT-6 REQUIRES UPDATING. 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-6 is comprised of 3 sections. You can access the summary and full report here:

https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/961

Section 1:	**Recommendations**
Section 2:	**Recommendation Report Methods Overview**
Section 3:	**Evidence Review**

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PUBLICATIONS RELATED TO THIS REPORT

The EBS report Extra-corporeal Photopheresis in the Management of Graft-Versus-Host Disease in Patients who have Received Allogeneic Blood or Bone Marrow Transplants has been published as a Practice Guideline in the peer-reviewed Canadian journal *Current Oncology*. 2014 and is available electronically at:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3997461/

- Bredeson C, Rumble RB, Varela NP, Kuruvilla J, Kouroukis CT. Extra-corporeal Photopheresis in the Management of Graft-Versus-Host Disease in Patients who have Received Allogeneic Blood or Bone Marrow Transplants. Current Oncology. 2014;21(2) e310-e325

The EBS report Stem Cell Transplantation in Adults has been published on the CCO Web site. 2009 and is available at:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/951

- 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].

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Recommendation Report SCT-6: Section 1

Stem Cell Transplantation in the Treatment of Acute Lymphoblastic Leukemia: Recommendations

OBJECTIVES

1. To establish the indications for allogeneic stem cell transplantation (allo-SCT) in the management of acute lymphoblastic leukemia (ALL) in adults
2. To identify the role of reduced-intensity conditioning (RIC) regimens for SCT in the management of ALL of adult patients
3. To identify the role of tyrosine-kinase inhibitors (TKIs) for patients undergoing allo-SCT for Philadelphia chromosome-positive ALL (Ph+ ALL)
4. To identify the role of alternative donor transplantation (haploidentical, cord blood) in the management of adult patients with ALL who lack a suitable related or unrelated donor.

TARGET POPULATION

All adult ALL patients considered for treatment that involves SCT. Outcomes of interest are relapse, disease-free survival, relapse-free survival, progression-free survival, overall survival, and non-relapse mortality.

INTENDED USERS

This recommendation report is targeted for:

1. Healthcare physicians performing SCT in Ontario.
2. Healthcare institutions and system leaders responsible for providing resources for SCT.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1

Allogeneic stem cell transplantation (allo-SCT) is an option for adult patients with acute lymphoblastic leukemia (ALL) in first complete remission (CR1). Allo-SCT is recommended in CR2 or greater (refractory or relapsed).

Key Evidence for Recommendation 1

The studies involved patients with Philadelphia chromosome-negative ALL in first complete remission (CR1) and beyond (refractory or relapsed ALL). All patients were treated with total body irradiation (TBI)-based myeloablative conditioning, and sibling donor transplantation.

- One evidence-based review with recommendations (1), and two systematic reviews with meta-analysis (2, 3) showed that allo-SCT offers superior overall survival and disease-free survival in patients with chromosome-negative ALL in CR1.
- The recommendation surrounding allo-SCT in CR2 or beyond (refractory or relapsed) for adults with ALL represent the consensus of the Working Group members based on guidance provided by the 2012 American Society for Blood and Marrow Transplantation (ASBMT) guideline from USA (1).

Qualifying Statement for Recommendation 1

The studies looking at outcomes of allo-SCT in CR1 were older and many used less intensive regimens that may be currently used in adults with ALL, in particular regarding L-asparaginase. Thus, modern ALL therapy based on pediatric protocols may provide for better outcomes without the need to undergo allo-SCT in CR1.

Interpretation of Evidence for Recommendation 1

The primary outcomes considered to inform this recommendation include relapse, non-relapse mortality, disease-free survival and overall mortality/survival.

The certainty of the evidence on the efficacy of allo-SCT compared with other post-remission therapy (chemotherapy) is reasonable but with the caveat that current ALL chemotherapy protocols are more intensive than those used in the studies. This recommendation is generalizable to all adult patients with ALL in remission who are eligible for allo-SCT.

Recommendation 2

A myeloablative conditioning is the conventional regimen for most patients with leukemia; however, reduced-intensity conditioning (RIC) is an option for patients with acute lymphoblastic leukemia (ALL) in remission when they are deemed unsuitable for the standard myeloablative conditioning (MAC) regimen.

Key Evidence for Recommendation 2

This recommendation is supported by evidence obtained from the 2012 American Society for Blood and Marrow Transplantation (ASBMT) evidence-based review (1) and a systematic review with meta-analysis (4).

- The 2012 ASBMT review (1) recommended RIC regimens only for patients with ALL in remission who are unsuitable for MAC regimens, as it was shown that RIC may produce similar outcomes to MAC regimens. The systematic review (4) stated that RIC may be a potential therapeutic option in patients with high risk of treatment-related mortality (TRM) associated with MAC regimens, as there was a lack of overall survival benefit of MAC over RIC regimens.
- One retrospective cohort study (5) detected an improved overall survival for patients undergoing RIC when compared with MAC as conditioning for allo-SCT in ALL.

Qualifying Statement for Recommendation 2

Reduced-intensity conditioning may produce similar outcomes to myeloablative regimens, but available data are limited. Based on the evidence, the members of the Working Group have determined that RIC could be an effective therapeutic option for patients with ALL who are ineligible for MAC allo-SCT. There are important clinical differences in those patients undergoing the two types of conditioning that could affect outcomes. More prospective studies are required to better define the value of reduced versus MAC regimens.

Interpretation of Evidence for Recommendation 2

The primary outcomes considered to inform this recommendation include relapse, disease-free survival, non-relapse mortality, progression-free survival, and overall survival.

The certainty of the evidence on the efficacy of RIC in adults with ALL in remission is

moderate. This recommendation is generalizable to patients with ALL in remission who are not suitable for MAC regimens.

Recommendation 3

Post-transplant use of a BCR-ABL tyrosine-kinase inhibitor (TKI) in patients with Philadelphia chromosome-positive ALL (Ph+ ALL) is a reasonable option.

Key Evidence for Recommendation 3

- One evidence-based review with recommendations (1) and one prospective study (6) addressed this question. The consensus is that TKI therapy is useful pre and/or post-transplant. However, the evidence is not as strong as the 2012 ASBMT evidence-based review included one trial that evaluated the use of imatinib (TKI) in only five patients with Ph+ ALL (1).
- One prospective, comparative cohort study (6) evaluated the administration of imatinib in 62 patients based on BCR-ABL transcript levels after allo-SCT, and it showed a lower relapse rate, lower non-relapse mortality and a survival advantage in favour of imatinib.

Qualifying Statement for Recommendation 3

The standard of care is to administer TKIs in combination with chemotherapy for ALL and before SCT. Demonstrating benefits of TKIs post SCT may therefore be difficult, as most patients will have received TKIs pre-transplant.

Interpretation of Evidence for Recommendation 3

The primary outcomes considered to inform this recommendation include relapse, non-relapse mortality, progression-free survival, and overall survival.

The certainty of the evidence on the efficacy of TKIs post SCT is low. However, due to the poor prognosis for patients with Ph+ ALL, the members of the Working Group have determined that the use of TKI post SCT should be an option for this population.

Recommendation 4

Haploidentical hematopoietic Stem Cell Transplantation (haplo-SCT) for patients with ALL in CR1 or later who lack a suitable related or unrelated donor is a reasonable option.

Key Evidence for Recommendation 4

Two retrospective cohort studies compared the efficacy of haplo-SCT with chemotherapy alone when used as post-remission treatment in patients with ALL. Both studies showed improvement in relapse rate, disease control and overall survival in favour of the haplo-SCT patients. Non-relapse mortality was at acceptable levels. Patients in these studies had both standard and high-risk ALL.

Qualifying Statement for Recommendation 4

Haplo-SCT appears to be feasible in patients with ALL and it seems to provide an advantage over chemotherapy. As the evidence is somewhat limited, more prospective comparisons are required.

Interpretation of Evidence for Recommendation 4

The primary outcomes considered to inform this recommendation include relapse,

non-relapse mortality, progression-free survival, and overall survival.

The certainty of the evidence on the efficacy of haplo-SCT for patients in remission is low and therefore this recommendation cannot be generalized to all patients with ALL. This recommendation is generalizable only to patients with ALL who lack a suitable related or unrelated donor.

