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Guideline

Hematopoietic Cell Transplantation in the Treatment of Adult Acute Lymphoblastic Leukemia: Updated 2019 Evidence-Based Review from the American Society for Transplantation and Cellular Therapy

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A B S T R A C T

The role of hematopoietic cell transplantation (HCT) in adults with acute lymphoblastic leukemia (ALL) is reviewed and critically evaluated in this systematic evidence-based review. Specific criteria were used for searching the published literature and for grading the quality and strength of the evidence and the strength of the recommendations. A panel of ALL experts developed consensus on the treatment recommendations based on the evidence. Allogeneic HCT offers a survival benefit in selected patients with ALL, and this review summarizes the standard indications as well as the areas of controversy. There is now greater experience with pediatric-inspired chemotherapy regimens that has transformed upfront therapy for adult ALL, resulting in higher remission rates and overall survival. This in turn has increased the equipoise around decision making for ALL in first complete remission (CR1) when there is no measurable residual disease (MRD) at the end of induction and/or consolidation. Randomized studies are needed for adults with ALL to compare allogeneic HCT in CR1 with pediatric-inspired chemotherapy alone. Indications for transplantation in the evolving landscape of MRD assessments and novel targeted and immune therapeutics remain important areas of investigation.

INTRODUCTION

In 1999 the American Society for Blood and Marrow Transplantation (ASBMT), now the American Society for Transplantation and Cellular Therapy (ASTCT), began an initiative to develop evidence-based reviews of the scientific and medical literature for the use of hematopoietic cell transplantation

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(HCT) in the therapy of selected diseases. In 2009, the ASBMT Steering Committee determined that previously published reviews should be updated at regular intervals. This constitutes the second update of the adult acute lymphoblastic leukemia (ALL) evidence-based review, originally published in 2006 and then updated in 2012 [1,2]. Since 2012, significant changes to aspects of the treatment landscape for adult ALL have occurred, including greater experience with pediatric-inspired chemotherapy regimens, expanding application of assessments for measurable residual disease (MRD), and emergence of novel targeted and immune therapeutics. In this update, we assemble and critically evaluate new evidence regarding the role of HCT in the therapy of patients with ALL, make treatment recommendations based on the available evidence, and identify areas of needed research.

EXPERT PANEL AND GRADING SYSTEM

Experts in the treatment of ALL and members of the ASTCT Committee on Practice Guidelines were invited to join an independent panel of 18 members. The task of this panel was to examine the literature and provide subsequent treatment recommendations based on the available evidence. Members of the expert panel first reviewed and agreed on a list of topics formatted as "frequently asked questions" (FAQs) to be included in the review. Articles were then organized into subtopics. Reviewers were provided with a list of studies specific to the subtopic they were reviewing, as well as a master list of all studies.

A standardized grading system that includes grading the levels of evidence was used to assess the studies included in this review and the ensuing treatment recommendations [3], as recommended by the ASTCT Steering Committee for evidence-based reviews [4] (**Supplementary Tables 1** and **2**). Studies were also evaluated based on study design, sample size, patient selection criteria, duration of follow-up, and treatment plan. Articles in each subtopic were reviewed and graded by 2 experts, who then submitted treatment recommendations. Consensus among the extended panel was reached for the final grading and recommendation. This iterative process concluded when final versions of the treatment recommendation tables were approved by all panelists.

After the final draft, the review was approved by the disease-specific expert panel and additional members of the ASTCT Committee on Practice Guidelines and then by the ASTCT Executive Committee before submission to the Journal. Any changes requested during the peer-review process were reviewed and approved by all disease-specific expert panelists.

LITERATURE SEARCH METHODOLOGY

The literature search methodology was adapted from the search methodology used in previous ASTCT evidence-based reviews. PubMed was searched using the search terms "Acute lymphoblastic leukemia" AND "transplant" limited to "human trials," "English language," and a publication date of January 1, 2010, or later. The search terms were ("Lymphoblastic leukemia"[MeSH Terms] OR ("Lymphoblastic"[All Fields] AND "leukemia"[All Fields]) OR "Lymphoblastic leukemia"[All Fields] OR ("Lymphoblastic"[All Fields] AND "leukemia"[All Fields]) OR "Lymphoblastic leukemia"[All Fields]) AND ("transplants"[MeSH Terms] OR "transplants"[All Fields] OR "transplant"[All Fields] OR "transplantation"[MeSH Terms] OR "transplantation"[All Fields]) AND (("2010/10/01"[PDAT]: "2017/04/01"[PDAT]) AND "humans"[MeSH Terms] AND English[lang]).

Articles published before October 2010, including fewer than 25 patients with ALL, reported primarily in pediatric patients, or not peer reviewed were excluded. Also excluded were editorials, letters to the editor, phase I (dose escalation or dose finding) studies, reviews, consensus conference papers, practice guidelines, and laboratory studies with no clinical correlates.

The initial search identified 383 articles, from which 94 were selected for the evidence-based review. In addition, articles outside of this search window were reviewed based on the recommendations of expert reviewers and the previously published ALL guidelines [1,2]. All articles were briefly reviewed and classified. Additional relevant articles suggested by panelists at the time of the review were considered for inclusion on a case-by-case basis. Published evidence as of June 1, 2019, was incorporated into our conclusions.

