

What Is the Optimal Consolidation Strategy for Adult Philadelphia Chromosome Negative Acute Lymphoblastic Leukemia Patients in First Complete Remission if You Are Not Able to Look for Minimal Residual Disease?

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ABSTRACT

Compared to pediatric age group, the prognosis of adult patients with acute lymphoblastic leukemia (ALL) is still poor. Although most adult Philadelphia chromosome negative ALL (Ph- ALL) patients achieve complete remission following induction chemotherapy, half of them are destined to relapse, resulting 40% long term overall survival. Therefore, choosing the best available consolidation strategy in first remission is of utmost importance. Recently, most study groups rely on the evaluation of minimal residual disease (MRD) to guide the consolidation approach. But, in routine practice MRD assessment may be problematic in the management of Ph- ALL. In this review, we summarized the current evidence for optimal consolidation strategy in adult Ph- ALL in first remission, if facilities for MRD analysis are not in place.

Key words: Acute lymphoblastic leukemia; Philadelphia chromosome negative; Hematopoietic cell transplantation; Adult; Consolidation

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INTRODUCTION

The last two decades witnessed a remarkable improvement in terms of long-term outcome in pediatric patients presenting with acute lymphoblastic leukemia (ALL) with nearly 90% 5-year survival rates^[1]. Adult ALL is not simply the same disease presenting in later years of life. This fact is reflected with only 40% long-term overall survival (OS) rates in adults^[2]. Although 80% to 90% of adult patients achieve hematologic remission following induction therapy, half of them are destined to relapse in the course of their treatment. Prevention of recurrence with the best available consolidation strategy in first complete remission (CR1) is of utmost importance as the long-term outcome of relapsed ALL is very disappointing with 7% to 10% OS^[3,4]. The concurrent use of tyrosine kinase inhibitors (TKI) with chemotherapy and allogeneic hematopoietic cell transplantation (allo-HCT) as consolidation in eligible patients is the current standard of care of Philadelphia chromosome positive (Ph+) ALL. On the other hand, the best consolidation approach for adult Philadelphia negative (Ph-) ALL patients is an ongoing debate.

The recent evidence suggests that minimal residual disease (MRD) following completion of induction or consolidation chemotherapy is the most important independent prognostic marker predicting future relapse in the setting of conventional chemotherapy and

allo-HCT^[5]. Currently, many study groups use MRD-based risk stratification algorithms to determine the optimal consolidation approach for adult Ph-ALL patients: chemotherapy or allo-HCT^[6-8]. Being the case, evaluation of MRD may overcome many traditional risk factors at diagnosis like age, white blood cell count, immunophenotype, cytogenetic and molecular abnormalities. With the application of current methodologies, determination of leukemia-associated immunophenotype or immunoglobulin/T-cell receptor gene rearrangements is possible in 90% to 95% of patients presenting with ALL^[5,9]. According to recommendations of a panel of experts from Europe, assessment of MRD needs to be performed in specialized centers with sufficient expertise, quality control measures and standardization of procedures^[10]. The application of minimal recommended technical requirements may be difficult outside of highly specialized research centers. Many centers, without capabilities for MRD evaluation, use conventional risk factors to determine consolidation strategy following first complete remission in (Ph-) ALL. At this point, there are 2 potential problems: (1) There is no standard definition of risk groups in adult ALL; (2) Many risk factors are time/treatment dependent and prone to change with evolution of new therapies. In addition to MRD assessments, emerging developments in the era of chemotherapy (pediatric-inspired protocols, monoclonal antibodies, T-cell mediated approaches like bispecific T-cell engager (BiTE) and chimeric antigen receptor T-cells (CAR-T cells)) and allo-HCT (conditioning regimens, graft versus host disease prophylaxis, high resolution HLA typing, supportive care etc.) may change the risk classification of ALL. Therefore, determination of the optimal consolidation in patients with Ph- ALL in CR1 may be a real challenge, if facilities for MRD evaluation are lacking.

CONVENTIONAL RISK STRATIFICATION OF ALL

In general, adult ALL patients is classified as standard (SR) and high risk (HR) in terms of relapse probability and to determine the best consolidation approach following achievement of CR1. It is the common practice of many centers to offer allo-HCT for patients who have HR features at diagnosis or fail to get MRD negative disease status in predefined time points according to specific protocols, while others (SR) receive consolidation/intensification courses and maintenance therapy for 2-3 years. Although many study groups use similar factors for risk stratification, these are heterogeneous and standard definitions do not exist^[11]. Age is a continuous prognostic factor in ALL and older patients do poorly compared to younger counterparts^[2]. Age over 30^[12,13], 35^[14] and even 60^[15] was accepted as a HR feature according to different study groups. White blood cell count (WBC) at diagnosis $> 30,000/\text{mm}^3$ (B-ALL) and $> 100,000/\text{mm}^3$ (T-ALL) was generally accepted as a poor prognostic factor^[7,14,16]. Pro-B and early/mature T-ALL was used to define HR ALL patients only in some study groups^[7,17]. While there is a consensus that the presence of t(9;22), t(4;11) and abn11q23 define HR disease, one of the largest studies on adult ALL patients used only the presence of t(9;22) as a HR cytogenetic feature^[14]. Although the backbones of treatment protocols (induction, intensification, consolidation, maintenance and central nervous system prophylaxis) are similar, again, there is no standard chemotherapy for patients presenting with ALL in general and Ph- ALL in particular. Heterogeneity of treatment protocols and risk stratification across study groups complicates meaningful comparison of studies in terms of relevant endpoints.