IMPLEMENTATION CONSIDERATIONS

Should an increase in SCT for ALL result from this recommendation report, there may be issues related to capacity and timeliness of transplant in Ontario centres. Also, the use of haploidentical donors and RIC could increase the number of patients with ALL who may become eligible for a SCT. Due to the nature of the evidence showing improved outcomes in terms of survival and disease control, SCT for ALL would align with patient and provider values.

RELATED GUIDELINES

- Extra-corporeal Photopheresis in the Management of Graft-versus-Host Disease in Patients who have Received Allogeneic Blood or Marrow Transplants, C. Bredeson, R.B. Rumble, N.P. Varela, J. Kuruvilla, C.T. Kouroukis, the Stem Cell Transplant Steering Committee of Cancer Care Ontario's Program in Evidence-Based Care [Report Date: August 29, 201]. Available at: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/966

- 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]. Available at: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/951

Stem Cell Transplantation in the Treatment of Acute Lymphoblastic Leukemia: Recommendation Report Methods Overview

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

JUSTIFICATION FOR RECOMMENDATION REPORT

The initiation of this recommendation report was prompted by the need to harmonize practice in Ontario around the use of Stem Cell Transplantation (SCT) for acute lymphoblastic leukemia (ALL). There are perceptions that the practice of SCT for ALL varies across the transplant centres, that patients might be offered SCT at first complete remission (CR1) or CR2 with either myeloablative, or reduced-intensity conditioning, and that the value of a SCT in ALL is questionable. Therefore, the Working Group of the Stem Cell Transplant Steering Committee has prepared this report to summarize the available evidence and to standardize practice in Ontario amongst all SCT centres. Furthermore, these recommendations will assist referring physicians in knowing which patients with ALL might be best suited for an SCT.

RECOMMENDATION REPORT DEVELOPERS

This recommendation report was developed by a Working Group consisting of four haematologists/oncologist and a health research methodologist at the request of the SCT Committee.

The Working Group was responsible for reviewing the evidence base, drafting the recommendations, and responding to comments received during the document review process.

Information regarding members of the Working Group can be found in Appendix 1.

Conflict of interest declarations are summarized in Appendix 2, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

RECOMMENDATION REPORT DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle (7, 8). For Recommendation Reports this process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by a methodology experts and final approval by the Sponsoring Committee.

The PEBC uses the AGREE II framework (9) as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation, using the ADAPTE framework (10), or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), and the Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse.
- Electronic Databases: MEDLINE and EMBASE.

Only guidelines based on systematic review of the literature and published after 2010 were considered for inclusion. Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument (9). One guideline from the American Society for Blood and Marrow Transplantation (ASBMT) in the United States was found in the targeted search of the guideline databases that significantly overlapped in scope with the objectives and the research questions of this review (1). The guideline was evaluated by three independent methodologists (NV, CZ, RM), and retained because of its high-quality methods and comprehensive description of the process for developing recommendations. Agreement with the recommendations contained in the ASBMT guideline led to the Working Group members' decision to adapt its recommendations, with additional searching to be undertaken to ensure the currency of the evidence-base in the role of allogeneic SCT (allo-SCT) for the management of ALL in the adult population. The AGREE scores are presented in Table 1, and a brief description of this guideline is presented thereafter.

Table 1. AGREE II Scores for Identified Guideline.

ASBMT, 2012	
Domains	***Score (2 reviewers)***
Scope and purpose	83%
Stakeholder involvement	69%
Rigor of development	83%
Clarity of presentation	89%
Applicability	29%
Editorial independence	83%

ASBMT: American Society for Blood and Marrow Transplantation.

American Society for Blood and Marrow Transplantation (ASBMT) (1)

The 2012 ASBMT guideline is an update of the 2006 ASBMT publication "The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Therapy of Acute Lymphoblastic Leukemia in Adults: An Evidence-based Review". It was developed by the ASBMT Evidence-Based Review Steering Committee with the scientific support of clinical and research physicians, one third-party payer representative, a patient advocate, and a liaison to the ASBMT Steering Committee. The ASBMT document was developed to support the role of hematopoietic SCT in the therapy of ALL.The recommendations were based on systematic reviews of the scientific and medical evidence on SCT for the management of ALL. It focused on two key aspects of SCT in ALL population: (1) transplantation versus chemotherapy (allo-SCT versus chemotherapy for ALL in first complete remission and beyond, autologous [auto]-SCT vs. chemotherapy for ALL in first complete remission), and (2) transplantation techniques (allo-SCT versus auto-SCT, related versus unrelated allo-SCT, unrelated donor bone marrow versus cord blood SCT, imatinib versus. no imatinib therapy pre- and/or post-SCT in Philadelphia chromosome-positive ALL, comparison of induction therapies before SCT, comparison of SCT conditioning regimens).

A summary of the 2012 ASBMT recommendations is presented in Table 2. The recommendation surrounding the use of tyrosine kinase inhibitors, in patients with Philadelphia chromosome-positive ALL is mainly based on administration of imatinib before transplantation which is current practice, and on auto-SCT. Only one trial included an arm with five patients in the imatinib post-allo SCT. No guidelines were identified that compared haploidentical hematopoietic SCT versus chemotherapy in patients with ALL.

Table 2. Summary of the 2012 Recommendations from the American Society of Blood and Marrow Transplantation (ASBMT)

Research Question	Indication	Level of evidence*	Recommendations ASBMT, 2012 (1)
Q1: Allo-SCT in the Management of adult patients with ALL	Allo-SCT vs. CT **CR1**	I++	Myeloablative allo-SCT is an appropriate treatment for adult ALL in CR1 for all disease risk groups. Allo-SCT provides a significant improvement in overall and leukemia-free survival in younger (<35 years), standard risk, Ph-negative ALL patients compared with less intensive chemotherapy regimens. In older (>35), standard risk, Ph-negative ALL patients, a higher TRM diminishes the significant survival advantage with allo-SCT.
	CR2	2++	Allo-SCT is recommended over chemotherapy for ALL in CR2 or greater.

	Auto-SCT vs. Allo-SCT	2++	There is a preponderance of evidence favoring allogeneic over autologous SCT. There are insufficient data to determine whether this effect is more apparent in disease risk subgroups, including Ph+ ALL.
Q2: Conditioning Regimens for allo-SCT	RIC vs. MAC	2++	Reduced-intensity conditioning may produce similar outcomes to myeloablative regimens, but available data are limited, thus reduced intensity regimens are appropriate only for patients with ALL in remission who are unsuitable for myeloablative conditioning.
Q3: TKI post-allo SCT in adult patients with Ph-positive ALL	TKI vs. Non-TKI Therapy pre- and/or post-SCT in Ph-positive ALL	2++	Available data suggest imatinib therapy before and/or after SCT yields significantly superior outcomes in overall survival and leukemia-free survival. Ongoing studies using other tyrosine kinase inhibitors may enhance this recommendation.

ALL (acute lymphoblastic leukemia); Allo-SCT (allogeneic stem cell transplantation); CR1 (first complete remission); CR2 (second complete remission); MAC (myeloablative conditioning regimen); Ph (Philadelphia chromosome); RIC (reduced-intensity conditioning); TKI (tyrosine kinase inhibitor); TRM (treatment-related mortality)

*** Level of Evidence:** I++ (high-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias); 2++(high-quality systematic reviews of case-control or cohort studies; or high-quality case control or cohort studies with a very low risk of confounding bias, or chance and a high probability that the relationship is causal).

RECOMMENDATION REPORT REVIEW AND APPROVAL

Internal Review

The recommendation report was reviewed by the Director of the PEBC. The Working Group is responsible for ensuring the necessary changes are made. If those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

Report Approval by the Stem Cell Transplant Steering Committee

After internal review, the report was presented to the CCO-SCT Steering Committee (CCO-SCT). Members of the CCO-SCT previously reviewed the document, and formally approved the document.

ACKNOWLEDGEMENTS

The members of the SCT Steering Committee, and the Working Group would like to thank the following individuals for their assistance in developing this report:

- Melissa Brouwers, Sheila McNair, Hans Messersmith, for providing feedback on draft versions.
- Elizabeth Chan for conducting a data audit.
- Sara Miller for copy editing.

