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Which patients should I transplant with acute lymphoblastic leukemia?

Tsofia Inbar [a], Jacob M. Rowe [a, b, c], Netanel A. Horowitz [a, c, *]

[a] Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, 8, Ha'Aliya St, Haifa, 3109601, Israel
[b] Department of Hematology, Shaare Zedek Medical Center, 12, Shmu'el Bait St, Jerusalem, 9103102, Israel
[c] Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel

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ABSTRACT

Allogeneic hematopoietic cell transplantation for acute lymphoblastic leukemia (ALL) offers curative therapy for patients who are in complete remission. Historically, there was great hesitation to offer this modality to patients with ALL due to the high attendant morbidity and mortality. Furthermore, the outstanding results in childhood ALL led many to believe that significant long-term survival could be achieved using chemotherapy-based regimens alone. The International ALL Study jointly conducted by ECOG and MRC completely changed perceptions indicating, surprisingly to many, that transplantation – particularly for patients at standard risk – offered a significant survival advantage. There followed trials of more intensive chemotherapy demonstrating improved results that may obviate the need for allogeneic transplantation. While a certain controversy reigns, there are unequivocal high-risk scenarios where allogeneic transplantation still forms the core of curative therapy. Such transplants should be performed as early as possible in the course of the disease once remission has been obtained.

1. Introduction

Acute lymphoblastic leukemia (ALL) is a heterogonous and aggressive disease. In children, due to aggressive chemotherapeutic regimens, the cure rate of ALL approaches 90%. In adult patients the 5-year overall survival (OS) rate is relatively low, estimated to be 40–45% [1]. Allogeneic stem cell transplantation (allo SCT) was demonstrated to be significantly better than conventional chemotherapy in the largest prospective study of transplantation in ALL, the International ALL Study, conducted jointly by the Eastern Cooperative Oncology Group in the United States and the Medical Research Council in the United Kingdom – ECOG E2993/MRC UKALLXIII trial [2]. In a donor versus no donor analysis, allo SCT in first complete remission (CR1) resulted in better OS and disease-free survival (DFS) in standard-risk ALL patients. Despite a lower relapse rate also in high-risk patients, a survival advantage could not be demonstrated in patients older than 40 years; the high non-relapse mortality abrogated the benefit due to the potent graft-versus-leukemia (GvL) effect.

In recent years, many studies reported that adolescents and young adults (AYA) with ALL may benefit from pediatric-like (i.e., more intensive) chemotherapy protocols, leading to improved survival, which may even be superior to what can be

* Corresponding author. Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, 8, Ha'Aliya St, Haifa, 3109601, Israel.
E-mail addresses: z_inbar@rambam.health.gov.il (T. Inbar), rowe@jimmy.harvard.edu (J.M. Rowe), n_horowitz@rambam.health.gov.il (N.A. Horowitz).

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achieved with an allo SCT [3–8]. Moreover, the development of new and sensitive techniques to monitor minimal residual disease (MRD) may serve as a very potent tool in assessing response to therapy at critical milestones, suggesting that allo SCT may be reserved for specific high-risk subgroups of patients with ALL. However, importantly, both of these premises have yet to be proven to benefit the overall outcome in adult ALL. Lastly, continued discoveries of new disease-related genetic aberrations enhances the process of redefining the risk of ALL subgroups and, in some categories, developing new targeted therapies that currently are being integrated into existing therapeutic strategies. Considering this, the roles of allo SCT over the treatment course of ALL patients need to be continuously evaluated, ideally in prospective randomized studies.

This review will critically assess the overall strategy of transplantation in ALL, particularly in light of new prognostic factors and advances in therapeutic strategies. Specific subgroups of patients may be identified in whom allo SCT remains the cornerstone of management, irrespective of improvement in the chemotherapeutic management of ALL [Table 1].