CONSENSUS RECOMMENDATIONS

The consensus recommendations of the ASTCT Committee on Practice Guidelines are summarized in Table 1 (Transplantation Indications), Table 2 (Disease- and Transplantation-Related Factors), and Table 3 (Post-Transplantation Considerations). Comments on other treatment options are included. These recommendations are elaborated on further in this review.

Transplantation Indications

Question 1: What are the indications for allo-HCT in Philadelphia chromosome-negative disease?

Allo-HCT for patients in CR1. Large prospective studies have established, through donor versus no donor analyses, that

Table 1
Transplantation Indications

Indication	Recommendation	Grade of Recommendation	Highest Level of Evidence	References
Ph-negative disease				
Should allo-HCT be offered for adults with standard-risk ALL in CR1?	Unclear	A	1++	7-10,12-15
Should allo-HCT be offered for adults with high-risk ALL in CR1?	Yes	A	1++	5,6,9-15
Should allo-HCT be offered for adults with ALL in ≥CR2?	Yes	D	2+	16,17
Should allo-HCT be considered for refractory ALL?	Unclear	D	2+	18-20
Ph+ disease				
Should allo-HCT be offered for patients with Ph+ ALL in CR1 who receive TKIs?	Yes	B	1+	21,23-25
Should allo-HCT be offered for patients with Ph+ ALL in CR1 who receive TKIs who achieve complete molecular remission?	Unclear	B	2++	24,25
AYA with Ph-negative disease				
Should allo-HCT be considered for AYA with otherwise standard- isk, MRD-negative ALL in CR1 if treated with pediatric-inspired regimens?	No	A	1++	5-9,12,13,15,30
Should allo-HCT be considered for AYA in CR1 with high-risk features or persistent MRD after induction?	Yes	A	1++	5-9,12,13, 15,30
Auto-HCT				
Should auto-HCT be offered for Ph-negative ALL in CR1?	No	A	1++	5-9
Should auto-HCT be offered for Ph+ ALL in CR1?	Unclear	C	2+	31,32

Table 2
Disease- and Transplantation-Related Factors

Factor	Recommendation	Grade of Recommendation	Highest Level of Evidence	References
MRD				
Should the presence of MRD positivity be considered an indication to offer allo-HCT?	Yes	B	2++	14,15,17,26,34-42
Conditioning regimen				
Should an MAC regimen be the preferred conditioning intensity in fit patients?	Yes	C	2+	5-8,26,61,62
Should the preferred MAC regimen include TBI?	Yes	C	2+	5-8,69-73,76-78
Are RIC regimens an acceptable alternative for adults considered unfit for myeloablative regimens?	Yes	D	2+	26,61-68
Alternative donors				
Can UCB and haploidentical relatives be considered as alternative donor options?	Yes	C	2+	34,79-84,87-92
Graft source				
Should PBSCs, BM, and UCB be considered graft options for allo-HCT?	Yes	B	1+	80,83,84,93,94
Is there a preferred graft source for HLA-matched donor allo-HCT?	No	B	1+	93,94

Table 3
Post-Transplantation Considerations

Consideration	Recommendation	Grade of Recommendation	Highest Level of Evidence	References
MRD				
Should patients undergo routine evaluation for MRD following allo-HCT?	Yes	C	2++	43,44
Post-transplantation maintenance				
Should patients with Ph+ disease initiate BCR-ABL1 TKI as maintenance therapy following allo-HCT?	Yes	B	1+	25,27,97-105
Should patients with Ph+ disease initiate preemptive therapy on the detection of MRD following allo-HCT?	Yes	B	1+	98,105
Management of relapsed disease after transplantation				
Should chemotherapy, DLI, novel targeted or immunotherapies, and second allo-HCT be considered treatment options for relapsed disease after allo-HCT?	Yes	D	2-	106-112
Is there a preferred treatment choice for relapsed disease after allo-HCT?	No	D	2-	106-112

allogeneic HCT (allo-HCT) results in superior disease-free survival (DFS) and overall survival (OS) for standard-risk adult ALL compared with autologous HCT (auto-HCT) or chemotherapy alone [5-8]. A subsequent meta-analysis that used data from 2962 patients across 13 studies concluded that a myeloablative conditioning (MAC) regimen followed by matched sibling donor allo-HCT led to improved OS in younger patients [9]. In addition, a Cochrane systematic review and meta-analysis of 14 controlled trials (3157 patients) with a donor versus no donor comparison for adult ALL in first complete remission (CR1) showed DFS and OS advantages for the donor arms versus the no donor arms [10]. This review concluded that matched sibling donor allo-HCT was the optimal post-remission therapy for ALL at age 15 years or over. However, the authors acknowledged that these data were based on treatment with largely total body irradiation (TBI)-based MAC, sibling donor transplantation, and compared allo-HCT with adult chemotherapy approaches that had not been optimized for younger persons.