Recommendation Report SCT-6: Section 3

Stem Cell Transplantation in the Treatment of Acute Lymphoblastic Leukemia: Evidence Review

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a form of leukemia that if left untreated is fatal within a few weeks. The incidence of ALL is less than that of myeloid leukemia in adults and occurs most frequently in those younger than 20 years. The incidence is 1.7 per 100,000 people per year with an overall five-year relative survival of 70%. Many adults with ALL harbour the Philadelphia chromosome, which is associated with a worse prognosis. Treatment for curative intent involves combination induction, consolidation chemotherapy with central nervous system treatment and prolonged maintenance. Those patients with the Philadelphia chromosome would also receive a tyrosine kinase inhibitor (TKI) such as imatinib. Acute lymphoblastic leukemia is a standard indication for allogeneic transplant but there is often debate of whether to transplant patients in first or second complete remission (CR1 or CR2) and what to do with patients who have the Philadelphia chromosome.

In order to make recommendations for clinical practice and assist Cancer Care Ontario (CCO) around decision making with respect to allogeneic stem cell transplantation (allo-SCT) in the treatment of ALL, the Working Group of the Stem Cell Transplant (SCT) Steering Committee developed this evidentiary base upon which those recommendations are based. Based on the objectives of the guideline, the Working Group derived the research questions outlined below.

OBJECTIVES AND RESEARCH QUESTIONS

This Working Group developed the following objective(s) for this guideline in consultation with the CCO SCT Committee.

5. To establish the indications for allo-SCT in the management of ALL in adults
6. To identify the role of reduced-intensity conditioning (RIC) regimens SCT in the management of ALL in adult patients
7. To identify the role of TKIs for patients undergoing allo-SCT for Philadelphia chromosome-positive ALL
8. To identify the role of alternative donor transplant (haploidentical, cord blood) in the management of adult patients with ALL who lack a suitable related or unrelated donor.

From these objectives, the following research questions were derived to direct the search for available evidence to inform recommendations to meet the objectives.

1. Does allo-SCT improve the outcome of adult patients with ALL in CR1 or beyond when compared with conventional chemotherapy (CT)?
2. Does a RIC or non-myeloablative conditioning allo-SCT improve the outcome of adult patients with ALL who are not suitable for ablative regimens when compared with standard non-transplant therapies?
3. Does the use of BCR-ABL TKIs following allogeneic transplantation improve the outcome of adult patients with Philadelphia chromosome-positive ALL when compared with allogeneic transplantation without TKI?
4. Does alternative donor transplant (haploidentical, cord blood) improve the outcome of adult patients with ALL who lack a suitable related or unrelated donor compared with standard, non-transplant chemotherapy?

METHODS

Given the availability of the high quality 2012 American Society for Blood and Marrow Transplantation (ASBMT) guideline presented and described in Section 2, this evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described below.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. The website of the Cochrane database of systematic reviews (CDSR) (www.cochrane.org/evidence), along with the electronic databases MEDLINE (OVID) and EMBASE (OVID) were searched from January 2008 to July 2014 (and updated in May 2015). The full literature search strategy used to identify potentially relevant systematic reviews from OVID MEDLINE and EMBASE is presented in Appendix 3. The website of the CDSR was searched using the keyword "Acute Lymphoblastic Leukemia".

Systematic reviews were included if:

1. The existing systematic review searched for studies evaluating any of the following indications in the management of ALL: allo-SCT, RIC regimens for allo-SCT, TKIs following allo-SCT, and alternative donor transplants in the management patients who lack a suitable related or unrelated donor.
2. The literature search strategy for the existing systematic review is reproducible (i.e., reported) and appropriate.
3. The existing systematic review reported the sources searched as well as the dates that were searched.

Identified systematic reviews were evaluated based on their clinical content and relevance. Any identified systematic reviews that addressed the research questions were assessed using a Measurement Tool to Assess Systematic Reviews (AMSTAR) (11). The results of the AMSTAR assessment were used to determine whether or not any existing systematic review could be incorporated as part of the evidence base. In cases where multiple systematic reviews of similar quality exist, only the most recent review with the most recent literature search would be included.

Search for Primary Literature

Assuming that no existing guidelines or systematic review were identified, or that identified guidelines or systematic reviews were incomplete in some fashion, a systematic review of the primary literature was also planned. If a suitable guideline or systematic review were found, a systematic review of the primary literature would be conducted, from the end date of the reported search, only to update the evidence from the identified guideline(s) and/or systematic review(s).

Literature Search Strategy

The MEDLINE (OVID) (1996 through July 18, 2014) and EMBASE (OVID) (1996 through week 30, 2014) databases were searched for evidence on July 2014 and updated on May 2015. The search strategy included a logical combination of terms for the condition (ALL), the intervention (SCT), and studies of interest (systematic reviews, clinical trials, non-randomized studies with an appropriate control group). The full literature strategy used to retrieve potential relevant studies is presented in Appendix 3.

Study Selection Criteria and Process

Inclusion Criteria

Articles identified in this systematic review were eligible for inclusion if they met the following criteria:

1. Primary comparative studies evaluating any of the following indications in the management of ALL: allo-SCT, RIC regimens for allo-SCT, TKIs following allo-SCT, and alternative donor transplants in the management patients who lack a suitable related or unrelated donor.
2. Published full-report articles of randomized control trials and non-randomized studies with an appropriate control group
3. Studies reporting any of the outcomes of interest such as relapse, non-relapse mortality, disease-free survival, and overall survival.

Exclusion Criteria

Studies were excluded if they were:

1. Abstracts, letters, case reports, comments, books, notes, or editorial publication types
2. Articles published in a language other than English because resources were not available for translation services

A review of the titles and abstracts that resulted from the search was conducted by one reviewer (NV). For those items that warranted full text review, one reviewer (NV) reviewed each item and consulted members of the Working Group whenever there was uncertainty.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data extraction was conducted by one author (NV) and was reviewed by a second independent individual using a data audit procedure (EC) to verify the accuracy of the information obtained from the studies included in this report. All extracted data and information were reviewed independently by other members of the Working Group, (CB, WI, JK, TK).

The following items were extracted from each relevant article: author, publication year, study design, sample size, procedure/intervention, number of participants, and years of data collection. Outcomes of interest including relapse, non-relapse mortality, disease-free survival, and overall survival were extracted when available.

Ratios, including hazard ratios (HRs), were expressed with a ratio <1.0 indicating that the intervention/experimental procedure had a better outcome than the control group.

Clinical trials were assessed for quality by examining the following seven criteria: the method of randomization, reporting of blinding, the power and sample size calculation, length of follow-up, reporting details of the statistical analysis, reporting on withdrawals to treatment and other losses to follow-up, and reporting on the sources of funding for the research. Comparative, non-randomized and single-arm evidence would be assessed according to full reporting of the patient selection criteria, the interventions each patient received, all relevant outcomes, and the source of funding. All authors reviewed and discussed a draft of this report with the aim of assessing the quality of the evidence as a whole, without the use of a scoring system or cut-offs, according to the policy of the Program in Evidence-Based Care.

RESULTS

Search for Existing Systematic Reviews

A search for systematic reviews was conducted to update the 2012 ASBMT evidence-based review which was current to October 15, 2010. Seven out of 70 citations were identified as potentially relevant. From these, three systematic reviews with meta-analysis focused on the efficacy of allo-SCT versus chemotherapy in adults with ALL (2, 3, 12). The systematic review by Pidala et al. (2011) contain information of trials that were not included in the most recent systematic review reported by Gupta et al. (2013), and therefore both systematic reviews were considered in this evidentiary base. Gupta et al. (2013) recognized the existence of those trials but reported that data were not available. The list of the trials included in the two systematic reviews is presented in Table 1. One additional citation focused on reduced-intensity allo-SCT versus myeloablative allo-SCT for adults with ALL, and therefore it was also included (4). Overall, three citations were retained because they significantly overlapped in scope with some of the objectives and research questions of this evidentiary review.

