Current Hematologic Malignancy Reports (2019) 14:94–105
https://doi.org/10.1007/s11899-019-00502-2

ACUTE LYMPHOCYTIC LEUKEMIAS (K BALLEN AND M KENG, SECTION EDITORS)

Hematopoietic Stem Cell Transplantation in Pediatric Acute Lymphoblastic Leukemia

Pietro Merli[1] · Mattia Algeri[1] · Francesca Del Bufalo[1] · Franco Locatelli[1,2]

Published online: 26 February 2019

Abstract

Purpose of Review The remarkable improvement in the prognosis of children with acute lymphoblastic leukemia (ALL) has been mainly achieved through the administration of risk-adapted therapy, including allogeneic hematopoietic stem cell transplantation (HSCT). This paper reviews the current indications to HSCT in ALL children, as well as the type of donor and conditioning regimens commonly used. Finally, it will focus on future challenges in immunotherapy.

Recent Findings As our comprehension of disease-specific risk factors improves, indications to HSCT continue to evolve. Future studies will answer the year-old question on the best conditioning regimen to be used in this setting, while a recent randomized controlled study fixed the optimal anti-thymocyte globulin dose in unrelated donor HSCT.

Summary HSCT, the oldest immunotherapy used in clinical practice, still represents the gold standard consolidation treatment for a number of pediatric patients with high-risk/relapsed ALL. New immunotherapies hold the promise of further improving outcomes in this setting.

Keywords Acute lymphoblastic leukemia · Children · Hematopoietic stem cell transplantation · Relapsed/refractory ALL

Introduction

The prognosis of children and adolescents with acute lymphoblastic leukemia (ALL) has dramatically improved in the last half century, with current 5-year event-free survival (EFS) rates exceeding 80%, according to the most recently reported data [1]. This remarkable success has been driven both by the use of complex multiagent chemotherapy regimens and by recognition of clinical, biological, and treatment response characteristics that identify children at higher probability of treatment failure, allowing the administration of risk-adapted therapy. However, there are still subsets of children with ALL in whom the probability of EFS with chemotherapy alone remains unsatisfactory, because of the high chance of disease recurrence. In these very-high-risk patients, as well as in many relapsed patients, allogeneic hematopoietic stem cell transplantation (HSCT) continues to play a major curative role through the combination of intense preparative radiotherapy/chemotherapy and graft-versus-leukemia (GvL) effect.

Defining the appropriate use of HSCT in pediatric ALL is a dynamic process, requiring constant and careful assessment of the likelihood of cure with chemotherapy to identify the subset of children for whom transplant offers a better treatment option. Indeed, advances in chemotherapy schemes continue to occur in parallel with important changes in transplantation techniques, donor availability, and supportive care measures. In addition, the exponential growth of genomic medicine and immunotherapy approaches in the last decade is dramatically changing the treatment perspective of ALL. On the one hand, genome sequencing studies have led to better molecular characterization of pediatric leukemias, this translating into improved risk stratification and identification of targetable genetic lesions [2, 3]. On the other one, impressive clinical results obtained with immunotherapeutic approaches, such as

Pietro Merli, Mattia Algeri, Francesca Del Bufalo and Franco Locatelli contributed equally to this work.

This article is part of the Topical Collection on *Acute Lymphocytic Leukemias*

✉ Franco Locatelli
franco.locatelli@opbg.net

[1] Department of Pediatric Hematology and Oncology, Bambino Gesù Children's Hospital, Piazza Sant'Onofrio, 4, 00165 Rome, Italy

[2] Sapienza University of Rome, Rome, Italy

bispecific T cell engagers (BiTEs), targeted immunotoxins, and chimeric antigen receptor (CAR) T cells, have substantially revolutionized the treatment of high-risk B cell precursor (BCP) ALL [4–6]. In light of these considerations, the role of HSCT in childhood ALL is likely to continue to change as continuous advances are made in biology, chemotherapy, immunotherapy, and transplantation in future years.

In this review, we will define the current best and promising future practices of HSCT for pediatric ALL by discussing (1) current indications for HSCT, (2) type of donor and conditioning regimen to be used in this setting, and (3) novel immunotherapeutic approaches that may be employed before or after HSCT to improve leukemia-free survival (LFS).

To Whom and When Should Allogeneic HSCT Be Offered in Pediatric ALL?

