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Leukemia (PH Wiernik, Section Editor)

Indications for Allogeneic HCT in Adults with Acute Lymphoblastic Leukemia in First Complete Remission

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Opinion statement

Acute lymphoblastic leukemia (ALL) in adults is associated with poor outcomes as compared to children when treated with chemotherapy, leading to a considerably inferior cure rate. Historically, consolidation with allogeneic hematopoietic cell transplant (alloHCT) was routinely recommended for eligible adults with ALL in first complete remission (CR1) if a donor was available, since randomized studies showed superiority over continuing chemotherapy. With the increasing use of pediatric-inspired frontline regimens in young adults with ALL and the availability of novel salvage agents for relapsed/refractory B-cell ALL that have high potential in inducing a second CR, the role of early alloHCT in the treatment paradigm for ALL needs to be reevaluated, and the decision should be individualized for each patient. Simultaneously, alloHCT has evolved considerably lately, and historical randomized studies that have proven the benefit of alloHCT in adults with ALL in CR1 did not included the increasing use of reduced intensity conditioning and haploidentical transplants, and therefore, data may not entirely apply. Nowadays, detectable minimal residual disease (MRD) is the most prognostic determinant of ALL outcome and should be a major consideration in the decision to perform alloHcT in CR1. Nonetheless, other biological and clinical factors remain relevant and can support the complex decision-making. Such factors include high-risk leukemia genetics, the type of administered chemotherapy regimen and the ability of the patient to tolerate all key

components of the regimen, and the availability of effective salvage therapies that allow alloHCT to be performed in CR2 in case of relapse after chemotherapy.

Introduction

Acute lymphoblastic leukemia (ALL) is characterized by clonal proliferation of immature lymphoid cells that infiltrate bone marrow and other tissues, with a higher tendency towards involvement of central nervous system compared to any other forms of acute leukemia. ALL is predominantly diagnosed during childhood, but there is a second modest peak observed in adults [1]. Chemotherapy treatment is effective in curing the majority of pediatric patients with ALL [2]. In contrast, the chemotherapy approach is only successful in curing half of young adults with ALL [3]. Outcomes are even more disappointing for older adults with only 20% of them enjoying long-term survival [4–6].

There are different prognostic factors that determine response of ALL to conventional chemotherapy and thereby determine their long-term outcomes. The kinetics and the depth of response to initial therapy remain the key factors that predict the risk of ALL relapse. Historically, this was evaluated by enumerating bone marrow lymphoblasts using standard morphology and immunophenotyping in order to define complete remission (CR). While most adults attain morphological CR (defined as < 5% bone marrow lymphoblasts) in response to initial induction therapy, over half of these patients eventually relapse. The introduction of minimal residual disease (MRD) as a routine assessment tool for response to ALL therapy has provided the most important prognostic factor that determines outcome and has largely surpassed the majority of traditional risk factors. Nonetheless, other leukemia and patient-related factors remain important as they can help stratifying patient risk and guide post remission therapy [7–22].

Consolidation with allogeneic hematopoietic cell transplantation (alloHCT) in ALL has a proven record in reducing risk of relapse and improving the survival in high-risk patients [23–25]. The anti-leukemic effect for alloHCT is mediated through the direct effect of conditioning regimens in eradicating residual disease as well as the activity of graft versus leukemia (GVL) effect on eliminating residua leukemia over time. Nevertheless, alloHCT carries non-trivial risks of therapy-related mortality and morbidity, and therefore, precise stratification of ALL risk to determine who would clearly benefit from alloHCT in CR1 is imperative to avoid HCT-related morbidity and mortality in patients who would otherwise be cured with chemotherapy approach. Today, recommendations for alloHCT consolidation in adult with ALL in CR1 beyond persistent MRD have remained an area of debate, and the decision to transplant should be individualized for each patient based on a complex risk-benefit analysis. In this article, we will summarize data supporting alloHCT in adults with ALL and illustrate our approach in recommending alloHCT based on available data. Table 1 summarizes published alloHCT studies for in ALL.