Table 1. Studies included in the Reviews Assessing the Effect of Allogeneic Stem Cell Transplantation for Adults with Acute Lymphoblastic Leukemia In First Complete Remission

Systematic Review / Studies	Gupta et al., 2013(2)	Pidala et al., 2011(3)
Labar et al., 2004 (13)	✓	✓
Goldstone et al., 2008 (14)	✓	✓
Ribera et al., 2005 (15)	✓	✓
Thomas et al., 2004 (16)	✓	✓
Labar et al., 2007 (17)*	✓	
Richards et al., 1996†	✓	
Gupta et al., 2004 (18)	✓	
Takeuchi et al., 2002 (19)	✓	✓
Huguet et al., 2009 (20)‡	✓	
Cormelissen et al., 2009 (21)§	✓	✓
Cormelissen et al., 2009 (21)**	✓	✓

* Short communication
† Reference not found
‡ Patients in the chemotherapy arm received a pediatric-inspired therapy
§ HOVON-18 ALL trial: patients 15-50 years old
** HOVON-37 ALL trial: patients 16-55 years old

Hunault et al., 2004 (22)	✓	✓
Bassan et al., 2001(23)††	✓	
Attal et al., 1995 (24)	Data not available	✓
Bernasconi et al., 1992 (25)	Data not available	✓
De Witte et al., 1994 (26)	Not included b/c small study, (n=63) including patients with lymphoblastic lymphoma	✓
Fielding et al., 2009 (27)	Not included b/c use of unrelated donors recommended	✓
Ifrah et al., 1999 (28)	Not included b/c small study (n=50) with donor versus no donor comparison not reported	✓
Sebban et al., 1994 (29)	Data not available	✓
Ueda et al., 1998 (30)	Not included b/c small study (n=71) with donor availability not reported	✓

Search for Primary Literature

The primary literature review was used to address domains and/or outcomes of interest not covered by the included guidelines and systematic reviews. For Research Questions 1 – 3, only the literature published from 2010 was considered because it corresponds to the end date of the search in the identified guideline addressing these questions. For Research Question 4, no date restrictions were used.

Literature Search Results

As presented in Figure 1, of the 7780 titles and abstracts identified in the search of MEDLINE and EMBASE, 7360 appeared potentially eligible on initial review, and 233 of these were verified to be eligible for full text review. From these, four full-report publications were identified that evaluated treatment modalities that include allo-SCT for the management of adult patients with ALL, and reported the outcomes of interest. The remaining 229 publications were excluded because they failed to pass the inclusion criteria, or they were published after the end date of the search of either the adapted 2012 ASBMT guideline (1) or the two included systematic reviews (2-4). Studies selected for inclusion are listed in Table 2.

†† This study mainly focus on validation of a therapeutic option for specific risk group of ALL patients

Figure 1. Literature Search Flow Diagram of Included Studies Addressing Allogeneic Stem Cell Transplantation (allo-SCT) for the Management of Adult Patients with Acute Lymphoblastic Leukemia (ALL)

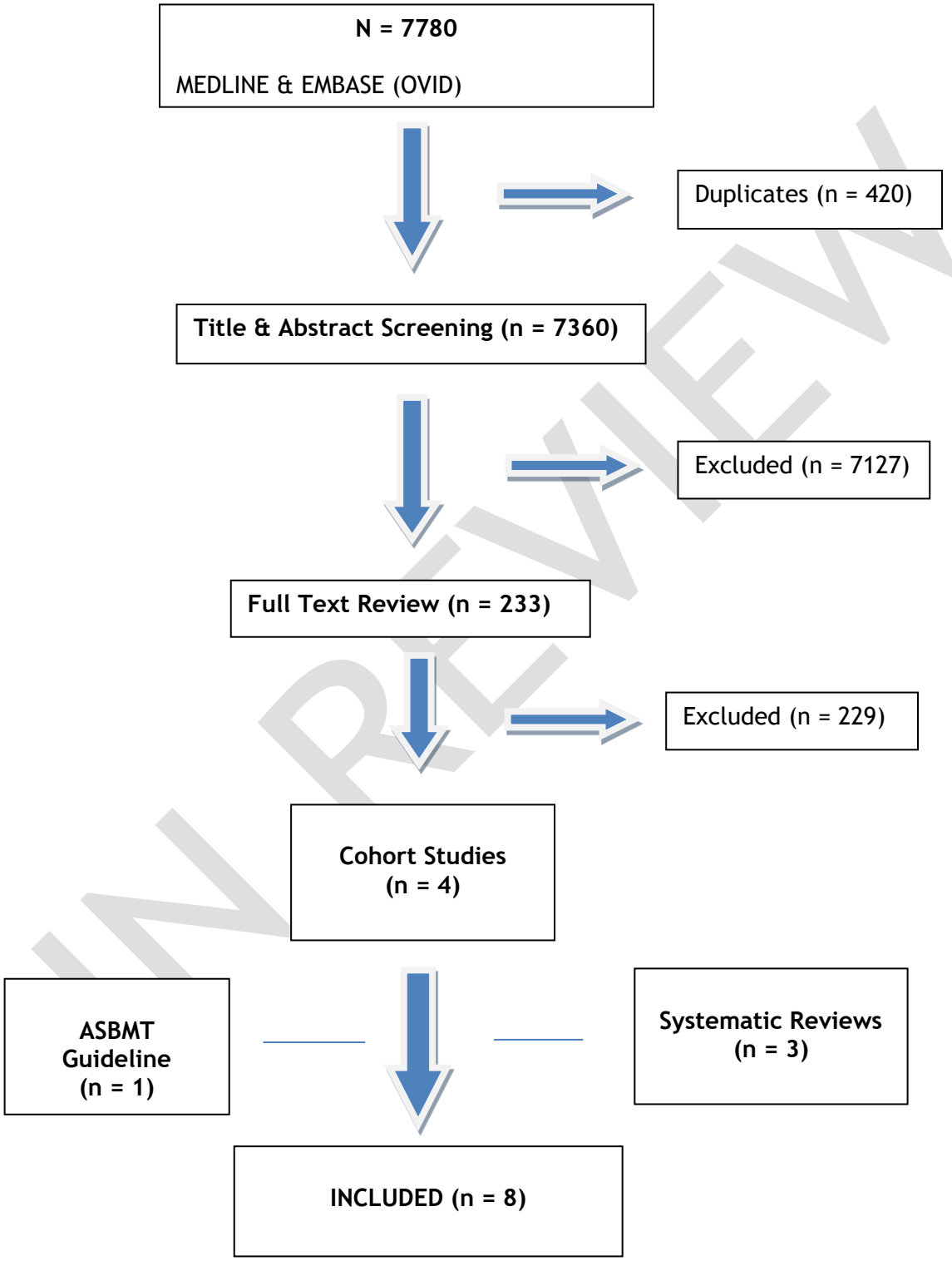

Table 2. Studies selected for inclusion

Question	Included Studies
1. Allo-SCT for the management of acute lymphoblastic leukemia in either CR1, CR2 or greater	1 Guideline (1) 2 Systematic Reviews (2, 3)
2. RIC regimens for SCT in the management of acute lymphoblastic leukemia of patients who deemed unsuitable for myeloablative conditioning regimens	1 Guideline (1) 1 Systematic Review with meta-analysis (4) 1 Cohort study (5)
3. Tyrosine-kinase inhibitors for patients with Philadelphia positive acute lymphoblastic leukemia undergoing allo-SCT	1 Guideline (1) 1 Cohort study (6)
4. Haploidentical hematopoietic SCT for patients with acute lymphoblastic leukemia in CR1 or greater who lack a suitable donor	2 Cohort studies (31, 32)

Allo-SCT: allogeneic stem cell transplantation; CR1: first complete remission; CR2: second complete remission; RIC: reduced-intensity conditioning; SCT: stem cell transplantation

Study Design and Quality

Systematic reviews were assessed for quality using the AMSTAR criteria described at www.amstar.ca. All the systematic reviews scored well; they provided valuable evidence to inform the clinical questions addressed in this review. The results of the AMSTAR assessment are presented in Appendix 4.