TREATMENT OF ADOLESCENTS AND YOUNG ADULTS (AYA)

As stated before, there is a clear inverse correlation between age and prognosis of ALL patients. There are many potential explanations for strong impact of age on long-term outcome. Adolescents and young adults (AYAs) have more favorable cytogenetic/molecular profile compared to older patients^[18]. Because of comorbidities or poor organ reserve, older patients are more vulnerable to cytotoxic chemotherapy, and cannot tolerate intensive regimens as their younger counterparts^[19].

The age limits defining AYAs are quite variable. The National Comprehensive Cancer Network accepted 15 to 39 years as age limits for AYA patients. In recent years, several retrospective observations from both sides of Atlantic suggested better outcomes for AYAs treated by pediatric study groups with more intensive regimens compared to adult protocols^[20-24]. In all studies, AYA patients (15-20 years) had a significantly better 5-year event-free survival (EFS) (one study reported 7-year EFS) compared to patients who received adult type regimens (63-74% vs 34-49%). This better outcome was attributed to incorporation of higher cumulative doses of cytostatic drugs like steroids, vincristine and L-asparaginase in pediatric protocols. The weighed mean of these 5 studies including a total of 776 AYAs with ALL indicated 27% advantage in terms of EFS with application of pediatric protocols^[20-24]. Following the success of pediatric protocols in AYAs, upper age limit of recent studies using pediatric-inspired approach increased up to 60 years. Compared to former experience in adult patients with 5-year OS of %24.1 in ALL patients between 40 to 59 years of age at the population level, the long-term outcome of adult ALL patients with pediatric-based protocols are quite encouraging^[2,25-29] (Table 1). A systematic review and meta-analysis including 11 trials and 2489 AYAs with ALL demonstrated significantly improved EFS in patients who received pediatric-inspired regimens (RR 1.66; 95% CI 1.39-1.99)^[30]. However, the upper age limit of most (8/11) studies was below 26 years, and the authors stated that the conclusions were valid only for ALL patients up to the age 20.

TO TRANSPLANT OR NOT TO TRANSPLANT? THAT IS THE PROBLEM

The primary aim of post-remission therapy in ALL is eradication of MRD and preventing relapse. Following achievement of CR1 there are 3 basic options for consolidation in patients presenting with Ph-ALL: chemotherapy, autologous HCT (autograft) and allo-HCT. There are no reports directly comparing consolidation chemotherapy with allo-HCT in a randomized fashion. Instead, studies relied on genetic randomization, where patients with matched-related donor were directed to allo-HCT, while others received chemotherapy or autograft according to study design and risk stratification. The heterogeneous risk classification/study design and intend-to-treat analysis, where patients were analyzed in the allo-HCT arm even if they did not receive HCT, made it difficult to compare the conflicting results of various studies. A 2006 meta-analysis including 7 studies (4 studies in HR ALL) showed a significant advantage in terms of OS in HR ALL patients who had a donor (hazard ratio: 1.42; $p: 0.019$)^[31]. Nonetheless, recently conducted large prospective trials in ALL indicated favorable outcome especially in SR patients who underwent matched-sibling donor (MSD) allo-HCT compared to no donor arms (autograft or chemotherapy) (Table 2)^[32-35]. It should

Table 1 Recent studies using pediatric-based regimens in adult ALL patients.

Study	Risk group	Age range	n	OS (%)
PETHEMA ALL-96 ^[24]	Ph- SR	15-30	81	69 (6-year)
GRAALL-2003 ^[25]	Ph- SR/HR	15-60	225	60 (42-month)
USC ^[26]	SR(33%)/HR(67%) Ph+ (22%)	18-57	51	51 (7-year)
CALGB 10403 ^[27]	Ph-	17-39	296	66 (2-year)
DFCI ^[28]	SR(45%)/HR(55%) Ph+ (20%)	18-50	92	67 (4-year)

*: the study is ongoing, final results not published yet; HR: high-risk; SR: standard-risk.

Table 2 Large trials in adult ALL: MSD allo-HCT vs autograft/chemotherapy.