Typically, only a minority of children with ALL in first complete remission (CR1) are considered for HSCT. Most study groups define these patients as having an estimated EFS probability lower than 50%, according to specific biologic features and response to induction treatment. Primary induction failure (PIF) is rarely seen in pediatric ALL (< 2% of patients), but continues to represent a strong indication for HSCT in CR1, being one of the most unfavorable prognostic factors. A large retrospective study conducted by Schrappe et al. reported outcomes for pediatric patients with ALL experiencing PIF [7], the 10-year survival rate being only 32%. Patients older than 10 years, those with T cell phenotype, or those with an M3 marrow (i.e., > 25% blasts) at the end of induction were considered at particular risk. A significant survival advantage was observed in children older than 6 years receiving HSCT from an HLA-identical sibling compared with chemotherapy (59% compared to 39% of those not transplanted) and in T-ALL after any HSCT (5-year EFS of 40–45% versus 26% for chemotherapy) [7].

Minimal residual disease (MRD) measured at selected time points is currently the single most powerful prognostic factor in childhood ALL [8•]. It may be measured through flow cytometry or through detection of specific rearrangements of immune receptor genes *IgH*/*TCR* (heavy immunoglobulin/T cell receptor) [9]. The Italian Association of Pediatric Hematology-Oncology (AIEOP)-Berlin-Frankfurt-Muenster (BFM) 2000 study used prospective molecular (i.e., PCR-measured) MRD evaluation at day 33 (end of induction (EOI), timepoint 1 (TP1)) and day 78 (end of consolidation (EOC), timepoint 2 (TP2)) for treatment stratification in 3184 BCP-ALL patients. In this study, MRD predicted outcome more precisely than either genetic factors, white blood cell (WBC) count or prednisone response. BCP-ALL patients with MRD < 0.01 % at both TPs (standard risk (SR) patients) had a 5-year EFS of 92%, compared with 50% if MRD was > 0.1% at TP2 (high risk (HR)) on day 78 and 78% in intermediate-risk (IR) patients [10•]. In the same study, TP2-MRD was found to be the best predictor of outcome also in T-ALL. Indeed, HR patients had a much worse outcome, with a 7-year EFS of 50%, regardless of other factors, as compared with other risk groups (91% for SR, 81% for IR; $P < 0.001$) [11]. On the basis of such data, the successor AIEOP-BFM ALL 2009 study used a combination of PCR-MRD response at days 33 and 78, genetic features, and prednisone response to allocate BCP-ALL patients to different risk groups and formulate indications for performing HSCT (Table 1).

Children with severe hypodiploidy (< 44 chromosomes) have a particularly poor outcome progressively worsening with the decrease of chromosome number. A retrospective analysis on 139 hypodiploid ALL patients with < 45 chromosomes, treated by ten different national ALL study groups between 1986 and 1996, reported an 8-year EFS of 38.5% and overall survival (OS) of 49.8%. Patients with fewer than 44 chromosomes fared significantly worse than those with 44 chromosomes (EFS, 30% versus 52%; $P = 0.01$; OS, 37% versus 69%; $P = 0.017$) [12]. However, controversial results have been recently reported for this subset, making indications for HSCT in CR1 less clear. Indeed, data from a small series of patients treated at single institution suggest that children with hypodiploid ALL and negative MRD at the end of induction may be cured through risk-directed chemotherapy alone [13]. Another report by the Children's Oncology Group (COG) observed that, while chemotherapy alone results were still suboptimal in hypodiploid ALL, HSCT in CR1 did not confer a survival benefit, thus indicating the need for alternative therapeutic strategies in this subset of patients [14].

In addition to aneuploidy, a number of chromosomal translocations or structural aberrations have been demonstrated to have a prognostic impact in childhood BCP-ALL. Rearrangements involving the MLL gene on chromosome 11q23 are observed in up to 80% of infants ALL, while they are more rarely detected in children older than 1 year [15]. The majority of infants with MLL-rearranged ALL are characterized by a high white blood cell count, together with a pro-B cell phenotype of leukemic cells, which lack CD10 expression. The prognosis of these patients is relatively poor with only half of cases being cured with conventional chemotherapy [16, 17]. In an attempt to improve the outcome of infant ALL, a number of collaborative groups have investigated the use of HSCT in CR1. In a COG study, EFS for HSCT and chemotherapy alone were identical (49%; $P = 0.6$) [18], and the authors concluded that routine HSCT in CR1 may not be required for infants. However, that analysis included both lower risk and very-high-risk infants (younger children with high WBC), this mixture potentially diluting the impact of HSCT in the highest risk subgroup. Indeed, the Interfant group found that HSCT offered an advantage for a subgroup of