Since these earlier studies, the expanded use of matched unrelated donors (URDs) and alternative donors has expanded the availability of allo-HCT to a greater number of patients. Furthermore, the increased use of reduced-intensity conditioning (RIC) and nonmyeloablative conditioning and improvements in supportive care have led to decreased nonrelapse mortality. Similarly, significant improvements have been achieved in the outcomes for patients treated with chemotherapy. The adoption of pediatric-inspired chemotherapy ALL regimens for adults have transformed upfront therapy for adult ALL in the US (Alliance for Clinical Trials in Oncology) and in Europe (GMALL, GRALL, and PETHEMA). Pediatric regimens adapted for adults that contain asparaginase and more dose-intensive nonmyelosuppressive agents have resulted in high CR rates and promising survival [11,12]. Mitigating regimen-related toxicities requires skillful management in adults, yet study outcomes suggest that relatively low treatment-related mortality (TRM) is achievable. An adult age-matched Center for International Blood and Marrow Transplant Research (CIBMTR) analysis in Philadelphia chromosome (Ph)-negative ALL CR1 compared allo-HCT with continued pediatric-inspired chemotherapy and suggested that non-HCT therapy may be superior for younger adults. However, that study lacked information on MRD [13]. A major gap limiting the development of evidence-based indications for allo-HCT in adult ALL is the lack of randomized clinical trials comparing allo-HCT with pediatric-inspired chemotherapy alone for adults who achieve CR1.

The definition of disease risk has also evolved over time, with increasing emphasis being placed on the evaluation of post-treatment MRD as opposed to only clinical characteristics at diagnosis. MRD assessments potentially can be used to help

identify patients who should proceed to allo-HCT in CR1. A large analysis of patients with Ph-negative ALL treated on the GMALL study found that molecular CR versus morphologic CR but molecular failure after consolidation was associated with a higher probability of achieving continuous CR and better OS. Furthermore, patients with molecular failure who did not undergo allo-HCT in CR1 had a median time to relapse of 7 months and poor long-term survival [14]. In another analysis of 522 adults with at least 1 conventional high-risk factor who achieved CR1 after the pediatric-inspired GRAALL protocol and who were candidates for allo-HCT, there was no significant overall difference in relapse-free survival (RFS) between the allo-HCT and nontransplantation cohorts. However, among patients with postinduction MRD, RFS was longer for those selected for allo-HCT [15]. In the PETHEMA ALL-AR-03 trial, patients with Ph-negative high-risk ALL were assigned to chemotherapy or allo-HCT according to early disease response. Patients with good early cytogenetic response after day 14 of induction and low or negative flow cytometry-measured MRD after consolidation had favorable DFS and OS compared with those with chemotherapy consolidation alone [11]. The phase II CALGB 10403 study treated 295 patients (age 17 to 39 years) with pediatric-inspired chemotherapy regimen and reported a median event-free survival (EFS) of 78.1 months, significantly longer than the EFS of 30 months in historical controls [12]. Of note, all patients with detectable MRD after induction had worse outcomes.

The role of allo-HCT in patients with Ph-negative ALL in CR1 is an area of active investigation. The current recommendation is that allo-HCT should be considered for patients with standard-risk ALL in CR1, based on the earlier donor versus nondonor studies. Data for patients with standard-risk ALL who achieve MRD-negative CR1 while being treated on pediatric-inspired protocols suggest that they may achieve equal or superior outcomes with continued chemotherapy alone without upfront allo-HCT. Disease-related outcomes for patients with persistent MRD-positive disease in CR1 are often inferior to those for patients in molecular remission, and data suggest that allo-HCT may improve outcomes for these patients.

Allo-HCT for patients in ≥CR2. There are no randomized studies comparing allo-HCT and nontransplantation therapies for patients in a second remission. Although CR2 can be attained with chemotherapy, long-term survival is poor. Therefore, it has been considered standard of care to offer allo-HCT to fit patients in CR2 or beyond, even though transplantation outcomes are traditionally thought to be inferior compared with allo-HCT in CR1 [16]. A recent analysis incorporating MRD data suggests that allo-HCT for MRD-negative ALL at or beyond CR2 may result in long-term survival [17]. Thus, the current recommendation remains that allo-HCT should be offered to adult patients at or beyond CR2, and that achieving MRD-negative status before allo-HCT is preferred. Whether the use of novel therapeutics, such as blinatumomab, inotuzumab ozogamicin, and/or chimeric antigen receptor T (CAR-T) cells, for patients in CR2 may supersede this recommendation remains to be seen.

Allo-HCT for refractory disease. There are no randomized studies to direct the management of primary refractory ALL. Although outcomes are generally considered poor, allo-HCT is sometimes considered for this population given its curative potential [18]. A CIBMTR analysis of 582 patients with ALL who underwent allo-HCT for active relapse or primary induction failure reported a 3-year OS of 16% but identified pretransplantation variables that could identify subgroups associated with different survival outcomes. OS was worse for first refractory or second or greater relapse, ≥25% marrow blasts, cytomegalovirus-seropositive donor, and age of 10 years or older [19]. An European Society for Blood and Marrow Transplantation (EBMT) registry analysis of 86 patients with primary refractory ALL likely was enriched for those with clinically favorable performance status and other features. Those undergoing allo-HCT had a 5-year OS of 23%. In multivariable analysis, the use of TBI was associated with improved survival [20]. However, the patients who were able to proceed to allo-HCT and were included in these studies likely represent a select population among this overall high-risk population. The current recommendation is that allo-HCT may be considered for adult patients with refractory disease in an investigational setting, with consideration of pretransplantation variables. However, the panel favored considering novel therapeutics to attempt to achieve disease response before proceeding to allo-HCT.

Question 2: What are the indications for allo-HCT in Ph-positive disease?