Three retrospective (5, 31, 32) and one prospective non-randomized trials (6) were also included in this review to inform recommendations surrounding allo-SCT for adult patients with ALL. In all studies the patients were fully described, and were representative of the population of interest. Two of these trials (31, 32) were conducted in China and assessed the use of haploidentical-allo-SCT for adult patients with ALL who lack a suitable related or unrelated donor versus chemotherapy. These two trials did not report any source of funding. The National Natural Science Foundation of China, National High-tech R&D Program of China and Leading Program of Clinical Faculty accredited by the Ministry of Health of China provided financial support to the trial by Chen et al. (6). This trial was designed to investigate the efficacy of imatinib when administrated after allo-SCT in patients with Philadelphia chromosome-positive ALL. The trial by Mikell et al. (5) comparing the outcome of patients with ALLL undergoing RIC with those undergoing myeloablative conditioning (MAC) for allo-SCT did not report any source of funding. Common limitations of these trials mainly included small sample size, confounding factors, and selection bias; however, these trials were retained because in the absence of high-quality randomized controlled trials, they represent the best available evidence to answer the research questions stated above.

Study and Patient Characteristics

The systematic review identified seven studies assessing treatment modalities that include SCT in the management of ALL in adults, and reporting the outcomes of interest (relapse, non-relapse mortality, disease-free survival, and overall survival): three systematic reviews with meta-analysis (2-4), and four non-randomized primary studies (5, 6, 31, 32). See Table 3 for details. One guideline had been previously identified in the search for existing guidelines (1).

Table 3. Summary of the Studies Evaluating Treatment Modalities that Include Allogeneic Stem Cell Transplant (allo-SCT) in the Treatment of Adult Patients with Acute Lymphoblastic Leukemia (ALL)

Question 1: Allo-SCT vs. conventional chemotherapy for the treatment of patients with ALL in first complete remission (CR1) or beyond					
Study [Country]	**Inclusion Criteria**	**Data Collection**	**Treatment Allocation**	**Statistical Analysis**	**Outcome Reported**
Systematic Reviews with Meta-analysis					
Gupta et al., 2013 (2) [Canada]	**Graft Source:** HLA-matched sibling donor. Trials in adult ALL that include: 1. HLA-matched sibling donor transplantation if a matched donor was available (Donor arm) 2. Transplantation with CT and/or auto-SCT if not matched donor was available (No-donor arm) 3. Ph-negative ALL patients in first complete remission (CR1).	Data were collected for each individual patient on initial characteristics, donor availability or treatment allocated, outcome, and date and type of HCT received. Note: principal investigators from identified trials were invited to join the group and to provide individual data.	**Donor vs. no-donor (overall)** Donor: 1097 No-donor: 1865 **Donor vs. no-donor (CT)** Donor: 157 ▪ Allo-SCT: 119 ▪ Auto-SCT: 0 ▪ CT: 38 No-donor: 308 ▪ Auto-SCT: 38 ▪ CT: 225 ▪ Other: 45 **Donor vs. no-donor (auto)** Donor: 141 ▪ Allo-SCT: 117 ▪ Auto-SCT: 3 ▪ CT: 19 ▪ Other: 2 No-donor: 286 ▪ Auto-SCT: 217 ▪ CT: 53 ▪ Other: 16	*Individual patient data meta-analysis: individual patient data were analyzed from studies with information on availability of matched sibling donor (used to mimic randomization)* Analysis by intention-to-treat	Relapse Non-relapse mortality Overall mortality

			Donor vs. no-donor (CT/auto) Donor: 799 ▪ Allo-SCT: 569 ▪ Auto-SCT: 15 ▪ CT: 209 ▪ Other: 6 No-donor: 1271 ▪ Auto-SCT: 300 ▪ CT: 897 ▪ Other: 74		
Pidala et al., 2011 (3) [USA]	**Graft Source:** HLA-matched sibling donor. Trials in adult ALL that include: 1. HLA-matched sibling donor transplantation if a matched donor was available (Donor arm) 2. Additional consolidation and maintenance chemotherapy or auto-SCT if not matched donor was available (No-donor arm)	Data were collected from 14 trials representing a total of 3157 patients.	**Donor vs. no-donor** Relapse: 7 trials (2213 pts) ▪ High-risk: 5 (1296 pts) ▪ Std-risk: 2 (712 pts) NRM: 9 trials (2524 pts) ▪ High-risk: 5 (1197 pts) ▪ Std-risk: 2 (712 pts) DFS: 9 trials (2423 pts) ▪ High-risk: 5 (1145 pts) ▪ Std-risk: 3 (873 pts) OS: 10 trials (2,499 pts) ▪ High-risk: 6 (1192 pts) ▪ Standard-risk: 2 (712 pts)	Mainly, analysis by intention-to-treat (see note below) Note: of the trials included in the analysis, only one did not report data according to intention-to-treat, but rather reported outcomes according to actual treatment received	Relapse Non-relapse mortality Disease free-survival Overall survival

CT (chemotherapy); NRM (non-relapse mortality); DFS (disease-free survival); OS (overall survival).

Question 2: Reduced-intensity conditioning allo-SCT vs. non-transplant therapies for the treatment of adult patients with ALL who are not suitable for ablative regimens					
Systematic Review with Meta-analysis					
Study [Country]	**Inclusion Criteria**	**Data Collection**	**Treatment Allocation**	**Statistical Analysis**	**Outcome Reported**
Abdul Wahid et al., 2014 (4) [Malaysia]	Clinical trials of adult patients with AML and ALL that compared RIC-HCT versus MAC-HCT regimens (only ALL data were extracted)	Data were collected from 5 individual trials representing a total of 3017 patients with ALL.	**Relapse** RIC-HCT: 725 MAC-HCT: 2840 **Non-relapse Mortality** RIC-HCT: 519 MAC-HCT: 2471 **Progression-free survival** RIC: 518 MAC: 2452 **Overall survival** RIC-HCT: 519 MAC-HCT: 2471	Subgroup meta-analysis (ALL)	Relapse Non-relapse mortality Progression-free survival Overall survival
Retrospective Cohort Study					
Mikell et al., 2014 (5)	Patients undergoing HSCT who received TBI (RIC and MAC) as part of their conditioning regimens	Prospectively acquired database of HSCT patients treated at the Winship Cancer Institute, Atlanta, Georgia	RIC-HCT: 12 MAC: 71	Descriptive and multivariable statistical analysis	Relapse Disease-free survival Non-relapsed mortality Progression-free survival Overall survival

RIC (reduced-intensity conditioning); MAC (myeloablative conditioning).

Question 3: Allo-SCT + BCR-ABL tyrosine-kinase inhibitors (TKI) vs. allo-SCT without TKI for the treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+) ALL				
Study [Country]	**Inclusion Criteria**	**Treatment Allocation**	**Imatinib Treatment**	**Outcome Reported**
Prospective Cohort Study				
Chen et al., 2012 (6) [China]	Patients < 60 years of age with Ph+ ALL that received allo-HCT regardless of the source of HCT **Imatinib arm** One of the two following criteria 1. ANC >1x10^9/L w/o G-CSF and platelet count >50x10^9/L, or 2. Detectable levels of *BCR-ABL* transcript in bone marrow and transcript levels increased for two consecutive tests, or *BCR-ABL* transcript levels ≥10^{-2} after initial engraftment, although patients ANC or platelet count were below the above values Plus, the condition that patients could tolerate oral imatinib w/o gut GVHD or life-threatening infection.	Imatinib: 62 Non-imatinib: 20	**Schedule** 3-12 months post-HCT, until negative *BCR-ABL* transcript levels for at least 3 consecutive tests or CR^{mol*} was sustained for at least 3 months. **Doses** ▪ >17 years: 400 mg/d ▪ <17 years: 260 mg/m^2/d ▪ Dose reduced to 300 mg/d if ANC <1x10^9/L, despite administration of G-CSF, or if platelet count <20x10^9/L **Minimum acceptable dose** 300 mg/d (260 mg/m^2/d for <17 years) for at least 5 days/week	Relapse Non-relapse mortality Disease-free survival Overall survival

ANC (peripheral blood absolute neutrophil counts), GVHD (graft-versus-host disease)