Early experience of sibling donor alloHCT for ALL in CR1

Due to the historical limitations of unrelated donor availability, early transplant studies compared outcome of patients with ALL who underwent alloHCT versus chemotherapy consolidation based on the availability of matched sibling donor (MSD), so-called "genetic" randomization. Four such prospective studies reported outcomes of patients with ALL in CR1 after a variety of induction therapies who underwent alloHCT from MSD. Ribera et al. reported outcomes of the Programa de Estudio y Tratamiento de las Hemopatías Malignas (PETHEMA) group's

Table 1. Published studies on outcomes of allogeneic HCT in adults with ALL in CR1

Study	Patients	Survival	Relapse	NRM
Ribera et al. PETHEMA group (Prospective, randomized)	*n* = 222 Age: 15–50 years MSD = 84 No donor = 138	5-year DFS Donor group = 37% No donor group = 46% is 5-year OS Donor group = 40% No donor group = 49%	At 5-years Donor group = 62% No donor group = 51%	Donor group = 10% No donor group = 2%
Goldstone et al. MRC-ECOG (Prospective, randomized)	*n* = 1031 Age: 15–64 years MSD = 443 No donor = 588	High-risk 5-year OS Donor group = 41% No donor = 35% Standard-risk 5-year OS Donor group = 62% No donor = 52%	High-risk 10-year Donor group = 37% No donor = 63% Standard-risk 10-year Donor group = 49% No donor = 24%	High-risk at 2-years Donor group = 36% No donor = 14% Standard-Risk at 2-years Donor group = 20% No donor = 7%
Cornelisson et al. HOVON study (Prospective, randomized)	*n* = 257 Age: 15–55 MSD Donor = 96 No donor = 161	5-year DFS Donor group = 60% No donor = 42%	At 5-years Donor group = 24% No donor = 55%	At 5-years Donor group = 16% No donor = 3%
Kako et al. Japan Adult Leukemia Study Group (JALSG) (Prospective, randomized)	*n* = 649 Age: 15–54 MSD Donor = 408 No donor = 241	High-risk 10-year OS Donor group = 38% No donor = 25% Standard-risk 10-year OS Donor group = 54% No donor = 40%	NR	NR
Jamieson et al. City of Hope and Stanford Group (Retrospective)	*n* = 85 CR1 = 55 CR2 = 30 MSD donor = 85 Conditioning: FTBI/VP-16	OS for CR1 = 66% OS for CR2 = 62% (*p* = .67) EFS for CR1 = 64% EFS for CR2 = 61%	At 10-years For CR1 = 15% For CR2 = 32%	NR
Srour et al. 2017	*n* = 109 CR1 = 32 ≥ CR2 = 77 Median age: 32 years Donor = haploidentical GVHD Prophylaxis: PTCy based	At 1-year DFS = 51% OS = 66% At 3-years DFS = 31% OS = 37% 3-year DFS for CR1 = 52%	At 1 year = 27% At 5-years = 40%	At 1-year = 21% At 5-years = 30%
Santoro et al. EBMT	*n* = 208 CR 1 = 44%	At 3-years LFS = 31%	At 3-years = 37%	At 3-years = 32%

Table 1. (Continued)

Study	Patients	Survival	Relapse	NRM
	≥ CR2 = 56% Median age: 32 Donor = haploidentical GVHD Prophylaxis: PTCy based: 57% ATG based: 43% MAC: 66% RIC: 57%	OS = 33% At 3-years for CR1 LFS = 47% OS = 52%		
Al Malki et al. CIBMTR	*n* = 1461 Donor: Haplo = 487 MUD = 974 MAC: 74% RIC: 26%	OS at 3-years for MAC Haplo = 44% MUD = 51% (*p* = .56) OS at 3-years for RIC Haplo = 43% MUD = 42% (*p* = .60)	3-year Relapse Haplo = 37% MUD = 34% (*p* = .68)	3-year NRM Haplo = 24% MUD = 24% (*p* = .19)
Chalandon et al. GRAAPH-2005 (Randomized prospective)	*n* = 268 Ph + ALL Median Age: 47 years Arm A: HD imatinib with RI chemotherapy Arm B: SD imatinib with hyper CVAD HCT in CR1; *n* = 161 MSD = 76 MUD = 72 CBU = 13	5-year EFS = 37.1% 5-year OS = 45.6% (No difference in arms) 5-year post-HCT RFS = 48.3% OS = 56.7%	At 5-years, 92 patients relapsed (43 in Arm A and 49 in Arm B)	5- year NRM for HCT patients= 25.8%
Ravandi et al. US intergroup	*n* = 94 Ph + ALL Median age: 44 years (20–60) Hyper CVAD with dasatinib CR1 = 83 (88%) HCT; *n* = 41	For whole cohort; 3-year OS = 69% 3-year EFS = 55% 3-year RFS = 62% For HCT Cohort; 1-year RFS = 71% 1-year OS = 87%	At 20 months: Relapse rate = 43% 2 patients undergoing HCT relapsed	NR
Bachanova et al. CIBMTR (Retrspective)	*N* = 197 Ph + ALL, CR1 MAC: 130 RIC: 67	3-year OS MAC: 35% RIC: 39% (*p* = .62)	3-year relapse rate MAC: 28% RIC: 49% (*p* = .058) Higher risk of relapse for pre-HCT MRD+ with RIC (HR 1.97, *p* = .026)	1-year NRM MAC: 36% RIC: 13% (*p* = .001)
Brissot et al. EBMT	*N* = 473 Ph + ALL, CR1	5-year LFS: 38% 5-year OS: 46%	Relapse at 5-years: 36%	5-year NRM: 26%