The previous 2012 guidelines identified the need to better understand the role of allo-HCT in Ph-positive (Ph+) ALL versus more intensive chemotherapy in combination with tyrosine kinase inhibitor (TKI) therapy targeting BCR-ABL1 [2]. Since that time, multiple prospective studies attempting to address this gap have been reported.

For patients with Ph+ ALL treated in the UKALL12/ECOG2993 study (imatinib cohort, n = 175; pre-imatinib cohort, n = 266), the addition of imatinib to standard treatment regimens improved long-term OS (4-year OS, 38% versus 22%; $P = .02$). Some of the OS benefit observed was thought to derive from imatinib's ability to facilitate allo-HCT by achieving disease response before transplantation [21]. Long-term follow up of 45 patients with Ph+ ALL treated with imatinib as part of the GRAAPH-2003 trial showed improved OS compared with patients treated on the pre-imatinib era LALA-94 trial [22]. Despite the selection of patients who underwent transplantation, allo-HCT or auto-HCT seemed to help overcome the poor prognosis of Ph+ ALL in the TKI era [23]. In GRAAPH-2005, 268 adults were randomized to high-dose imatinib plus reduced-intensity chemotherapy versus standard-dose imatinib plus hyper-CVAD. Subsequently, patients with donors who achieved a major molecular response after the third cycle proceeded to allo-HCT. In this study, allo-HCT was associated with significant benefits in RFS and OS, validating the role of imatinib in pretransplantation therapy for ALL and suggesting that allo-HCT in CR1 remains a good option [24]. In a multicenter US intergroup study, 94 evaluable patients were treated with dasatinib and hyper-CVAD, followed by TBI-based myeloablative allo-HCT in CR1 from a matched donor (if available) and post-transplantation maintenance dasatinib. A landmark analysis at 175 days from achievement of CR showed superior RFS and OS for patients receiving transplantation [25]; however, that study did not report on MRD status and could not formally evaluate the utility of the post-HCT dasatinib treatment. Two large registry studies have also been published. In a CIBMTR analysis of 197 patients with Ph+ ALL undergoing allo-HCT in CR1, RIC and MAC regimens were associated with similar overall outcomes for patients whose disease was MRD-negative before transplantation, whereas RIC was inferior in those whose disease was MRD-positive [26]. In an EBMT retrospective analysis of 473 patients with Ph+ ALL receiving allogeneic HCT in CR1 from an HLA-matched donor between 2000 and 2010, the administration of pretransplantation TKIs was associated with improved survival outcomes in multivariate analysis, confirming a critical role for TKIs in treatment of adult Ph+ ALL [27]. More recent studies have

evaluated the incorporation of newer-generation TKIs into the management of Ph+ ALL. A single-arm phase II study of 37 patients with Ph+ ALL treated with ponatinib in combination with chemotherapy reported early molecular responses and encouraging disease control (2-year EFS of 80%) [28], and long-term data reported on 76 patients showed continued good disease control, with a 3-year EFS of 70% [29].

Therefore, the current recommendation is to pursue allo-HCT from an HLA-matched donor for adults with Ph+ ALL who achieve CR1. Achieving BCR-ABL1-negative CR1 is likely favorable, but whether these patients can be treated with intensive combination chemotherapy plus extended TKI therapy and avoid allo-HCT remains an area of active investigation. Additional factors which require further research include the use of alternative donors for HCT in CR1 and the use of TKIs following transplantation as maintenance.

Question 3: What are specific considerations for adolescents and young adults (AYA) with Ph-negative ALL?

The strongest supporting evidence favoring allo-HCT for AYA with ALL in CR1 comes from older studies that enrolled predominantly young adults, including the UKALL12/ECOG2993 study that showed a benefit in a donor versus no-donor intention-to-treat analysis for patients age <35 years with standard-risk disease [5-8]. A subsequent meta-analysis confirmed these results [9]. However, the use of older, less-intensive induction regimens plus a lack of MRD evaluation in treatment allocation for these studies limit their applicability to the current management of the AYA population.

In a retrospective analysis of 522 patients age 15 to 55 years (median age, 32 years) with high-risk ALL treated with pediatric-inspired GRAALL regimens, the 3-year OS was 69.5% for patients undergoing allo-HCT in CR1 (n = 282; 54%) [15]. There was no significant difference in RFS between the allo-HCT and no transplantation cohorts, and allo-HCT was associated with better RFS in patients with poor early MRD response after induction therapy [15]. The results from several large retrospective registry studies provide further insight into the roles of allo-HCT and pediatric-inspired chemotherapy regimens in AYA with ALL. One CIBMTR registry study found improved OS after allo-HCT for the AYA population, at a rate similar to that seen in the younger pediatric population; the authors concluded that the improved survival was largely due to a decline in TRM, because relapse rates did not differ [30]. In another CIBMTR study, outcomes among adults (age 18 to 50 years) with Ph-negative ALL undergoing allo-HCT in CR1 were compared with those of age-matched patients with Ph-negative ALL achieving CR1 on a Dana-Farber Consortium pediatric-inspired non-HCT regimen. Although relapse rates were equivalent in the 2 groups, allo-HCT was associated with an elevated risk for nonrelapse mortality and subsequently inferior DFS and OS [13]. Most recently, as mentioned earlier, the multicenter CALGB 10403 phase II study reported encouraging EFS with pediatric-inspired chemotherapy. Additional analyses suggested that patients who were obese, had Ph-like signatures, or had detectable MRD after induction all had worse outcomes [12].