[*] Negative expression of *BCR-ABL* by qRT-PCR in patients bone marrow specimens

Question 4: Alternative donor transplants vs. non-transplant therapy (chemotherapy) for to treatment of patients with ALL who lack a suitable related or unrelated donor			
Study [Country]	**Inclusion Criteria**	**Treatment Allocation**	**Outcome Reported**
Retrospective, Non-Randomized Cohort Studies			
Sun et al., 2015 (31) [China]	▪ Patients aged 18-60 years ▪ Newly diagnosed high-risk ALL ▪ Had received ongoing CT or haplo-HSCT in CR1. <u>Definition of high-risk ALL</u> Patients >35 years old, with high white blood cells (WBC) count at presentation (≥100x10^9/L for T linage and ≥30x10^9/L for B linage); t(9;22) or BCR-ABL[6])	Haplo-HSCT: 79 CT: 104	Relapse Disease-free survival Cumulative incidence of relapse Overall survival
Yan et al., 2014 (32) [China]	▪ Patient aged 15-60 years ▪ Without high-risk features[†] ▪ Achieving CR after 1 to 2 cycles of induction CT.	Haplo-HSCT: 79 CT: 59	Relapse Disease-free survival Overall survival

[†] Elevated WBC count (≥30X10^9/L for B cell linage or ≥100X10^9/L foe T cell lineage), or high-risk cytogenetic abnormalities, determined according to the National Comprehensive Cancer Network 2013 guideline, such as hypodiploidy, complex karyotype (≥5 chromosomal abnormalities), t(9;22), or *BCR-ABL*, t(v;11q23) or mixed lineage leukemia (MLL) rearrangements

Outcomes

1. *Allo-SCT versus Chemotherapy for adult patients with acute lymphoblastic leukemia (ALL) (Table 4)*

Systematic Reviews

Two systematic reviews with meta-analysis were identified that compared donor (allo-SCT) versus no-donor (either autologous [auto]-SCT, chemotherapy, or auto-SCT/chemotherapy combined) for the treatment of patients with ALL (2, 3).

The 2013 individual patient meta-analysis by Gupta et al. (2) identified 13 trials with a median follow-up from four to 16 years. A pooled odds ratio (OR) for relapse of 0.58 demonstrated significantly fewer relapses in patients undergoing allo-SCT (donor arm) when compared with patients undergoing chemotherapy, auto-SCT, or chemotherapy/auto-SCT (non-donor arm); however, there was significant heterogeneity among trials indicating clinical differences among them. Subgroup meta-analysis demonstrated that reduction in relapse was not significant between those undergoing allo-SCT (donor) versus those using chemotherapy in the no-donor arm (*p=0.08)*. *Significant differences were maintained with the allo-SCT (donor) and the chemotherapy/auto-SCT comparison groups.*

Non-relapse mortality was substantially higher and similar across subgroups in the allo-SCT (donor arm) versus no-donor arm, but heterogeneity across trials was reported (*p = 0.02*). Subgroup meta-analysis demonstrated significant higher non-relapse mortality in patients undergoing allo-SCT (donor) when compared with patients undergoing chemotherapy in the no-donor arm (OR=2.76; *p=0.0005;* five trials) only.

Pooled overall survival was significantly longer in the allo-SCT (donor) ($OR_{mortality}$=0.87; *p=0.006; 13 trials*) versus no-donor arm, and heterogeneity among trials was not significant, $p[X^2]=0.07$.

In a second systematic review and meta-analysis, Pidala et al. (2011) identified 14 trials evaluating donor versus no-donor comparison rates in both high- and standard-risk groups with a median follow-up ranging from 2.7 to 9.5 years. Pooled data from these studies demonstrated a significant reduction in primary disease relapse in the donor (29%) versus the no-donor arm (52%) (RR=0.53; *p=0.0004;* seven trials), but significant heterogeneity was detected in both pooled and high-risk subgroup meta-analysis (*p*=0.00001) preventing interpretation and generalizability for these two populations. The subgroup meta-analysis of two trials comparing donor versus no-donor in standard-risk ALL patients alone demonstrated significant reduction in risk of relapse (18% versus 47% respectively; relative risk [RR]=0.39; *p=0.00001)*. Similarly, the meta-analysis of two trials comparing donor vs. no-donor in standard-risk ALL patients alone demonstrated better non-relapse mortality in patients with sibling donor (21% versus 6% respectively; RR=3.36; *p=0.00001*).

Significant advantages were observed in the donor vs. no-donor arm in terms of overall sample disease-free survival (62% vs. 52%; HR=0.82; *p=0.004*), and overall sample survival (53% versus 47%; HR=0.86; *p=0.01*); heterogeneity between trials was not significant. See Table 4 for details.

Primary Literature

No primary literature published after 2010 was identified that compared donor/allo-SCT versus no donor (chemotherapy, auto-SCT) in the treatment of adult ALL.

Table 4. Summary of the Outcomes Reported from Studies Comparing Allogeneic Stem Cell Transplantation (Allo-SCT) versus Chemotherapy in the Treatment of Adult Patients with Acute Lymphoblastic Leukemia (ALL)

Systematic Reviews					
Study [Country]	**Participants**	**Relapse Donor vs. no-donor [95% CI]**	**Non-relapse Mortality Donor vs. no-donor OR [95% CI]**	**Disease-free Survival**	**Overall Mortality or Survival Donor vs. no-donor [95% CI]**
Gupta et al., 2013 (2) [Canada]	Allo-SCT: 805 CT: 266 Auto: 18	Overall OR=0.58 [0.52-0.65] *p<0.00001;* *p[X]=0.0004* Donor vs. chemo OR=0.78 (0.59-1.03) *p=0.08;* Donor vs. auto OR=0.42 (0.31-0.57) *p<0.00001;* Donor vs. CT/auto OR=0.58 [0.51-0.66] *p<0.00001;*	Overall TRM OR=2.36 [1.94-2.86] *p<0.00001;* *p[X²]=0.02* Donor vs. chemo OR=2.76 [1.55-4.89] *p=0.0005;* Donor vs. auto OR=1.99 [1.06-3.72] *=0.03;* Donor vs. CT/auto OR=2.35 [1.89-2.93] *p<0.00001;*		Overall 5 year mortality OR=0.87 [0.79-0.96] *p=0.006;* No-donor - CT OR=1.03 [0.79 – 1.34] *p=0.8;* No-donor - auto OR=0.63 [0.47-0.83] *p=0.001;* No-donor - chemo/auto OR=0.89 [0.79-1.00] *p=0.05* Age 35+ OR=1.01 [0.85-1.19] *p=0.9* Age < 35 OR=0.79 [0.70-0.90] *p=0.0003*

Pidala et al., 2011 (3) [USA]	Donor: 1,268 No donor: 1,889	<u>Overall</u> Donor: 29% No-donor: 52% RR=0.53 [0.37 – 0.76] *P=0.0004;* *p[X²]< 0.00001* <u>High-risk ALL</u> Donor: 35% No-donor: 55% RR=0.63 [0.4 – 0.98] *p=0.04* <u>Standard-risk ALL</u> Donor: 18% No-donor: 47% RR=0.39 [0.29 – 0.53] *p<0.00001*	<u>Overall</u> Donor: 22% No-donor: 8% RR=2.80 [1.66 – 4.73] *p=0.001;* *p[X²]=0.0003* <u>High-risk ALL</u> Donor: 23% No-donor: 11% RR=1.95 [0.99 – 3.87] *p=0.05* <u>Standard-risk ALL</u> Donor: 21% No-donor: 6% RR = 3.36 [2.05 – 5.51] *p<0.00001*	<u>Overall</u> Donor: 38% No-donor: 48% HR=0.82 [0.72 – 0.94] *P=0.004;* *p[X²]=0.17* <u>High-risk ALL</u> Donor: 39% No-donor: 47% HR=0.77 [0.51 – 1.15] *p=0.2* <u>Standard-risk ALL</u> Donor: 32% No-donor: 45% HR=0.66 [0.43 – 1.0] *p=0.05*	<u>Overall Sample Survival</u> Donor: 53% No-donor: 47% HR=0.86 [0.77 – 0.97] *p=0.01;* *p[X²] = 0.77* <u>High-risk ALL</u> Deaths donor: 50% Deaths no-donor: 55% HR=0.88 [0.68 – 1.13] *p=0.31* <u>Standard-risk ALL</u> Deaths donor: 37% Deaths no-donor: 49% HR=0.69 [0.45 – 1.06] *p=0.09*