Table 1 Indications to HSCT in CR1 in the BFM-AIEOP 2009 protocol

		PCR-MRD results[a]				
		MRD-SR	MRD-MR[b]	PCR-MRD results		No MRD results
				MRD TP2 $\geq 10^{-3}$–$< 10^{-2}$	MRD TP2 $\geq 10^{-2}$	
Criteria hierarchical	No CR d33	NO[f]	MMD	MMD	MMD	MMD
	t(4;11)[c]	NO	MD	MD	MMD	MD
	Hypodiploidy < 44 chromosomes[d]	NO	MD	MD	MMD	MD
	PPR + T-ALL	NO	NO	MD	MMD	MD
	None of the above features[e]	NO	NO	MD	MMD	NO

NO HSCT is not indicated, MD permitted: HLA-matched sibling or non-sibling donor, MMD permitted donor: HLA-matched or HLA-mismatched donor

[a] FCM-MRD results have no impact on HSCT indication

[b] Including MRD-MR SER (MRD TP1 $\geq 10^{-3}$ and TP2 $10^{-4/-5}$)

[c] Independently of prednisone response

[d] The finding of exactly 44 chromosomes qualifies for HR treatment but has no impact on HSTC indication

[e] Including patients with 44 chromosomes

[f] Non-remission in patients with this rare constellation should be due to extramedullary disease. HSCT indication in these cases should be discussed

infants with MLL-rearranged ALL with two additional unfavorable prognostic features: age less than 6 months and either poor response to steroids or leukocytes $\geq 300 \times 10^6/\mu L$ at diagnosis [19•] Many cooperative groups consider patients older than 1 year with MLL-AF4 BCP-ALL candidates to receive an allograft in CR1.

Intrachromosomal amplification of chromosome 21 is a recurrent lesion found in up to 3% cases of pediatric ALL and has been associated with increased risk of relapse when treated with standard therapy [20]. Although intensive therapy including transplantation has led to improved survival in studies from the UK, whether HSCT has to be offered to patients who become MRD negative early in treatment still remains unclear [21].

BCP-ALL harboring the translocation t(17;19), which results in the TCF3-HLF fusion gene, represents a rare subset (< 1% of all BCP-ALL cases) characterized by low sensitivity to conventional chemotherapy and a dismal prognosis. Preclinical data suggests that these patients may be particularly sensitive to treatment with BCL-2 inhibition [22]. Moreover, recent observations documenting high expression of CD19 on leukemia cell surface suggest that immunotherapy with blinatumomab is effective in lowering the leukemia burden in this high-risk subset of ALL [23]. Once achieved CR, early consideration of HSCT for these patients is warranted.

Patients with T-ALL and poor MRD clearance at TP2 are considered candidate to receive an allograft in CR1. Indeed, in contrast with BCP-ALL, leukemia T cell blasts so far cannot benefit from approaches of immunotherapy, this contributing to the lower chance of rescue when a relapse occurs. This observation corroborates the choice of offering an allograft in CR1 to those patients that, mainly because of poor MRD clearance, are predicted to have a chance of EFS in the order of 50% or less.

Allogeneic HSCT is used much more commonly after ALL relapse (i.e., in ≥ 50% of patients) than during in CR1 [24•]. Protocols for treatment of relapsed ALL are based on patient stratification according to the time of relapse, the site of relapse, and the immunological lineage of ALL. Isolated BM relapse carries the worst prognosis, isolated central nervous system (CNS), and testicular or other extramedullary sites of relapse having a better prognosis, with combined BM and extramedullary relapse being associated with an intermediate prognosis [25–27]. Moreover, children with T cell ALL BM relapses have a much worse prognosis than BCP-ALL, irrespective of the time elapsing between diagnosis and recurrence [28].

More recently, persistence of MRD after induction/consolidation therapy (i.e., after 5 and 12–13 weeks from the beginning of treatment for relapse) has been shown to influence prognosis in children with relapsed ALL [29–32].