Taken together, the reported data indicate that improvements in chemotherapy-based outcomes are changing the role of allo-HCT in the management of AYA patients. For standard-risk AYA patients in CR1 treated with pediatric-inspired regimens who achieve early MRD-negative response, we recommend continued treatment with intensive chemotherapy consolidation and maintenance phases, with allo-HCT reserved for patients in CR2. For AYA patients with high-risk features and those with persistent MRD after induction, we recommend strongly considering allo-HCT as upfront consolidation.

Question 4: What are the indications for auto-HCT in ALL?

The previous 2012 guidelines concluded that the preponderance of evidence favors allo-HCT over auto-HCT, but there was insufficient data to determine whether this effect is more apparent in disease risk subgroups, including Ph+ ALL [2].

For patients with Ph-negative ALL, multiple prospective studies designed on the basis of an available HLA-matched sibling donor found auto-HCT to be inferior to allo-HCT and chemotherapy in terms of disease control and survival outcomes [5-8]. Furthermore, a meta-analysis of older studies comparing auto-HCT and conventional chemotherapy showed that standard autografting does not have a beneficial effect compared with chemotherapy for adult patients with ALL in CR1 [9]. Therefore, auto-HCT should not be offered to patients with Ph-negative ALL in CR1 regardless of risk stratification.

Other published studies have attempted to further the understanding of the role of auto-HCT in Ph+ ALL. An EBMT registry study suggested improved auto-HCT outcomes over time, most likely associated with the introduction of TKIs targeting BCR-ABL1 that allowed for better disease control before transplantation [31]. In patients with Ph+ disease, the CALGB study 10001 randomized patients to receive imatinib plus sequential chemotherapy followed by allo-HCT (for those with a matched sibling donor) or auto-HCT followed by maintenance imatinib (for those without sibling donors). Although this study was limited by a small sample size and lack of detailed MRD data, OS and DFS were similar in the allo-HCT and auto-HCT cohorts, suggesting that auto-HCT may be a safe and effective alternative for patients with MRD-negative Ph+ ALL and without a matched sibling donor [32]. Regardless of Ph status, MRD-positivity before auto-HCT is associated with high rates of relapse and worse DFS and OS [33]. These recommendations should be considered speculative without confirmation in a well-characterized MRD-negative population.

We conclude that auto-HCT can be considered as a possible consolidative option in Ph+ patients who achieve MRD-negative status and are not suitable for allo-HCT. Post-auto-HCT TKI therapy is likely beneficial, although specific data evaluating this are not available. However, MRD-positive patients should not be offered auto-HCT.

Disease- and Transplantation-Related Factors

Question 5: What is the role of MRD assessment?

The previous 2012 guidelines recommended MRD testing as a needed research area for monitoring during initial treatment and guiding HCT eligibility, and post-HCT monitoring for detecting early relapse [2]. Since that time, additional studies have been published to further our understanding of the role of MRD in allo-HCT for ALL.

The presence of pretransplantation MRD is generally associated with inferior outcomes irrespective of technique used to identify MRD. Multiple techniques can be used to detect MRD, although multiparameter flow cytometry [34-36] is most widely used. In addition, BCR-ABL1 PCR [26,37-40], Ig/T cell receptor (TCR) PCR [14,41], and Ig/TCR gene high-throughput sequencing [42] have been reported. No published prospective studies have randomized transplantation and non-HCT approaches according to MRD status. An analysis of patients with Ph-negative ALL treated on the GMALL study found that patients in molecular CR (MRD-negative) after consolidation had a higher probability of continuous CR and improved OS compared with patients with MRD. Among patients with MRD, those who did not undergo allo-HCT in CR1 had short-duration CR and poor long-term survival [14]. Retrospective analyses in patients who proceed to allo-HCT have suggested that MRD status should be considered when

selecting conditioning regimen and intensity. A retrospective study analyzed transplantation outcomes of 522 patients with high-risk ALL treated on the GRAALL pediatric-inspired regimen, of whom 282 underwent allo-HCT in CR1. Allo-HCT was associated with longer relapse survival compared with no transplantation in MRD-positive patients (hazard ratio [HR], .40; $P = .001$), but not in good MRD responders [15]. In the aforementioned CIBMTR analysis of 197 patients with Ph+ ALL in CR1 undergoing allo-HCT, RIC was inferior to MAC in patients with MRD-positive disease pre-HCT, whereas outcomes were similar in MRD-negative patients pre-HCT [26]. Similarly, in a single-center analysis of 89 adults with ALL who achieved MRD-negative CR1, OS was comparable for allo-HCT (with RIC or MAC) and deferred transplantation, in part because allo-HCT in MRD-negative CR2 yielded better long-term survival [17]. Following allo-HCT, the presence of MRD-positivity strongly predicts disease relapse and thus can identify a population in need of preemptive drug or cellular therapy for antileukemia treatment [43,44].

Therefore, the current recommendation is to pursue MRD testing both before and after allo-HCT.