Table 1. (Continued)

Study	Patients	Survival	Relapse	NRM
(Retrspective)		Pre-HCT TKI use led to improved LFS (HR = 0.44; *P* = .002) and OS (HR = 0.42; *P* = .004)	Pre-HCT TKI use led to lower relapse incidence (HR = 0.40, *p* = .01)	
Cassaday et al	*N* = 89 ALL MRD- CR1 Ph + ALL *n* = 28 MAC = 33 RIC = 17 Deferred HCT = 39	3-year OS MAC = 71% RIC = 69% Deferred HCT = 68% 3-year EFS MAC = 65% RIC = 54% Deferred HCT = 28% 3-year OS for MRD- CR1 vs. MRD-CR2+ = 70% vs. 69% 3-year EFS for MRD- CR1 vs. MRD-CR2+ = 62% vs. 62%	3-year cumulative incidence of relapse MAC: 10% RIC: 40% Deferred HCT: 72%	1-year cumulative incidence of NRM CR1 = 19% CR2 = 15% (*p* = .59)

PETHEMA, Programa de Estudio y Tratamiento de las Hemopatías Malignas; *n*, number; *NRM*, non-relapse mortality; *MSD*, matched sibling donor; *DFS*, disease free survival; *OS*, overall survival; *NR*, not reported; *CR1*, first complete remission; *CR2*, second complete remission; *EFS*, event free survival; *FTBI*, full total body radiation; *VP-16*, etoposide; *GVHD*, graft-versus-host disease; *PTCy*, post-transplant cyclophosphamide; *EBMT*, European society of blood and marrow transplantation; *ATG*, anti-thymocyte globulin; *MAC*, myeloablative conditioning; *RIC*, reduced intensity conditioning; *CIBMTR*, Center for international blood and marrow transplant research; *MUD*, matched unrelated donor; *Haplo*, haploidentical donor; *Ph+*, Philadelphia chromosome positive; *HD*, high dose; *RI*, reduced intensity; *SD*, standard dose; *CBU*, cord blood unit; *RFS*, relapse free survival; *HCT*, hematopoietic cell transplant; *HR*, hazard ratio; *LFS*, leukemia free survival; *MRD*, minimal residual disease.

multi-center randomized study of adults with high-risk ALL after induction therapy and showed no significant difference in outcomes between the patients undergoing MSD transplant (n = 84), chemotherapy (n = 48), or autologous HCT (n = 50) [26]. All patients who had MSD available were assigned to the alloHCT group, and remaining patients were randomized to chemotherapy maintenance or autoHCT. Non-relapse mortality (NRM) (10% vs. 2%), and unexpectedly, relapse rate at 5 years (62% vs. 51%) were higher in the donor group. Disease-free survival (DFS) and overall survival (OS) were not significantly different in either group. Goldstone et al reported outcomes of multi-center prospective randomized study of ALL patients in CR1 after induction [23]. Patients were assigned to alloHCT if they had MSDs available, and the rest were randomized to chemotherapy and autologous HCT. At 5 years, Philadelphia chromosome negative (Ph-) ALL patients with a MSD had significantly improved OS (53% versus 45%, P = 0.01) and lower relapse rate (P < 0.001) as compared to no donor patients. The difference in survival was significant in standard-risk patients but not in high-risk patients, where the reduced relapse was offset by increase in NRM in the latter group.

The Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) study analyzed results of two prospective clinical trials of alloHCT in ALL CR1 [24]. A total of 257 adult patients were included; 96 patients with available donors and 161 patients had no donors available. Significant higher 5-year DFS was observed in the donor group (60% vs. 42%, P = .01). Although NRM was

significantly higher in the donor group (16% vs. 3%, $P = .002$), the incidence of relapse at 5 years was significantly lower (24% vs. 55%, $P \leq .001$). These results were consistent with better disease control in patients who had available donors and underwent alloHCT, and both standard and poor-risk patients had significantly improved outcomes. The Japan Adult Leukemia Study Group (JALSG) reported outcomes of 2 studies; ALL93 and ALL97, that enrolled 649 patients with Ph- ALL in CR1 who underwent consolidation with MSD HCT ($n = 408$) or chemotherapy ($n = 241$). Patients who underwent alloHCT had significantly higher 10-year OS as compared to patients who underwent consolidation with chemotherapy (48.3% versus 32.6%, respectively).