Based on the above observations, most recent relapse protocols have integrated MRD evaluation in the decision process for treatment stratification and indication to HSCT [29, 32, 33]. Notably, none of the classifications in use considers other risk factors, such as genetic abnormalities, this representing a relevant limitation. Indeed, it has been shown that, in intermediate-risk relapsed patients with low MRD (currently considered to have a good prognosis), deletion of IKZF1 and alteration of TP53 identify patients with significantly worse outcome [34]. Likewise, patients with relapsed BCP-ALL and either t(1;19) or hypodiploidy or MLL rearrangement should all be offered HSCT, since their probability of definitive cure without transplantation is low.

According to recommendations of the worldwide largest International Study for Children and Adolescents with Relapsed ALL (IntReALL), HSCT should be offered to any child with either HR features (very early isolated extramedullary relapse of BCP-ALL or T-ALL, early isolated or any very early bone marrow relapse of BCP-ALL, any bone marrow relapse of T-ALL) or poor clearance of blast after induction therapy for reaching a CR2 (i.e., high levels of MRD) (Table 2). Indeed, these patients (accounting for approximately two thirds of the overall population of children who relapse) have a probability of survival of 30% without HSCT [24•]. All patients who have experienced two or more relapses are candidates to an allograft, irrespectively of the type of donor available.

Which Is the Best Donor to Be Used in Pediatric ALL?

Historically, an HLA-identical related donor (or matched family donor (MFD)) was considered the best donor for patients in need of an allograft. However, given the theoretical 25% probability of finding such a donor [35], use of alternative donors (e.g., unrelated donors (UD)) has been investigated. Locatelli et al. demonstrated in 2002 that after the introduction of high-resolution molecular typing for both class I and II HLA loci, EFS of UD-HSCT in children with ALL in CR2 improved, mainly due to a decreased transplant-related mortality (TRM) [36]. Registry data from the Center for International Blood and Marrow Transplant Research (CIBMTR) showed that, although TRM was higher after HSCT from a mismatched unrelated donor (MMUD) or cord blood (UCB) donor, there were no differences in LFS between MFD and MUD, MMUD, or UCB [37]. These data were further confirmed by the ALL-SCT-BFM-2003 Trial [38•], comparing allogeneic HSCT from MFD or UD in 411 high-risk ALL patients. Indeed, this was the first prospective study to compare HSCT from different donor types in well-defined cohorts of children with high-risk ALL by using a standardized transplantation protocol, as well as homogeneous supportive care. Although TRM was higher in the UD group, LFS was superimposable to that of patients transplanted from a MFD. Since the probability of finding a suitable/compatible MUD within the international volunteer registries is conditioned by the patient's ethnic background, with a markedly lower probability for patients belonging to ethnic minorities [39], in the last decade, the use of haploidentical donors increased significantly. Indeed, this kind of donor is characterized by several desirable features, including availability for virtually all patients, choice of the best donor from a panel of candidates, immediate accessibility to the allograft, no delay in obtaining the graft, and easy access to donors' adoptive cell therapies in case they are required after transplantation. Recently, the Rome pediatric group demonstrated in a prospective monocentric study [40•] and in a large multicenter retrospective study [41] that TCRαβ-depleted haploidentical HSCT (αβhaplo-HSCT) is a suitable therapeutic option for children with ALL in need of transplantation. Indeed, in the first study, LFS was superimposable in the three groups analyzed, namely MFD, MUD, and αβhaplo-HSCT [40•]. In the second study, LFS was comparable between MUD and αβhaplo-HSCT, while it was lower when HSCT was performed using a MMUD [41]. Notably,

Table 2 Indications to HSCT for relapsed ALL in the IntReALL 2010 protocol

Risk group		MRD[a]		
	Patient subgroup	GR[b]	PR[b]	NA
SR	• Late isolated or combined bone marrow relapse of BCP-ALL	NO	MMD	MD
	• Early combined bone marrow relapse	MD	MMD	MMD
		Time of relapse		
	• Isolated extramedullary relapse	Early	Late	
		MD	NO	
HR	• Very early isolated extramedullary relapse of BCP or T-ALL • Early isolated or any very early bone marrow relapse of BCP-ALL • Any bone marrow relapse of T-ALL	HSCT in ALL patients (with a MD or a MMD)		