Patients with MRD-positive disease may proceed with allo-HCT with curative intent, but their outcomes likely are inferior compared with those of patients with MRD-negative disease. For MRD-positive patients, myeloablative allo-HCT likely is preferred over RIC HCT or nontransplantation. For B-ALL, additional treatment with blinatumomab to reduce leukemic burden before allo-HCT should be considered, but the impact on post-transplantation outcome is uncertain. For patients who are quick to achieve and maintain MRD-negative status, the role of allo-HCT is now more controversial, especially in patients with standard-risk disease. For patients with high-risk disease, allo-HCT should still be strongly considered, given that no available randomized data support the idea that patients achieving MRD-negative disease can forego allo-HCT.

Question 6: How should abnormal cytogenetic, molecular, and phenotypic risk factors be considered?

Publications have addressed a number of disease-related factors that should be considered, although the role of transplantation in these subgroups has yet to be determined. Information about the potential impact of cytogenetic abnormalities on transplantation outcomes beyond Ph+ disease is emerging. For patients with t(4;11)-positive ALL uniformly treated on the UKALL12/ECOG2993 protocol, myeloablative allo-HCT was associated with a very low relapse rate, suggesting that the adverse prognosis of this cytogenetic abnormality may be overcome for patients in CR who are consolidated with allo-HCT [45]. Alternatively, the role of HCT in young adults with hypodiploid ALL is now less clear; 2 large retrospective studies have shown that HCT does not improve outcomes in this high-risk subgroup [46,47]. However, for patients with Ph+ ALL, a single-center experience suggests that additional cytogenetic abnormalities for patients with Ph+ ALL receiving TKIs and allo-HCT yielded significantly inferior 3-year LFS and OS compared with patients without additional cytogenetic findings, despite adjustments for MRD at the time of transplantation [48]. Ph-like ALL, characterized by a range of genomic alterations that activate signaling pathways possibly amenable to inhibition with TKIs, is associated with poor long-term outcomes, particularly in patients with *CRLF2* mutations and Ikaros deletions [49,50]. The impact of TKI therapy and allo-HCT in Ph-like ALL has yet to be determined [51]; however, the response to standard chemotherapy and elimination of MRD may overcome the expected prognosis based on data from the pediatric literature, in which outcomes of patients with Ph-like ALL are best described [52]. CD20 expression has previously been associated with early recurrence and inferior survival in patients with precursor B-ALL. The recent CALGB 10403 study of intensive pediatric-inspired therapy in AYA patients observed that CD20 had no impact on outcomes [12]. However, a large prospective study from the GRALL group demonstrated that adding rituximab to the pediatric-inspired chemotherapy protocol reduced the risk of relapse and improved EFS in younger patients [53]. A single-center analysis of 125 evaluable patients suggested that allo-HCT overcomes the adverse prognostic impacts of CD20 [54]. Among patients with T cell ALL, early thymic precursor disease has been identified as a high-risk subgroup whose outcomes may be improved with the use of allo-HCT in CR1 [55,56].

Question 7: How to approach patients with central nervous system (CNS) disease?

The approach to patients with CNS disease and the role for CNS-directed prophylaxis are areas of uncertainty. For patients with CNS disease at diagnosis, a French registry study reported that high-dose TBI and remission status had favorable impacts on OS, regardless of whether the patients underwent auto-HCT or allo-HCT [57]. A single-center analysis showed that patients with a pretransplantation history of CNS involvement were at increased risk for post-transplantation CNS relapse, inferior EFS, and worse OS. Interestingly, pretransplantation cranial irradiation, TBI-based conditioning, and post-transplantation prophylactic intrathecal chemotherapy were associated with reduced risk of post-transplantation CNS relapse [58]. A recent multicenter retrospective analysis of 452 adults with ALL failed to find a significant effect of post-transplantation CNS prophylaxis on preventing relapse after transplantation, even in those with previous CNS involvement [59]. A recent position statement from the ASTCT Practice Guidelines Committee concluded that high-quality prospective data are lacking to guide the use of intrathecal prophylaxis in patients with ALL undergoing allo-HCT in CR. The current recommendation is to consider allo-HCT as consolidative therapy in patients with a history of CNS disease. The available evidence does not support routine post-allo-HCT CNS prophylaxis for ALL in the contemporary treatment era, regardless of previous CNS involvement at the time of diagnosis [60]. Active CNS disease at the time of allo-HCT is associated with a dismal prognosis.

Question 8: How is conditioning intensity factored into pre-HCT decision making?

Randomized data supporting allo-HCT for ALL comes from older studies in younger patients treated with intensive MAC regimens [7,8]. However, there are no randomized data comparing RIC allo-HCT with chemotherapy or comparing MAC and RIC in patients with ALL undergoing allo-HCT. Multiple large registry studies and institutional reports have recently investigated this issue [26,61-68]. A CIBMTR study of 1521 patients with Ph-negative ALL receiving a MAC regimen (n = 1428) or an RIC regimen (n = 93) found similar TRM in the 2 groups but a greater risk of relapse in the RIC group, resulting in similar age-adjusted survival in the 2 groups despite a substantially older median age (median age, 45 years versus 28 years) [61]. Similarly, an EBMT study of 576 patients with ALL found that the type of conditioning regimen (RIC versus MAC) was not significantly associated with leukemia-free survival (LFS), concluding that RIC allo-HCT is a potential therapeutic option for patients not eligible for MAC [62]. A CIBMTR analysis of patients with Ph+ ALL demonstrated similar OS after RIC and MAC regimens, as a result of significantly lower TRM and

higher risk of relapse with RIC regimens [26]. RIC regimens make transplantation accessible to older adults with ALL and has been associated with promising outcomes (3-year OS of 38% for all patients and 45% patients in CR1, with no relapse occurring after 2 years) in patients age >55 years [63]. The current recommendation is to use MAC in fit patients and reserve RIC for patients not eligible for MAC. However, we acknowledge that other disease- and transplantation-related factors, such as MRD status, may influence the choice of conditioning intensity [26].

