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Reviews

Refining the Role of Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia as Novel Therapies Emerge

Riad El Fakih [1,*], Mohamed A. Kharfan-Dabaja [2], Mahmoud Aljurf [1]

[1] *King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia*
[2] *Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida*

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A B S T R A C T

Acute lymphoblastic leukemia (ALL) is a rare adult neoplasm. The disorder consists of precursor B or T phenotypes. In the pediatric population, ALL was a success story in that 80% of children with ALL enjoy long-term survival. In adults, similar complete remission rates are achieved with current induction regimens; however, less than 50% of patients are alive at 5 years, with most deaths due to relapsed disease. Accordingly, optimizing post remission consolidation therapy might improve in outcomes. Such strategies may include chemotherapy and autologous or allogeneic transplant. Moreover, the ability to modify such therapy based on better disease risk stratification while taking into account patient characteristics such as performance status and presence of comorbidities is necessary to tailor treatment accordingly. Here, we review available medical literature on the use of hematopoietic cell transplantation as a consolidation modality in the treatment of adult ALL.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) constitutes around 5% of adult lymphoid neoplasms. Median age at diagnosis for adult precursor B ALL is 39 years, whereas precursor T ALL present usually in the second to third decade of life. In adults, complete remission (CR) can be achieved with the currently available induction regimens; however, maintaining remission for long-term and achieving ultimate cure remains challenging. Survival after relapse is poor [1]. Allogeneic hematopoietic cell transplantation (allo-HCT) is commonly used to consolidate remission; however, data from available literature about this modality of consolidation are controversial and sometimes conflicting. This article reviews the results of the major trials addressing the role of allografting after achieving first CR (CR1) and also in the setting of disease relapse. We also review standard conditioning regimens used, the role of transplant with the advent of pediatric protocols, donor choice, the role of autologous transplant, and the changing landscape of Philadelphia chromosome–positive (Ph+) ALL treatment. The review also sheds light on new emerging therapies for ALL.

ALLO-HCT IN CR1

Historically, allo-HCTs for adult ALL were predominantly offered in relapsed and refractory cases, with the exception of Ph+ ALL in which allografts are performed in CR1. Over the past 3 decades allografts have been increasingly performed in patients in CR1, based on the presence of high-risk features. Generally accepted conventional high-risk features include age (>35 years), elevated WBC count on presentation, immunophenotype (early thymocyte precursor in T-ALL and mature B cell phenotype in B-ALL), high-risk cytogenetics, CD20 expression in B cell precursor type, and prolonged time to CR1 (>4 weeks), among others [2-4]. However, with the advent of pediatric-based chemotherapy protocols and their incorporation into the therapeutic armamentarium of young adults with ALL, the adverse prognosis of some of these traditional high-risk factors are being brought into question. Efficacy of allo-HCT relies in part on the cytotoxicity of the conditioning regimen and the graft-versus-leukemia (GVL) effect mediated by alloreactive donor T cells. The GVL effect has been described in adult ALL [5], and multiple studies have confirmed an association between development of graft-versus-host disease and a decreased relapse incidence in ALL, as is the case for other hematologic malignancies [6]. The guidelines of various major organizations such as the American Society for Blood and Marrow Transplantation, the National Marrow Donor Program (http://marrow.org/Physicians/When_to_Transplant/Referral_Guidelines.aspx), and the European Group for Blood and Marrow Transplantation

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* Correspondence and reprint requests: Riad El Fakih, MD, Section of Adult Hematology/HSCT, Oncology Centre (MBC-64), King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh 11211, Saudi Arabia.
E-mail address: relfakih1@kfshrc.edu.sa (R. El Fakih).

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Table 1
Conclusions from key studies of Allo-HCT in CR1