Another retrospective study analyzed outcomes of consecutive high-risk ALL patients transplanted with MSD in CR1 at City of Hope Medical Center and Stanford University [25]. High-risk features included WBC > 25,000; cytogenetics including t(9;22), t(4;11), t(8;14); age greater than 30 years; extramedullary disease at the time of diagnosis and/or requiring more than 4 weeks to achieve CR. Two thirds of the patients had one risk factor, and other patients had 2 or more risk factors at presentation. This analysis showed that alloHCT in CR1 yielded prolonged DFS in patients with high-risk ALL. After a median follow-up exceeding 5 years, probabilities of event-free survival (EFS) and relapse rate were 64 and 15%, respectively.

Therefore, most early MSD transplant studies show favorable outcomes for alloHCT consolidation in adults with Ph- ALL in CR1 as opposed to chemotherapy consolidation. Nonetheless, these results are outdated given the progress that has been made in transplant supportive care, the availability of alterative donors, the feasibility of reduced intensity conditioning (RIC), as well as the introduction of contemporary pediatric inspired regimens that have improved the cure rate of young adults treated with chemotherapy alone. Furthermore, the recent availability of effective salvage therapies such as blinatumomab, chimeric antigen receptor (CAR) T cell therapy, and inotuzumab has allowed many relapsed patients to enter a second CR and then be bridged successfully to alloHCT.

Experience of unrelated donor HCT for ALL in CR1

HLA matched unrelated donors (MUD) have been increasingly used for patients with high-risk ALL without MSD. The European Society for Blood and Marrow Transplantation (EBMT) published data on trends of the use of donors for alloHCT in patients with ALL between 2001 and 2015 [27••]. Among 13,460 alloHCT performed, 52% were MUD, 43% were MSD, and 6% were mismatched unrelated donor. There was a continuous increase in trends of alloHCT over time, mostly in patients with CR1.

Multiple reports have shown that outcomes of alloHCT for ALL are comparable for MSD and MUD. Investigators from the American Society for Blood and Marrow Transplantation (ASBMT) showed comparable LFS rates (approaching 60%) for both MSD and MUD alloHCT's performed between 2008 and 2012 in ALL patients in CR1 [28]. However, in multivariate analysis, the use of MUD was associated with an increased risk of NRM (HR = 2.11, $P = .01$) but with the caveat that this study had a significant proportion of mismatched unrelated donor HCT. This study also reported an overall improvement in transplant

outcomes in recent years (2008–2012) as compared to older time period (1993–2007).

Alternative donors

Either MSD or MUD are preferred choices of donors for HCT. Nonetheless, many patients with ALL, particularly older patients and ethnic minorities may not have a suitable fully matched donor available for curative alloHCT. Therefore, haploidentical related donors and cord blood (CB) grafts have emerged as acceptable alternative donor choices for transplant. Almost all patients in need for HCT would have at least one suitable haploidentical donor available. With the availability of post-transplant cyclophosphamide (PTCy), outcomes of haploidentical transplant have improved, and nowadays, they are broadly comparable to those of MUD transplant. Srour et al., in 2017, published multicenter outcomes of haploidentical transplant with PTCy for 109 patients with high-risk ALL, of whom only 32 were in CR1 [29]. The NRM, relapse rate, and DFS at 1-year post transplant were 21, 27, and 51%, respectively. The 3-year DFS for patients in CR 1 was 52% [29]. The EBMT investigators reported outcomes of 208 patients with ALL who underwent haploidentical transplant between 2007 and 2014, including 44% of patients were in CR1 [30•] This study included 57% of the patients who received PTCy and 43% who received antithymocyte globulin (ATG)-based GVHD prophylaxis. The 3-year NRM, relapse rate, OS, and LFS were 32, 37, 33, and 31%, respectively. For patients in CR1, OS and LFS at 3-year were 52 and 47%, respectively. Al Malki et al. reported a CIBMTR analysis of 1461 adults with ALL who underwent alloHCT from either a haploidentical donor (n = 487) with PTCy or MUD (n = 974) between 2005 and 2018 [31•]. Among patients who received myeloablative conditioning (MAC), 3-year OS were 44 and 51% for haploidentical and MUD (P = .56), respectively. Corresponding rates after RIC were 43 and 42% (P = .60). These studies suggest that haploidentical donor HCT is a feasible option for patients with ALL.