Question 9: How is TBI-based conditioning factored into pre-HCT decision-making?

There are no randomized trials comparing the use of myeloablative TBI-based conditioning to non-TBI, chemotherapy-based regimens. Most older studies establishing the role of allo-HCT in ALL used TBI-based conditioning in the transplantation arm [5-8]. In an attempt to avoid short- and long-term toxicities of ablative TBI, non-TBI regimens have been investigated, including thiotepa [69,70], busulfan/cyclophosphamide [71,72], busulfan/melphalan [73], busulfan/clofarabine [74], and busulfan/fludarabine [75]. These studies have suggested that non-TBI-containing regimens may result in similar survival compared with TBI-containing regimens, although TBI is often associated with lower rates of relapse [76]. An EBMT analysis of 2780 patients with ALL suggested that TBI is associated with improved LFS and OS compared with chemotherapy-based MAC, regardless of pretransplantation MRD status [77]. A recent CIBMTR study also concluded an advantage for TBI in limiting relapse for patients with ALL [78]. Taken together, the current recommendation is that TBI-based conditioning remains the standard of care for patients deemed fit for MAC.

Question 10: How are alternative donors considered in pre-HCT decision making?

At the publication of the 2012 guidelines, alternative donor transplants were identified as an area of needed research, given the limited data at that time. Multiple reports have validated umbilical cord blood (UCB) as an alternative donor source for adults with ALL [34,79-83]. A multicenter analysis of 149 patients with poor-prognosis ALL suggest similar transplantation outcomes with UCB or URD HCT, with disease status and chronic graft-versus-host disease (GVHD) the main factors influencing disease relapse [79]. A large registry study compared the outcomes of 1525 transplantation recipients with acute leukemia (645 with ALL) according to graft source: UCB, peripheral blood stem cells (PBSCs), or bone marrow (BM). UCB transplantation was associated with higher TRM, a lower incidence of chronic GVHD, and similar LFS compared with HLA-matched or mismatched transplantation with PBSCs or BM [80]. A subsequent CIBMTR analysis of 802 adult patients with ALL in CR1 or CR2 found that UCB transplantation was associated with slower engraftment and less acute GVHD compared with matched or mismatched URD transplantation, but similar other transplantation outcomes [84].

With the introduction of post-transplantation cyclophosphamide [85], the use of haploidentical transplantation has been steadily increasing [86-92]. A multicenter retrospective analysis of 124 consecutive adult patients with ALL predominantly past CR1 reported promising DFS with haploidentical HCT with post-transplantation cyclophosphamide, especially for patients in CR1 and patients receiving an MAC regimen [91]. An EBMT analysis of 208 patients with ALL further demonstrated that T cell-replete haploidentical transplantation is a valid option for adult patients with high-risk ALL lacking an HLA identical donor, preferably in early disease status [92].

Although high quality evidence is lacking, the current recommendation is that both UCB and haploidentical transplantation be considered as alternative donor options for patients with ALL lacking an HLA-matched donor. The results of BMT CTN 1101 (ClinicalTrials.gov identifier NCT01597778), a phase III randomized study comparing outcomes between RIC UCB and haploidentical transplantations for patients with hematologic malignancies (including ALL) are expected in 2020, although the study might not be sufficiently powered to provide ALL-specific results.

Question 11: How are graft source options considered in pre-HCT decision making?

In BMT CTN 0201, among 551 patients randomized to URD PBSC or BM grafts, including 117 patients (21%) with ALL, no significant survival differences between graft sources were detected. However, PBSCs were associated with less graft failure and shorter time to engraftment, whereas BM was associated with less extensive chronic GVHD [93]. A subsequent EBMT registry analysis of 9848 patients with AML and ALL receiving RIC transplantations suggested that PBSCs was associated with a lower risk of relapse and higher OS and LFS, but a higher risk for chronic GVHD. The effect of stem cell source (BM versus PBSCs) on survival was independent of disease [94]. A possible association between graft source and risk of relapse has been identified. A single-center retrospective analysis of 582 patients with acute leukemia or MDS (including 185 with ALL) undergoing first myeloablative allo-HCT with persistent MRD found UCB to be associated with a lower rate of relapse compared with HLA-matched or -mismatched URDs [83]. Finally in the setting of HLA-matched donors, graft manipulation with ex vivo CD34 selection using the CliniMACS CD34 Reagent system has been shown to have similar RFS and OS, but less GVHD, compared with unmodified grafts in a 2- center retrospective analysis of patients with ALL in CR [95]. A trial comparing 3 GVHD prophylaxis regimens including CD34 selection and post-transplantation cyclophosphamide compared with standard of care in adults age <65 years with 8/8 HLA-matched donor recipients (BMT CTN 1301; NCT02345850) has completed accrual, and results are pending. PBSCs, BM, and UCB all remain viable graft options, and additional transplantation-related factors will likely guide the selection of donor and graft source.

Post-Transplantation Considerations

Question 12: What are the indications for post-transplantation maintenance therapy in ALL?