Study	Accrual period	Patients number	High risk features	Overall survival	Conclusion	Notes
LALA-87 [7]	1986-1991	161	Philadelphia positive, undifferentiated ALL, age > 35, WBC > 30, time to CR > 4 weeks	5 years OS in the high risk group 44% versus 20% for the standard risk group. *P* value = .03	Survival benefit with Allo-HCT for high risk patients based on conventional risk factors	All risk groups were randomized to Allo-HCT vs. no Allo-HCT based on the availability of MSD
LALA-94 [8]	1994-2002	259	B cell ALL with any of the following: failure to achieve CR after one induction course, t (4,11) or other 11q23 abnormalities, WBC > 30, undifferentiated ALL	In the high risk group, 5 years OS was 38% for the whole group and 51% for patients who received allo-HCT	Survival benefit with Allo-HCT for high risk patients based on conventional risk factors	Only high risk patients were randomized to Allo-HCT vs. no Allo-HCT based on the availability of MSD
GOELALA02 [9]	1994-1998	156	age > 35, non–T-ALL, WBC > 30, t(9;22), t(4;11), t(1,19), failure to achieve CR after one induction course	6-year OS 75% vs. 39% for Donor vs. no Donor in the high risk group	Survival benefit with Allo-HCT for high risk patients based on conventional risk factors	
MRC/ECOG [11]	1993-2006	562	Age > 35, WBC > 30 for B lineage and > 100 for T lineage, Philadelphia positive	Patients at high risk had a 5 years OS of 41% versus 35% for donor versus no donor, *P* value = .2. Patients at standard risk had a 5 years OS of 62 % versus 52 % for donor versus no donor, *P* value = .02	Survival benefit with Allo-HCT for standard risk patients based on conventional risk factors. Showed significant LFS benefit with Allo-HCT in the high risk group	NRM was 35.8% in the high risk group vs. 19.5% in standard risk abrogating the OS benefits from allo-HCT
HOVON trials [12]	1992-2005	138	Time to CR > 4 weeks, t(9;22), t(4;11), t(1;19), pro–B-cell immunophenotype, WBC > 30 for B-ALL, and > 100 for T-cell ALL	61 versus 47% OS at 5 and 8 years in the donor group compared with the no-donor group (HR: .70; 95% CI .46-1.05; *P* = .08), no obvious difference in prognostic value of donor availability between standard risk and poor risk patients	Survival benefit with Allo-HCT more pronounced for high risk patients based on conventional risk factors	Similar NRM between all risk groups

(EBMT; http://www.ebmt.org/Contents/Resources/Library/EBMTESHhandbook/ Documents/EBMT2008_Cap21.pdf) on the use of transplant in adult patients with ALL in CR1 are not in accordance. Some of the discrepancies have led to differing practices for the application of transplant in adult patients with ALL in CR1 as reflected by the ongoing debate on this issue.

The French LALA-87 (Leucemie Aigue Lymphobalstique de l'Adulte) trial evaluated 257 patients with ALL in CR1 in a biologic randomization fashion and with an intention-to-treat analysis [7]. It showed that patients with high-risk disease features who had an available HLA-compatible donor had a survival advantage compared with patients without an available donor (5-year overall survival [OS] rates 44% versus 20%). In their following study, the LALA-94 trial [8], which only stratified high-risk patients with donors to allo-HCT, a similar benefit was seen in patients with available donors (5-year leukemia-free survival [LFS] 45% in those with available donors compared with 23% without a donor). Similar results were also shown by the GOELAL02 (Groupe Ouest-Est des Leucémies Aiguës et Maladies du Sang) trial [9], which described an almost 2-fold improved OS in the high-risk groups with available donors (6-year OS, 75% versus 39%). In contrast, a number of studies, including the EORTC (European Organization for Research and Treatment of Cancer) ALL 3 trial [10] and the pivotal Medical Research Council/Eastern Cooperative Oncology Group (MRC/ECOG) trial [11], have not been able to demonstrate similar survival benefit for the high-risk group when assigned to receive an allo-HCT. The largest randomized study comparing postremission therapies in adults with ALL in CR1 (the collaborative MRC/ECOG trial [11]) demonstrated a significant survival advantage for allo-HCT in adults with ALL with standard-risk disease when offered the procedure in CR1 but did not support this conclusion in the setting of high-risk disease. It is possible that the resulting high nonrelapse mortality (NRM) in the latter group of patients might have offset the favorable reduction in relapse from allografting (the cumulative incidence of NRM was 19.5% in standard-risk patients and 35.8% high-risk patients) [11]. As a result, survival advantage was demonstrated in the standard-risk but not the high-risk group. Similarly, the Haemato Oncology Foundation for adults in the Netherlands (HOVON) trials showed that differences in OS were more pronounced in the standard-risk group (5-year OS rates, 69% versus 49%) than in the high-risk group despite a relatively low NRM in both risk groups [12]. It is important to note that relapse rates in the allo-HCT arms remain distinctly lower compared with both autologous transplantation (auto-HCT) or chemotherapy (EORTC trial, 38% versus 56%; MRC/ECOG trial, 63% versus 37%), perhaps suggesting that the conflicting results might have been because of a higher NRM rate in the high-risk groups, ultimately abrogating the OS benefits resulting from the allo-HCT. The other possibility for why standard-risk patients did better (in addition to less NRM) is that perhaps their relapse risk is more modifiable and more responsive to HCT than poor-risk patients. In the sense that poor-risk patients have such a high relapse risk, that mode of treatment possibly has no great effect on overall prognosis. Table 1 illustrates outcomes of allo-HCT in ALL in CR1 from a selected number of studies.