Another alternative option for patients who lack a donor is umbilical cord blood (UCB). Terakura et al. compared outcomes of 8/8 HLA MUD, 7/8 matched unrelated donors (MMUD), and UCB-HCT. A total of 2472 patients who underwent alloHCT for AML and ALL with MAC between 2000 and 2010 were included [32]. With adjusted analyses for AML, UCB and MUD showed similar OS, whereas MMUD showed inferior OS. For ALL, there was no significant difference in OS among the three groups. Authors concluded that UCB-HCT may be considered as an alternative choice to MUD for both AML and ALL [32]. However, with the introduction of haploidentical transplant, UCB transplant is falling out of favor given the high cost and the recent randomized study showing inferior survival as well as its higher NRM [33].

The role of alloHCT consolidation for young adult ALL in the era of pediatric-inspired chemotherapy regimens

While historical randomized studies have shown benefit for alloHCT in adults with ALL in CR1 compared to non-transplant approaches, the chemotherapy

regimens used to consolidate non-transplant patients were outdated and not representative of currently used regimens in younger adults with ALL. Recent studies have documented the benefit of extended pediatric-inspired regimens in young adults with ALL [34–39]. Nowadays, the cure rate for patients treated with pediatric regimens approaches 60–70%, and this is comparable to, if not exceeding, transplant outcomes for adults with ALL in CR1 in the same age group. Studies have compared outcomes of pediatric inspired regimens with alloHCT; however, these studies suffer from several confounding factors, mainly related to comparing consortium outcomes of patients treated on prospective studies to retrospective transplant data.

One study compared outcomes of 108 young adults (age; 18–50 year) treated with Dana-Farber Cancer Institute (DFCI) regimens and achieved CR on 2 randomized clinical studies with 422 patients with the same age range with ALL transplanted in CR1 from matched donors [40]. While 4-year relapse rates were comparable (24% vs. 23%), NRM was higher in the transplant cohort (37% vs. 6%) compared to chemotherapy. This resulted into improved OS (73% vs. 45%) and DFS (71% vs. 40%) in chemotherapy cohort compared to the transplant cohort, respectively. Furthermore, transplant was the only factor negatively influenced OS in multivariate analysis [40]. Another retrospective study showed no survival benefit of alloHCT in CR1 in young adults treated according to the to the Berlin-Frankfurt-Münster-95 (BFM-95) regimen [41].

Indications of alloHCT in adults with Ph-negative ALL

Based on our interpretation of available data, published guidelines and our own experience, we have summarized recommendations for alloHCT in CR1. We also discuss the data supporting our recommendations for various clinical scenarios [42••, 43••].

- **Persistent MRD**: MRD analysis plays the most important role in decision-making for consideration alloHCT after initiating induction therapy [14, 15]. MRD monitoring strongly correlates with clinical outcomes, and it is considered as the utmost key factor that predicts ALL relapse [16–18, 43••, 44, 45]. Bruggemann et al. studied the predictive value of MRD during the first year of therapy for standard risk ALL [18]. Late MRD negativity was associated with higher risk of relapse and patients who became MRD+ after initial MRD- status were at a much higher risk of relapse as compared to the patients with persistent MRD- status (61% vs. 6%) [18]. The Polish Adult Leukemia Group (PALG) 4-2002 study prospectively evaluated the significance of MRD analysis in Ph- ALL [46]. In a total of 116 patients (age 17–60 years), MRD level ≥ 0.1% after induction was found to be a strong and independent predictor for disease relapse ($P < .0001$), in both standard risk (SR, $P = .0003$) and high-risk ($P = .008$) groups. However, there was no significant impact for MRD after consolidation on outcomes. The German Multicenter Study Group for adult ALL (GMALL) prospectively studied molecular response after induction/consolidation chemotherapy in patients with Ph- ALL [15]. Patients with molecular CR after consolidation had a significantly higher probability of continuous complete remission (CCR) (74% vs. 35%; $P < .0001$) and of OS (80% vs. 42%; $P = .0001$).

Patients with molecular failure who did not undergo alloHCT in CR1 relapsed after a median time of 7.6 months, with CCR and survival at 5 years only of 12 and 33%, respectively.