Whether post-HCT maintenance therapy, defined as therapy initiated while the patient remains in complete remission, or preemptive therapy, defined as therapy triggered by the detection of MRD, provides benefit in disease control or survival remains unknown [96].

Currently, there are no published reports of maintenance therapy for Ph-negative disease, owing to the lack of a suitable agent. For Ph+ ALL, increasing evidence suggests that post-HCT TKI therapies targeting BCR-ABL1 may be associated with improved outcomes compared with historical data, including small prospective clinical investigations that used imatinib [97,98], dasatanib [25], or nilotinib [99,100], as well as institutional experiences with various TKIs [101-104]. In a now-dated EBMT analysis of 473 patients with Ph^+ ALL undergoing allo-HCT between 2000 and 2010, only 60 received maintenance TKI therapy, but the practice was associated with improved LFS (HR, .44; $P = .002$) and OS (HR, .42; $P = .004$) [27]. However, a randomized phase II study of 55 patients comparing maintenance imatinib with preemptive, MRD-triggered imatinib therapy in patients with Ph+ ALL resulted in low rates of hematologic relapse and no significant difference in overall outcomes between the 2 arms,

although maintenance imatinib was associated with lower molecular recurrence (40% versus 69%; $P = .046$) [105].

Therefore, the current recommendation for patients with Ph+ ALL is to consider post-transplantation TKI as either maintenance or preemptive MRD-guided therapy, even though there are limited controlled data to support either choice. Additional factors that merit further research include how disease- and transplantation-related factors, such as conditioning intensity and MRD status, may identify a subpopulation most likely to benefit from post-HCT therapy, which TKI is preferred, and when and how long TKI therapy should be administered after transplantation.

Question 13: How should relapsed disease post-transplantation be managed?

The outcomes for relapsed ALL after allo-HCT are generally poor, irrespective of approach. A large single-center study of 123 patients found a 2-year OS of only 10% after first allo-HCT for relapsed ALL, despite a 38% rate of CR after first-line salvage therapy [106]. Similarly, an EBMT registry study of 465 patients with relapsed ALL after allo-HCT found a 2-year OS of 16% and a 5-year OS of 8%. CR2 or beyond at transplantation, early relapse after transplantation, and blast percentage at relapse were adverse factors for survival [107]. Donor lymphocyte infusion (DLI) has traditionally been associated with limited efficacy and lack of durable responses for ALL, although the MRD status was unknown in reported cases [108,109]. No controlled trials have identified the optimal treatment strategy for relapse after allo-HCT. The bulk of the data suggest some benefit of further consolidation therapy with second transplantation if the patient is able to achieve remission, as selected patients who achieved a long remission after their first transplantation and are re-induced into remission may benefit from second transplantation [110,111]. However, a recent EBMT study of 245 patients undergoing second allo-HCT as salvage treatment for transplantation reported poor long-term outcomes, with a 5-year OS of 14% and a high incidence of relapse [112]. Therefore, the current recommendation is to consider chemotherapy, DLI, and second allo-HCT as treatment options for selected patients. Novel targeted and immune therapies, including CAR-T cell therapy, are poised to become the preferred treatment options.

AREAS OF NEEDED RESEARCH

Although there are established data supporting the role of HCT in adult patients with ALL, several areas would benefit from further study. One major area is further investigation into the role of MRD assessments in evaluating individualized risk for disease relapse and determining the benefit of MRD-eradicating therapy in either improving HCT outcomes or perhaps forgoing the need for HCT. Prospective studies are needed to establish whether certain subpopulations of adults with ALL who achieve MRD-negative status may not need consolidation with allo-HCT in MRD-negative CR1 if their ongoing non-HCT therapy is of sufficient intensity. It will be important to determine the timing of MRD assessments (ie, early in the disease course, before transplantation) and how this impacts other transplantation-related decisions, including the intensity of conditioning as well the initiation and duration of post-transplantation maintenance. The intensity of additional therapy needed to achieve MRD-negative status may further influence the toxicity and tolerability of subsequent HCT. Elucidation of how to best incorporate MRD assessments into clinical decision making may improve patient selection for HCT and identify populations that may benefit from risk-adapted alternative strategies to reduce disease relapse.

Additional study is needed to determine how HCT and novel targeted and immune therapies should be incorporated into treatment algorithms for patients with ALL. Patients with relapsed/refractory disease are increasingly being treated with targeted agents, such as blinatumomab [113-115], inotuzumab ozogamicin [116], or CAR-T cells [117,118]. Longer follow-up on with larger series will clarify the expected duration of response. These data will help determine which therapies should be applied as a bridge to transplantation and which therapies in selected patients may supplant allo-HCT. Pre-HCT bridging therapy, including additional pre-HCT consolidation [119], might increase toxicities such as GVHD and veno-occlusive disease, when these therapies are used sequentially. Targeted and immune therapies may also have an expanding role for patients with MRD after allo-HCT. Substantial additional studies are needed to determine the timing and best implementation of HCT in the era of novel therapeutics.

CONCLUSIONS

Allo-HCT offers a survival benefit in selected patients with ALL and is currently part of standard clinical care. Future studies assessing the indications and timing of transplantation in the evolving landscape of MRD assessment and novel targeted and immune therapies remain important areas of investigation.

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SUPPLEMENTARY MATERIALS

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