Time point of relapse: very early, < 18 months after primary diagnosis and < 6 after completion of primary therapy; early, ≥ 18 months after primary diagnosis and < 6 after completion of primary; late, ≥ months after completion of primary. MD permitted donor: HLA-matched sibling or non-sibling donor, MMD permitted donor: HLA-matched or HLA-mismatched donor

GR good response, *HR* high risk, *HSCT* hematopoietic stem cell transplantation, *MRD* minimal residual disease, *NA* not available, *NO* HSCT not indicated, *PR* poor response, *SR* standard risk

[a] MRD response after induction

[b] MRD cutoff is defined by the specific treatment arm

the risk of both acute and chronic GvHD after αβhaplo-HSCT was significantly lower than after MFD/UD HSCT, this potentially representing a further advantage in terms of patients' acute morbidity and long-term quality of life.

Post-transplantation, early administration of two doses of cyclophosphamide is an option largely used to prevent acute GvHD in unmanipulated haploidentical HSCT, thanks to the ability of the drug to kill preferentially cycling, donor-derived alloreactive T cells, while sparing hematopoietic stem/progenitor cells [42]. Many studies have shown the efficacy of unmanipulated haplo-HSCT in adults with ALL [43, 44]; however, data on pediatric patients are limited to few reports enrolling small numbers of patients [45, 46], this precluding the possibility of drawing firm conclusions on what can be offered by this transplant option in children with ALL.

UCB transplantation (UCBT) has been largely employed in the past for treating patients with either relapsed or high-risk CR1 ALL children [47, 48]. Although registry data showed that unrelated UCBT is able to offer a long-term outcome similar to that observed using an unrelated adult volunteer as donor, the last few years have witnessed a progressive decline in the number of UCBT performed for children with hematological malignancies, including ALL [49].

What Kind of Conditioning Regimen and GvHD Prophylaxis Should Be Used?

Conditioning regimens are given before the infusion of the graft with two goals: further reduction of leukemia burden (ideally disease eradication) and immune suppression to overcome host rejection of the graft. The choice of the optimal conditioning regimen for any given patient is based on disease-related factors, such as diagnosis and disease phase, as well as patient-related factors (e.g., age, type of donor, source of stem cells, and presence of comorbidity conditions) [50].

Total body irradiation (TBI)-based regimens are considered the standard conditioning for pediatric patients affected by ALL [51, 52]. High-dose cyclophosphamide (Cy) (120 mg/kg) has been associated since the first studies to TBI [53]. A large retrospective study comparing TBI + Cy and busulfan (Bu) + Cy showed improved OS and LFS when the former conditioning was used. Since relapse is the main cause of treatment failure, intensification of this type of conditioning with a number of cytotoxic agents has been investigated [54]. In particular, the use of thiotepa (TT) (10 mg/kg), a drug that is characterized by cell cycle-independent effect, good CNS diffusion, and limited extramedullary toxicity, has been shown to be safe and effective [55]. Another drug frequently associated with TBI and TT is the purine analogue fludarabine (Flu) [40•]. With the limitation related to the nature of the study, a retrospective registry analysis from the Japan Society for Hematopoietic Cell Transplantation identified melphalan (LPAM) as the best single agent to be coupled with TBI, since this conditioning resulted into the lowest relapse incidence as compared with other combinations of radiotherapy and cytotoxic agents [54]. The same study showed improved outcome, especially when an alternative donor is used, with the addition of etoposide (VP16) to TBI and Cy [54]. The combination of TBI and high-dose VP16 (60 mg/kg) [56], although characterized by considerable mucosal and dermatologic toxicity [57], compared favorably with TBI + Cy for children in CR2 in a large CIBMTR registry study [58]. This kind of regimen has been used in the ALL-SCT-BFM-2003 trial [38•], confirming the good toxicity profile, and is currently investigated in the multicenter, randomized controlled trial (RCT) "FORUM" (NCT01949129). Given the well-known long-term toxicity of TBI in children [59, 60], this study, conducted by the international BFM consortium, is aimed at comparing non-TBI-based conditioning (Bu-based or treosulfan-based) with TBI + VP16. So far, the only RCT comparing Bu with TBI in children with ALL suggested comparable rates of relapse in the two arms, although transplant-related mortality was higher in the Bu group [61]. Thus, the results of the FORUM trial are urgently awaited. Although reduced intensity conditioning (RIC) regimens have been developed in the last years to reduce treatment-related toxicities, myeloablative conditioning (MAC) still remains the gold standard for pediatric patients undergoing HSCT for malignant disorders. Indeed, for children not eligible to MAC, RIC based on Bu and Flu has been studied, resulting in low TRM, but burdened by a high incidence of relapse [62] (see Table 3 for further details).