Auto: autologous; CI: confidence interval; CT: chemotherapy; OR: odds ratio; RR: relative risk; TRM transplant-related mortality

2. Reduced-intensity conditioning allo-SCT for the treatment of acute lymphoblastic leukemia in adults not suitable for ablative regimens (Table 5)

Systematic Reviews

A systematic review with meta-analysis by Abdul Wahid et al. (2014) assessed five clinical trials involving 3017 adult patients with ALL and that compared survival outcomes after reduced-intensity conditioning (RIC) vs. myeloablative conditioning (MAC) transplants (4). The meta-analysis indicated a reduction in non-relapse mortality (OR=0.76; 95% CI 0.61-0.95; *p*=0.02) and progression-free survival (OR=0.76; 95% CI 0.61-0.93; *p*=0.009) after RIC allo-SCT, but relapse rate was increased (OR=1.77; 95% CI 1.45-2.17; *p*<0.00001). The authors of this meta-analysis reported no overall survival benefit of MAC vs. RIC across the entire cohort of patients (OR=1.03; 95% CI 0.84-1.26; *p*=0.76), and therefore suggested that RIC could be an effective therapeutic option for ALL patients who are ineligible for MAC allo-SCT (see Table 5).

Retrospective Cohort Study

One clinical trial was identified to be published between 2013 and 2015 that compares RIC allo-SCT versus MAC allo-SCT (5). The rates of relapse (16.7% versus 33.8%; *p*=0.342) and non-relapse mortality (HR= 0.72; 96% CI 0.20-2.58; *p*=0.616) were not significantly different between arms. Relapse-free survival trended toward improvement with RIC compared to MAC transplants (HR=0.33; 95% CI 0.11-1.01; *p*=0.052), and RIC allo-SCT was associated with improved overall survival when compared with MAC allo-SCT (HR=0.25; 95% CI 0.07-0.86; *p*=0.028). See Table 5 for details.

Table 5. Summary of the Outcomes reported by Studies Comparing Reduced-Intensity and Myeloablative Conditioning Regimens for allogeneic Stem cell Transplantation (allo-SCT) in Acute Lymphoblastic Leukemia (ALL) patients

Systematic Review with Meta-analysis					
Study [Country]	**Relapse [95% CI]**	**DFS/RFS[*] [95% CI]**	**NRM[†] [95% CI]**	**PFS[‡] [95% CI]**	**OS[§] [95% CI]**
Abdul et al., 2014 (4) [Malaysia]	OR: 1.77 [1.45-2.17] RIC: 30% MAC: 23% *p=<0.00001*		OR: 0.76 [0.61-0.95][**] RIC: 29% MAC: 33% *p=0.02*	OR: 0.76 [0.61-0.93] RIC: 36% MAC: 41% *p=0.009*	OR: 1.03 [0.84-1.26] RIC: 49% MAC: 49% *p=0.76*
Retrospective Cohort study					
Mikell et al., 2014 (5)	RIC: 16.7% MA: 33.8% *p=0.342*	HR: 0.33 [0.11-1.01] *p=0.052*	HR: 0.72 [0.20-2.58] *p=0.616*		HR: 0.25 [0.07-0.86] *p=0.028*

RIC (reduced-intensity conditioning); MAC (Myeloablative conditioning); OR or HR < 1 indicates better outcome in the RIC regimen when compared to MA regimen.

[*] Disease-free Survival / Relapse-free Survival: Probability of being alive with no evidence of disease relapse
[†] Nonrelapse Mortality: any death with no evidence of disease relapse or progression, including death due to treatment
[‡] Progression-free survival: probability of being alive with no indication of disease progression
[§] Overall Survival: Time from transplantation until death from any cause
[**] Moderate heterogeneity I^2=55%

3. Efficacy of tyrosine-kinase inhibitors (TKI) after allo-SCT for the treatment of Philadelphia chromosome—positive ALL patients (Table 6)

Systematic Reviews

No systematic reviews published from 2010 to 2015 were identified that compared TKI after allo-SCT versus allo-SCT without TKI after transplantation in patients with ALL.

Prospective Cohort Study

For the purpose of this review, primary studies published from 2010 to 2015 comparing TKI after allo-SCT versus allo-SCT without TKI in Philadelphia chromosome-positive ALL patients are described here.. One prospective cohort study was identified (6) in which treatment with TKI (imatinib) was based on particular clinical conditions and BCR-ABL transcript levels after allo-SCT; treatment was scheduled for three to 12 months. Patients in the imatinib maintenance therapy post allo-SCT had lower relapse rate (10% versus 33%; p=0.016) and survival advantage in terms of disease-free survival (82% versus 34%; p=0.000) and overall survival (87% versus 34%; p=0.000) when compared with non-imatinib allo-SCT treated patients; however, more patients died from non-relapse complications in the non-imatinib arm when compared with the imatinib arm (37% vs. 7%; p=0.0006). See Table 6 for details.

Table 6. Summary of the Outcomes Reported by Studies Comparing Allogeneic Stem Cell Transplantation (allo-SCT) Followed by the Administration of Tyrosine-Kinase Inhibitors (TKI) versus allo-SCT without TKI in Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leuemia (ALL)

Study [Country]	Relapse [95% CI]	NRM	DFS/RFS* [95% CI]	OS† [95% CI]
Prospective Cohort Study				
Chen et al., 2012 (6)	5-year Imatinib: 10.2%±3.9% Non-imatinib: 33.1±10.8% *P = 0.016*	5-year Imatinib: 6.66±3.24% Non-imatinib: 37.19±10.89% *p=0.0006*	5-year Imatinib: 81.5%±5.0% Non-imatinib: 33.5±10.6% *p=0.000*	5-year Imatinib: 86.7%±4.4% Non-imatinib: 34.3±10.5% *p=0.000*

Non-imat (non- imatinib)

* Disease-free Survival / Relapse-free Survival: Probability of being alive with no evidence of disease relapse

† Overall Survival: time from treatment until death from any cause

4. Haploidentical Hematopoietic Stem Cell Transplantation versus Chemotherapy for the Treatment of Acute Lymphoblastic Leukemia (ALL) Patients who Lack a Suitable Related Donor (Table 7)

Systematic Reviews

No systematic reviews were identified that compared haploidentical hematopoietic SCT versus chemotherapy in patients with ALL.

Retrospective Cohort Studies

Two retrospective cohort studies reported that patients undergoing haploidentical haematopoietic SCT had statistically significant lower relapse and survival advantages in terms of disease-free survival, non-relapse mortality, and overall survival, when compared with chemotherapy alone (see Table 7).

Table 7. Summary of the Outcomes Reported by Trials Comparing Haploidentical Hematopoietic Stem Cell Transplantation (haplo-SCT) and Chemotherapy for the Treatment of Acute Lymphoblastic Leukemia (ALL) patients who Lack a Suitable Related Donor

Study [Country]	Relapse [95% CI]	DFS/RFS* [95% CI]	NRM† [95% CI]	OS‡ [95% CI]
Retrospective Cohort Studies				
Sun et al., 2015 (31)	3-year Haplo: 18.7% CT: 60.5% *p<0.001*	3-year Haplo: 63.9% CT: 21.1% *p<0.001*	3-year NRM Haplo: 19.2% CT: 14.4% *p=0.80*	3-year OS Haplo: 72.5% CT: 26.6% *p<0.001*
Yan et al., 2014 (32)	5-year Haplo: 29.9% CT: 66.3% *p<0.01*	5-year Haplo: 54.4% CT: 23.9% *p<0.01*	5-year TRM Haplo: 15.7% CT: 9.8% *p<0.057*	5-year OS Haplo: 70.4% CT: 28.0% *p<0.01*

UR (unrelated donor)

DISCUSSION

Acute lymphoblastic leukemia (ALL) is less frequently seen compared with acute myeloid leukemia (AML), but the principles of treatment are similar. It has been the general perception that outcomes with chemotherapy and/or SCT are not as good with ALL compared with AML. We believed that a literature review and guideline around SCT in ALL was needed to review the up to date literature and to harmonize practice and, therefore, outcomes across all SCT centres in Ontario.

