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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**

Report Date: February 1, 2016

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PEBC Report Citation (Vancouver Style): Bredeson C, Varela NP, Walker I, Kuruvilla J, Kouroukis T. Stem cell transplantation in the treatment of acute lymphoblastic leukemia. Toronto (ON): Cancer Care Ontario; *2016 February 1*. Program in Evidence-Based Care Recommendation Report No.: SCT-6.

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].

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