2. The graft-versus-leukemia effect in ALL

The graft-versus-leukemia (GvL) effect remains the fundamental immunotherapeutic strategy that leads to the potent anti-leukemic action of allogeneic transplantation. This effect was convincingly demonstrated, for the first time in humans, by Paul Weiden and his colleagues from Seattle in 1979 [9] [Fig. 1]. Interestingly, this anti-leukemic effect was particularly demonstrated in patients with ALL, reporting a significant reduction in relapse among patients with clinical graft-versus-host disease (GvHD). Despite these historic data in the early years of allo SCT, there remained much skepticism regarding the potency of the GvL effect in ALL. While allogeneic transplantation was readily incorporated into clinical studies of acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), there was almost a uniform reluctance to consider this in ALL (with the exception of Ph-positive ALL). This was due to the rapidly improving clinical results in childhood ALL, and the belief that this would be, similarly followed in adult ALL [10], and also buttressed by the disappointing impact of donor lymphocyte infusions (DLI) in relapsed ALL compared with CML or AML [11]. The effect of DLI, particularly without chemotherapy, was the strongest evidence for the GvL effect in leukemia. The data reporting that only a few patients with relapsed ALL have a meaningful response to DLI was erroneously extrapolated to all patients with ALL, including those in CR1.

Since then, the positive role of the GvL effect in ALL was prospectively and convincingly demonstrated in two major studies. The UKALL XII/E2993 was the first large prospective ALL study in which the role of matched related SCT in CR1 was assessed. A donor versus no-donor analysis demonstrated that Philadelphia chromosome-negative patients with a donor ($n = 443$) had a 5-year improved overall survival (OS), 53% versus 45% for patients without a donor ($n = 558$) ($P = 0.01$) [Fig. 2], and the relapse rate was significantly lower ($P \leq 0.001$) both in standard- and high-risk disease [Figs. 3 and 4]. The survival difference was significant in standard-risk patients, but not in high-risk patients due to high toxicity of this procedure [2]. Similar data was also demonstrated in the HOVON study, which evaluated the role of allo SCT in CR1 [12]. The cumulative incidences of relapse at 5 years were, respectively, 24% and 55% for patients with a donor ($n = 96$) versus those without a donor ($n = 161$; $P < 0.001$). The non-relapse mortality (NRM) was 16% at 5 years after allo SCT. As a result, disease-free survival (DFS) at 5 years was significantly better in the donor group: 60% versus 42% in the no-donor group ($P = 0.01$) [12]. Furthermore, a Cochrane Database meta-analysis which included 14 trials with 3157 patients confirmed these findings and supports a matched sibling donor allogeneic hematopoietic cell transplantation as the optimal post-remission therapy in ALL patients aged 15 years or over [13]. The positive effect of allo SCT was also demonstrated in Philadelphia chromosome positive ALL (Ph+ ALL) [14].

The positive role of the GvL effect in ALL was also retrospectively assessed by Passweg et al. [15]. In this retrospective study, 1133 ALL (B and T lineage) were transplanted in CR1 or CR2. The occurrence of GvHD was associated with a decreased relapse rate to a similar extent in T and B lineage ALL. For first remission transplants, the relative risks of relapse for patients with versus those without GvHD was decreased by 2.5 fold [hazard ratio (HR) 0.40] for T lineage and B lineage ALL [15]. Taken

Table 1
Indications for allogeneic stem cell transplantation in ALL.

Clinical scenario	Recommendation	Comment
Relapsed/Refractory ALL	Allo SCT is only curative modality	Timing of transplant, preferably when MRD-status achieved, requires considerable clinical expertise
All adults with ALL in CR1	Transplant from related donor Potent GvL effect	Potent rationale, based on prospective randomized data. Recent advances in chemotherapy may abrogate the need for a transplant. Prospective studies needed.
High-risk ALL	Transplant from related or matched unrelated donor	Justified, also if MRD negativity achieved post induction
•Ph+ ALL	Historically, the most unequivocal indication for an allogeneic transplant.	Ongoing studies in TKI era to determine if an allogeneic transplant is still an imperative.
•Ph-like ALL	Recently recognized as very high-risk	Best if performed after MRD negativity achieved.
•T-cell ALL		Particularly for early pre-T-cell ALL
•Older patients with ALL	RIC transplant feasible	Prospective studies needed. May be largest group to be transplanted.
•Morphologic CR, but MRD + post induction		Best, if MRD negativity achieved