We found evidence of some benefit of SCT in ALL in CR1 based on two meta-analyses, one of which was an individual patient data meta-analysis. Both overall survival and disease-free survival was improved for patients receiving a SCT for ALL in CR1. The evidence was strongest in Philadelphia chromosome negative ALL in CR1. However, we recognize that the

* Disease-free Survival / Relapse-free Survival: Probability of being alive with no evidence of disease relapse
† Non-relapse Mortality: any death with no evidence of disease relapse or progression, including death due to treatment
‡ Overall Survival: Time from transplantation until death from any cause

chemotherapy protocols in the studies contained within the meta-analyses used traditional adult-style chemotherapy. Pediatric inspired protocols that are more aggressive and incorporate more L-asparaginase appear to have better results and may be preferred over allo-SCT. We therefore believed that with the current use of more aggressive chemotherapy regimens along with potential allo-SCT toxicities, that allo-SCT could be an option but not routinely recommended in CR1. In addition the studies within the meta-analyses varied by the age of the patient where allo-SCT was allowed, the timing of the allo-SCT after induction/consolidation and the type and intensity of chemotherapy used, including the amount of L-asparaginase, if any. The SCT committee believed that by consensus relapsed ALL is higher risk and therefore allo-SCT would be recommended in CR2 or later and this aligns with a previously published guideline from the ASBMT.

As many of the patients with ALL are older, they may not be fit or eligible for myeloablative conditioning regimens. We found that the outcomes for reduced intensity conditioning appeared acceptable and that such conditioning regimens would be an option for those patients unsuitable for myeloablative conditioning. We were not in a position to determine exact criteria for the choice of conditioning, but likely this would be based largely on comorbidities, organ function, performance status, and to a lesser extent, age.

As a significant proportion of patients with ALL harbour the Philadelphia chromosome we sought out specific recommendations of the use of TKIs. We recognize that the use of TKIs during induction/consolidation treatment for ALL is standard and thus this complicates the evaluation of the benefit of TKIs post-transplant. We felt that given the poorer outcomes for the Philadelphia chromosome positive patients, the use of a TKI post-transplant was an option, particularly if there was evidence for detectable disease by molecular testing.

Unfortunately many patients in whom a SCT is indicated may not have a suitable related or unrelated donor. Haploidentical transplantation is gaining momentum and we specifically searched for such data in SCT for ALL. Although the data is retrospective, it shows that the outcomes appear beneficial and that the non-relapse mortality is acceptable when using haploidentical donors for SCT in ALL.

CONCLUSIONS

To summarize, allogeneic SCT is an option for adults with ALL in CR1, but is recommended for those in CR2 or greater. The use of reduced intensity conditioning is acceptable only if the patient is not eligible for myeloablative conditioning. The use of TKIs post-transplant is reasonable if patients have Philadelphia chromosome positive ALL. If a suitable related or unrelated donor is not available, then a haploidentical donor is acceptable for such transplants.

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Appendix 1: Members of the Working Group

Members of the Stem Cell Transplantation Treatment for Acute Lymphoblastic Leukemia Working Group

Name	Affiliation
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Appendix 2: Conflict of Interest

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors of this recommendation report and internal reviewers were asked to disclose potential conflicts of interest. The authors, members, and reviewers reported that they had no conflicts of interest.

Appendix 3: Literature Search Strategies

Search strategy to Identify Potential Systematic Reviews

Database: Cochrane Database of Systematic Reviews (CDSR), Ovid MEDLINE(R) and EMBASE, 2008 – 2015.

1. (Acute Lymphoblastic Leukemia or Acute Leukemia or Lymphoblastic Leukemia).mp.
2. exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/
3. or/1-2
4. exp Bone Marrow Transplantation/ or exp Stem Cell Transplantation/
5. (bone marrow transplantation or stem cell transplantation or peripheral stem cell transplantation).mp.
6. or/4-5
7. exp Clinical Trial/ or exp Clinical Study/ or exp Controlled Clinical Trial/ or exp Multicenter Study/ or exp Phase 1 Clinical Trial/ or exp Phase 2 Clinical Trial/ or exp Phase 3 Clinical Trial/ or exp Phase 4 Clinical Trial/ or exp Clinical trial, controlled/ or exp Clinical trial, Phase 1/ or Clinical trial, Phase 2/ or exp Clinical trial, Phase 3/ or exp Clinical trial, Phase 4/ or exp Clinical trial, Phase I/ or Clinical trial, Phase II/ or Clinical trial, Phase III/ or exp Clinical trial, Phase IV/ or exp Comparative studies/ or exp Prospective Studies/
8. (((Clinical Trial$ or random$) adj3 trial$) or Comparative Study).mp.
9. or/7-8
10. meta-Analysis as topic/
11. meta analysis.pt.
12. (meta analy$ or metaanaly$).tw.
13. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
14. (systematic adj (review$ or overview?)).tw.
15. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
16. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
17. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
18. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
19. (study adj selection).ab.
20. or/10-19
21. 3 and 6 and 20
22. limit 21 to yr="2008 -Current"
23. remove duplicates from 22

Search strategy to Identify Potential Primary Literature

Database: Ovid MEDLINE(R) and EMBASE, 2008 – 2015.

1. (Acute Lymphoblastic Leukemia or Acute Leukemia or Lymphoblastic Leukemia).mp.
2. exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/
3. or/1-2
4. exp Bone Marrow Transplantation/ or exp Stem Cell Transplantation/
5. (bone marrow transplantation or stem cell transplantation or peripheral stem cell transplantation).mp.
6. or/4-5
7. exp Clinical Trial/ or exp Clinical Study/ or exp Controlled Clinical Trial/ or exp Multicenter Study/ or exp Phase 1 Clinical Trial/ or exp Phase 2 Clinical Trial/ or exp Phase 3 Clinical Trial/ or exp Phase 4 Clinical Trial/ or exp Clinical trial, controlled/ or exp Clinical trial, Phase 1/ or Clinical trial, Phase 2/ or exp Clinical trial, Phase 3/ or exp Clinical trial, Phase 4/ or exp Clinical trial, Phase I/ or Clinical trial, Phase II/ or Clinical trial, Phase III/ or exp Clinical trial, Phase IV/ or exp Comparative studies/ or exp Prospective Studies/
8. (((Clinical Trial$ or random$) adj3 trial$) or Comparative Study).mp.
9. or/7-8
10. 3 and 6 and 9
11. limit 10 to yr="1970 - 2010"
12. remove duplicates from 11
13. limit 10 to yr="2011 -Current"
14. remove duplicates from 11
15. remove duplicates from 13
16. 14 or 15

Appendix 4. Quality Assessment of Included Systematic Reviews (AMSTAR) (Yes/No/CA)

		Allo-SCT vs. CT		RIC vs. CT
	AMSTAR Tool	**Gupta et al, 2013(2)**	**Pidala et al, 2011(3)**	**Abdul Wahid et al., 2014(4)**
Q1.	Was an '*a priori*' design provided?	Yes	Yes	Yes
Q2.	Was there duplicate study selection and data extraction?	C/A	Yes	Yes
Q3.	Was a comprehensive literature search performed?	Yes	Yes	Yes
Q4.	Was the status of the publication used as an inclusion criterion?	Yes	Yes	Yes
Q5.	Was a list of studies (included and excluded) provided?	Yes	Yes	Yes
Q6.	Were the characteristics of the included studies provided?	Yes	Yes	Yes
Q7.	Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes
Q8.	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes
Q9.	Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes
Q10.	Was the likelihood of publication bias assessed?	No	Yes	Yes
Q11.	Was the conflict of interest stated?	Yes	Yes	Yes

Abbreviations: CA (can't answer); allo-SCT (allogeneic stem cell transplantation); RIC (reduced-intensity conditioning); CT (chemotherapy)