Bassan et al. reported outcomes of prospective clinical study of MRD as a predictive factor for ALL recurrence and the decision-making tool for post-consolidation maintenance [47]. Patients with t(9;22) or t(4;11) were immediately eligible for alloHCT. Patients who achieved MRD negativity or low positive ($< 10^{-4}$) PCR signal at week 16 and completely undetectable signal at week 22 were considered lower risk of relapse and received maintenance with chemotherapy. Patients who did not fulfill the above-mentioned criteria were considered to be at high risk for relapse and, thus, were candidates for alloHCT if a donor is available or intensified courses of chemotherapy followed by maintenance. Of 54 patients with detectable MRD at the end of consolidation, 36 were treated with alloHCT (n = 22) or intensified courses of chemotherapy consolidation (n = 14), and these patients had better DFS as compared to MRD+ patients who did not undergo either therapy (n = 18) [47]. The PETHEMA ALL-AR03 trial enrolled high-risk patients with Ph- ALL and evaluated their treatment based on early morphological response and MRD assessment after consolidation [48]. AlloHCT was recommended in patients with poor early morphological response or MRD level $\geq 10^{-4}$. MRD clearance was the only prognostic factor that affected OS and DFS.

In the CALGB 10403 study, detection of MRD after induction showed a strong correlation with worse DFS and OS young adults treated with a pediatric-inspired regimen. DFS rate at 3 years was 85% in patients with MRD- status after induction therapy as compared to only 54% in MRD+ patients (P =.001) [49]. The GRAALL-2003 and the GRAALL-2005 studies treated adults with Ph- ALL with pediatric-inspired regimen and for patients with at least one high-risk feature were candidates for transplant in CR1 [50]. There was no difference in RFS between patients who did or did not undergo alloHCT. However, alloHCT was associated with improved RFS as compared to chemotherapy among patients who achieved CR1 with persistent post-induction MRD ($\geq 10^{-3}$) but not in good responders.

In summary, alloHCT in CR1 is recommended in adults with Ph- ALL if they continue to exhibit persistent MRD post-consolidation (12–16 weeks from induction), and this is regardless of the ALL regimen or genetic risk. For adults treated with modern ALL regimens and have persistent MRD post-induction that clears post-consolidation (weeks 12–16), it is debatable if alloHCT is indicated or not. For these patients, our decision to recommend alloHCT is performed case by case, and it depends on the presence of other individual high-risk features such as adverse genetics, regimen intolerability, early toxicities that preclude administration of key agents such as asparaginase, as well as the availability of suitable matched donor.

- **High-risk genetics:** Cytogenetic abnormalities in ALL have important prognostic influence on treatment outcomes [20, 21]. The CALGB reported a prospective study of cytogenetic abnormalities for newly diagnosed patients with ALL [9]. Patients with t(9;22), t(4;11), −7, or +8 had significantly lower probabilities of continuous CR and survival at 5 years (11% and 12%) than patients with a normal karyotype (38% and 37%) or patients with miscellaneous cytogenetic abnormalities (52% and 49%; P <.001 for each

comparison). Patients with cytogenetic abnormalities other than t(9;22), t(4;11), −7, or +8 had better CR rates, DFS, and OS (P =.001, P =.04, and P =.004, respectively) after switching to more intensive chemotherapy regimens. Patients with normal cytogenetics had improved CR rate, but there were no improved DFS or survival, whereas in contrast, no significant benefit for patients with t(9;22), t(4;11), −7, or +8 was observed. In a multivariate analysis, karyotype retained its prognostic significance for DFS but not for overall survival [9]. Among 1522 adult patients with ALL enrolled on MRC UKALLXII/ECOG 2993 trial, patients with t(9;22), t(4;11)(q21;q23), t(8;14) (q24.1;q32), complex karyotype (5 or more chromosomal abnormalities), or low hypodiploidy/near triploidy had inferior rates of EFS and OS when compared with other patients. In contrast, patients with high hyperdiploidy or a del(9p) had a significantly improved outcome. Multivariate analysis depicted that the prognostic significance of t(8;14), complex karyotype, and low hypodiploidy/near triploidy was independent of gender, age, white cell count, and T-cell status among Ph- ALL patients.

Given the poor outcomes of high-risk cytogenetics with chemotherapy approach, consolidation with alloHCT has been traditionally recommended to these patients. We have reported outcomes of a retrospective study of alloHCT for 333 adult patients [51]. In a multivariate analysis, high-risk cytogenetics did not impact OS or LFS for the whole cohort or for the patients who underwent alloHCT in CR1 [51]. In a large CIBMTR retrospective analysis of 1731 patients with Ph- B-cell ALL who underwent alloHCT in CR1, alloHCT overcame many high-risk cytogenetics abnormalities. However, monosomy 7, complex karyotype, and t(8;14) predicted inferior outcomes with alloHCT as opposed to other findings [52].