Study group	Patients	Age range	OS (%) 5-year	p
PETHEMA ^[32]	(Ph-) HR n: 156	15-50	49% (no donor) 40% (donor) HR: 41% (donor)	0.56 0.2
MRC-ECOG ^[33]	Ph- n: 1031	15-64	35% (no donor) SR: 62% (donor) 52% (no donor)	0.02
HOVON ^[34]	donor: HR 48%; Ph+ 22% no donor: HR 45%; Ph+ 16%	15-55	HR: 53% (donor) 41% (no donor) SR: 69% (donor) 49% (no donor)	0.5 0.05
JALSG ^[35]	n: 257 Ph- n: 641	15-54	HR*: 38% (HCT) 25% (chemotherapy) SR*: 53.8% (HCT) 39.8% (chemotherapy)	NR

*: Results indicate 10-year survival probabilities; NR: not reported, MSD: matched-sibling donor; Statistically significant p values are presented in bold.

be emphasized that these studies are not uniform in terms of risk classification, chemotherapy regimens and design. One of the largest studies conducted in ALL patients showed superiority of MSD allo-HCT in Ph- ALL only in SR group. The major reasons of this finding seem to be the definition of HR (age over 35 regarded as HR) and high transplant-related mortality in older patients (> 35)^[33].

Following publication of two large prospective studies^[33,34] in adult ALL patients, Ram et al. made a new meta-analysis to find out best consolidation strategy for ALL patients in CR1^[36]. The evaluation of 7 ITT trials (2 in SR and 5 in HR patients) including a total of 1863 patients showed that myeloablative (MA) matched-related donor allo-HCT in patients with ALL in CR1 significantly reduced all-cause mortality (ACM) compared to other consolidation options (autograft and chemotherapy) (risk ratio = 0.89; 95% CI, 0.82-0.97, *p* = 0.009). However, subgroup analysis revealed that the benefit of allo-HCT was valid only for SR (risk ratio = 0.82; 95% CI, 0.70-0.98, *p* = 0.02) and not for HR patients (risk ratio = 0.91; 95% CI, 0.80-1.04, *p* = 0.16). Emerging data resulted a major change of recent position of American Society of Blood and Marrow Transplantation (ASBMT), recommending MA allo-HCT for all patients presenting with ALL in CR1 instead of chemotherapy (grade A) or autograft (grade B). The ASBMT stated that the advantage of allo-HCT compared to chemotherapy was especially evident in younger (age < 35) Ph- SR patients, and high TRM in older patients counterbalanced the survival advantage of this approach^[37]. Finally, a 2013 meta-analysis including 13 trials and 2962 patients in Ph- ALL used updated individual patient data to clear this controversial issue. In line with the previous meta-analysis, the authors showed a significant survival benefit of MA-MSD allo-HCT in CR1 only for patients below 35 years of age (OR = 0.79; 95% CI, 0.70-0.90, *p* = 0.003) and a trend for inferior outcome for autograft versus chemotherapy (OR = 1.18; 95% CI,

0.99-1.41, *p* = 0.06)^[38].

The application of reduced-intensity conditioning (RIC) regimens enabled older patients to receive allo-HCT with its curative potential. Allo-HCT using RIC regimens preserve the beneficial graft-versus-leukemia effect while reducing the intensity and toxicity of preparative regimen. In general, MA and RIC regimens seem to be comparable in terms of efficacy in adult ALL patients especially in complete remission^[39-43].

As stated above, a recently published individual patient data meta-analysis including 5 studies comparing autograft with chemotherapy, showed no beneficial effect of autograft over chemotherapy in terms of overall survival^[38]. Owing to significantly reduced non-relapse mortality compared to allo-HCT, autograft may be an acceptable option in older adult Ph- ALL patients in CR1 who do not have evidence of MRD.

WHAT IS THE ROLE OF ALLO-HCT IN AYA PATIENTS WITH PH- ALL IN CR1?

The superiority of pediatric-inspired protocols in AYA patients with ALL is clearly demonstrated, especially in patients below 20 years of age^[30]. Although there is no consensus on the upper age limit defining AYA population, it seems reasonable to accept age below 40 due to the concern that older patients are expected to have more complications with dose intensive regimens. On the other hand, the same age group benefit most from MA-MSD allo-HCT compared to patients receiving chemotherapy or autograft^[36,38]. Thus, it is a big challenge for physicians to decide the best available consolidation therapy in an AYA patient presenting with Ph- ALL, who achieves CR1 following a pediatric-inspired regimen. The chemotherapy (control) arms of trials, which founded the basis for recommendation of consolidation with MA-MSD allo-HCT in SR, Ph- ALL at CR1, used standard adult chemotherapy regimens^[36,38]. Having a MSD in this setting provided an absolute 5-year OS benefit of nearly 10% (55% vs 45.1%) compared to patients without a donor (chemotherapy/autograft)^[38]. However, with application of pediatric-inspired protocols to adult ALL patients up to age 60, almost 20% higher (60%-69%) long-term survival (at 2 to 6 years) rates can be achieved compared to standard adult chemotherapy regimens^[24,25,27].