Ph-like ALL: Ph-like ALL has similar gene expression profile of Ph+ ALL but lacks *BCR-ABL1* translocation. Ph-like ALL represents around 20% of all adults cases with B-cell ALL in the USA [53], and it is associated with high rates for persistent MRD irrespective of the employed induction regimen [54], and this is translated into poor long-term ALL-related outcomes [53–55]. This inferior survival of Ph-like ALL is particularly more predominant in cases carrying *CRLF2* rearrangement and *IKZF1* deletion [54]. Furthermore, the inferior outcome of Ph-like ALL may not be overcome with early MRD response [54, 56]. In the GIMEMA LAL1913, more Ph-like ALL patients had persistent MRD post-induction and consolidation compared to other B-cell ALL (52.9% vs. 20% P =.025), and this was reflected by higher rates of alloHCT in Ph-like ALL patients compared to other genetics (40% vs. 11%) [57•]. Data supporting the benefit of alloHCT in Ph-like ALL are lacking, especially in cases who achieve early MRD-. We have recently presented outcomes of 94 patients with Ph- B-cell ALL, and we compared outcomes of Ph-like *CRLF2r* (n = 35) vs. Ph-like non-*CRLF2r* (n = 26) vs. non-Ph-like other B-cell ALL (n = 33). We have showed despite higher relapse rate in Ph-like *CRLF2r* patients, OS and RFS were comparable to other subtypes. The 3-yr OS was 55% for all Ph-like ALL patients [58]. Nonetheless, additional studies are urgently warranted to explore if alloHCT consolidation can overcome the inferior outcome of Ph-like ALL and, more importantly, to address the value of alloHCT performed in early

MRD responders with Ph-like ALL. At this time, we strongly consider alloHCT for all our adult patients with Ph-like ALL, irrespective of early MRD response. However, we decide on each case individually based on other additional factors, in particular the estimated NRM of allo HCT for the individual patient.

Ph-positive ALL: Before the era of tyrosine kinase inhibitors (TKI), outcomes of Ph+ ALL with chemotherapy were extremely poor, and alloHCT was the only curative therapy for these patients. However, the challenge was to achieve CR and maintain it with chemotherapy until the transplant can be performed. In pre-TKI era, a study showed improved outcomes with myeloablative conditioning alloHCT leading to reduced relapse and increased LFS [59].

With the introduction of TKI and their use during the induction and consolidation therapy, rate of CR with deeper remissions increased with more patients undergoing alloHCT in CR with significant improvement in OS [60–62]. In the GRAAPH-2005 study, 268 patients (median age, 47 years) with Ph+ ALL were randomized to imatinib either in combination with reduced intensity chemotherapy or hyper CVAD [63], and recipients of alloHCT on the study had significantly superior RFS and OS. [63]. The multicenter US intergroup study treated newly diagnosed patients with Ph+ ALL using dasatinib in combination with hyper CVAD [64]. Patients who achieved CR1 and MSD or MUD available underwent alloHCT followed by dasatinib maintenance starting at day 100. A landmark analysis at 175 days after achieving CR showed statistically significant increase in RFS and OS for patients who underwent alloHCT [64].

A retrospective study conducted by the CIBMTR on 197 patients with Ph+ ALL in CR1 who underwent alloHCT with RIC (n = 67) or MAC (n = 130) evaluated the outcomes based on pre-HCT MRD analysis and TKI use [65]. For patients who were MRD- before transplant, outcomes with RIC or MAC were comparable, however, RIC was associated with inferior outcomes in patients with pre-transplant MRD+ disease. In a multivariate analysis, RIC was associated with lower NRM (HR 0.6; P = 0.057), but the absence of pre-transplant TKI administration (HR 1.88; P = 0.018), RIC (HR 1.891; P = 0.054) and pre-transplant MRD+ (HR 1.6; P = 0.070) increased the risk of relapse [65]. In a similar analysis conducted by the EBMT of 473 patients with Ph+ ALL, TKI administered before alloHCT was associated with improved LFS and OS and lower incidence of relapse [66].