A recently collaborative effort of Center for International Blood and Marrow Transplant Research (CIBMTR) and Dana Farber Consortium focused on the impact of pediatric-inspired protocols on Ph- ALL in CR1. Seftel et al. retrospectively compared the outcome of 422 AYAs (18-50 years of age) with Ph- ALL in CR1 who received allo-HCT and 108 age-matched cohort of Ph- ALL in CR1 who were treated with a pediatric-based regimen and did not undergo allo-HCT^[44]. At 4 years of follow-up, patients who received pediatric-inspired protocol had a significant advantage in terms of OS compared to allo-HCT group (chemotherapy 73% [95% CI 63-81] vs allo-HCT 45% [95% CI 40-50]; *p* < 0.0001). The favorable outcome with pediatric-based regimens was the result of low treatment related mortality compared to allo-HCT arm (6% vs 37%; *p* < 0.0001) with similar relapse rates (23% vs 24%). Multivariable analysis revealed allo-HCT as the only relevant predictive factor associated with poor OS (hazard ratio: 3.12 [1.99-4.90]; *p* < 0.0001)^[44]. One of the shortcomings of the study was lacking MRD analysis.

Prospective data indicating applicability of pediatric-based regimens up to age 30-60 range with very encouraging long-term OS data (almost 60% at 2-7 years) and aforementioned retrospective analysis may obviate the need for MSD allo-HCT in AYAs presenting with Ph- ALL in CR1.

CONCLUSIONS

Although combination of MRD analysis at predefined points and conventional risk factors seems logical to tailor therapy in adult Ph-ALL patients, standardized MRD analysis may not always be possible outside of the academic centers. Current evidence suggest that allo-HCT in adult Ph- ALL works best in patients below 35 years of age who also have a favorable outcome with dose intensive pediatric-inspired regimens. Although there are no randomized trials in AYA population with Ph- ALL comparing pediatric-based chemotherapy and allo-HCT, recent data seems to be in favor of pediatric protocols even in HR patients.

Treatment decisions in older patients may be more difficult because of poor tolerability of intensive pediatric-inspired chemotherapy and high TRM with allo-HCT. There are convincing data that reduced-intensity conditioning (RIC) regimens are as effective as MA conditioning in terms of OS. Although pediatric protocols can be safely introduced up to age 60, we generally prefer adult chemotherapy regimens in this age group (40-60). We offer RIC allo-HCT to patients up to age of 60 who have a matched-related/unrelated donor, good performance status and HCT comorbidity index below 3^[45].

According to our interpretation of current knowledge, the way we treat adult Ph- ALL is presented in Figure 1. It is important to bear in mind that risk factors in ALL are relative to available treatment alternatives. In spite of still being unsatisfactory compared to pediatric patients, the prognosis of adult ALL up to the age of 60 significantly improved with time. The philosophy of ALL treatment is prone to change with new developments in the field of HCT and chemotherapy.

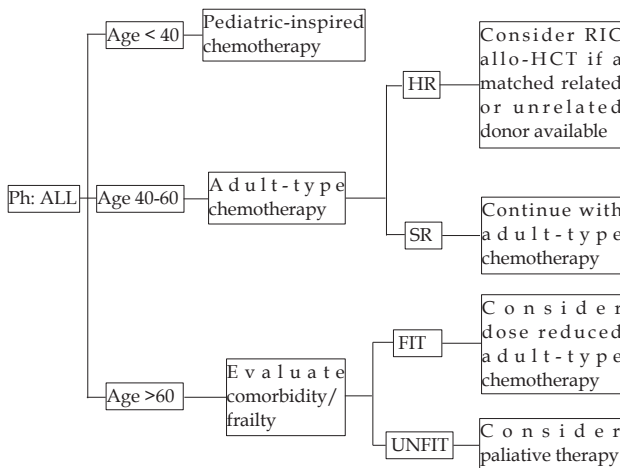


Figure 1 A proposal for off-study management of Ph- ALL if access to MRD evaluation is not in place.

HR: One of the following features should be present

WBC at diagnosis $\geq 30,000/\text{mm}^3$ (B-ALL); $\geq 100,000/\text{mm}^3$ (T-ALL)
t(4;11); 11q23 abnormality; hypodiploidy (< 44 chromosomes); complex karyotype (≥ 5 abnormalities)

time to achievement of CR1 > 4 weeks

SR: Patients without any HR factors

CONFLICT OF INTEREST

There are no conflicts of interest.

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