A single arm phase II study using ponatinib with chemotherapy has shown high MRD- response and durable remission, and in short follow-up, alloHCT did not appear to extend survival of these patients [67, 68]. The CR rate was 100% with 83% achieving complete molecular response, and the 3-year EFS was 70%. Fifteen patients underwent alloHCT in CR1, and 11 were alive in CR after alloHCT.

In summary, leukemia genetics at diagnosis continue to play an important part in risk stratification and decision-making for alloHCT in conjunction with MRD response. AlloHCT should be considered in adults with high-risk genetics even for early responders until additional data confirm otherwise. High-risk genetics that require alloHCT in CR1 include, but are not limited to, complex karyotype (≥ 5 chromosomal abnormalities), t(8;14), low hypodiploidy, *KMT2Ar*, and Ph+ ALL. For Ph+ ALL, future confirmatory studies may challenge

the recommendation for universal alloHCT for eligible adults in CR1 if the beneficial effect of ponatinib in frontline setting or early MRD remission are validated on longer follow-ups. For Ph-like ALL, there are lack of data supporting alloHCT for early MRD responders; however, given that poor outcome observed irrespective of MRD response [54], alloHCT consolidation should be strongly considered for all eligible patients.

- **Inadequate initial therapy:** Failure or inability to receive adequate planned curative therapy is associated with increased risk of relapse regardless of early MRD response or underlying genetics. Suboptimal therapy could be the result of inappropriate regimen/dosing choice particularly for older patients and mostly due to lack of experience with complex ALL regimens or patient characteristics that preclude administering these regimens in full doses and on time due to factors such as obesity or abnormal baseline organ function. All these factors could compromise the curative potential of these regimens and thereby increase risk of ALL relapse. Additionally, some of younger patients who are treated with pediatric regimens may encounter early toxicities with key drugs such asparaginase that precludes further dosing, and this could adversely impact long-term disease control despite being treated with potentially curative regimens [69–71]. For these scenarios that preclude administration of complete chemotherapy regimens, we would strongly consider alloHCT early on regardless of MRD response or ALL genetics if a donor is available.

- **T-cell ALL**: T-cell ALL represents 15–20% of adults with ALL. Outcomes of newly diagnosed T-cell ALL are comparable to B-cell ALL nowadays with modern ALL regimens [34–37]. However, as opposed to the availability of effective salvage novel therapies in B-cell ALL, salvage options for T-cell ALL are extremely limited, and r/r disease is associated with dismal prognosis [72]. Therefore, early consolidation with alloHCT in high-risk T-cell ALL is crucial in attempt to avoid the devastating relapse. Detectable MRD has remained the key predictor for relapse in T-cell ALL [72, 73]. There are other prognostic features in T-cell ALL that could assist in stratifying disease risk and formulating the decision of early alloHCT. Studies have shown CD1a expression and *NOTCH1* and/or *FBXW7* mutations were associated with improved outcomes as oppose to CD13 expression and complex cytogenetics that are associated with inferior outcomes [72, 74]. Early T-cell precursor (ETP) ALL represents ~ 15% of all T-cell ALL cases, and it is characterized by unique immunophenotype (CD1a-, CD8-, CD5-(dim), and expression for 1 or more stem cell or myeloid antigens) and molecular profile. ETP is associated with poor clinical outcomes when treated with standard chemotherapy regimens [75–78]. While the COG AALL0434 showed improvement in DFS with the addition of nelarabine during consolidation in children with T-cell ALL [79], the addition of nelarabine in adults failed to improve ETP outcomes when combined with hyper CVAD in one study, and alloHCT remained the most successful approach to cure adults with

ETP [78]. Therefore, we recommend alloHCT for adults with high-risk T-cell ALL in CR1 who fail to clear MRD early during therapy, have high-risk genetics or ETP phenotype, or are unable to tolerate potentially curative regimens.

In conclusion, alloHCT continue to have imperative role in curing large proportion of adults with high-risk ALL, and it should be considered for patients with persistent MRD as well as patients with high-risk genetics in CR1 if a donor is available. The increased utilization of modern pediatric-inspired regimens in young adults with ALL successfully led to cure more patients with chemotherapy and spare alloHCT for poor responders or those who relapse afterward. This progress was accompanied by the introduction of effective salvage novel therapies in B-cell ALL such as blinatumomab, inotuzumab, and chimeric antigen receptor (CAR) T-cell therapy that can salvage higher percentage of patients with relapsed/refractory ALL and, therefore, allow many of these patients who did not receive alloHCT in CR1 to proceed successfully in second CR or beyond.

Declarations

Conflict of interest

Based on the disclosure forms received, none of the authors has any potential conflicts of interest to disclose

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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