Anti-human T lymphocyte globulin (ATLG) is used in patients undergoing HSCT to tune bi-directional alloreactivity, with the aim of reducing the incidence and severity of the two main immune-mediated complications of the procedure, namely graft rejection and acute/chronic graft-versus-host disease (GvHD). Four RCTs comparing the use of pre-transplant ATLG administration to regimen without serotherapy have been conducted in adult patients, showing a significant reduction in the incidence of chronic GvHD when ATLG is added to the standard prophylaxis [63]. A recent trail RCT conducted in the USA showed an increased risk of relapse in adult patients allocated to receive ATLG [64]. The only RCT in children addressing the dosage of ATLG in HSCT from UD has been conducted by Locatelli and colleagues, who compared two different doses of rabbit anti-human T cell line (Jurkat) globulin (Grafalon®, Neovii Biotech), namely 15 mg/kg versus 30 mg/kg over 3 days [65••]. The authors showed that low-dose ATLG can reduce the incidence of life-threatening infections, without significantly affecting the incidence of acute and chronic GvHD, as well as that of recurrence of the original disease, thus resulting into an improved OS and EFS. They concluded that ATLG at 15 mg/kg should, thus, be

Table 3 Outcomes of different conditioning regimen

Conditioning regimen	Reference(s)	DFS (%)	TRM (%)	Relapse incidence (%)	Notes
Myeloablative conditioning (MAC)					
TBI + Cy	51, 53, 54	50–64*	12–19	13*–32	51, 53: Studies performed before 2000
Bu + Cy	51, 54	35			Studies performed before 2000
TBI + TT + Cy	55	65		23	Limited number of patients
TBI + TT + Flu	40	81	3	16	Only haplo-HSCT
TBI + LPAM	54	71	14	15	Retrospective study
TBI + Cy + VP16	54	68	9	23	Retrospective study
TBI + VP16	38, 58	57–71	3–27	13–24	
Reduced intensity conditioning (RIC)					
Bu + Flu	62	40	11	43	

The different studies varied greatly with respect to the disease status at time of the allograft and type of donor employed

*Only patients in CR2

regarded as the standard serotherapy regimen for UD allogeneic HSCT in pediatric patients affected by malignant disorders.

A correct tuning of GvHD prophylaxis remains a cornerstone of the transplant strategy for children with ALL. Indeed, several authors have demonstrated that the occurrence of GvHD can reduce the incidence of relapse [66, 67]; however, high-grade GvHD is associated with a lower OS due to an increased risk of TRM [67]. The COG has deeply investigated the role of GvHD, together with that of pre- and post-HSCT MRD detection, in the ASCT0431 protocol. In this study, it was clearly shown that that pre-HSCT MRD < 0.1% and acute GvHD occurring before day + 55 were independently associated with decreased relapse and improved EFS [66, 67], thus also identifying an optimal time window to initiate interventions to prevent relapse occurrence (e.g., rapid tapering of immunosuppression, donor lymphocyte infusions, or other cellular therapies [68]). The occurrence of chronic GvHD of limited severity has been shown to prevent the risk of disease recurrence, this resulting into an improved probability of OS in children with hematological malignancies, including those with ALL [69].

Children with ALL experiencing leukemia recurrence have a dismal outcome. A minority of them can be rescued by a second allograft [70, 71], whose efficacy is better if the time elapsing between the first transplant and relapse exceeds 6–12 months. To be effective, a second allograft can be performed only if a new state of morphological CR is achieved. Donor lymphocyte infusion (DLI) has a limited value in patients with overt relapse, while it can be more effective in patients with persistence/re-positivization of MRD after HSCT [72]. Either aggressive or low-dose chemotherapy can be used before DLI to reduce the leukemia burden and promote donor T cell expansion.

HSCT in Unique Pediatric Populations

Two categories of pediatric patients with ALL deserve special consideration in terms of indication to HSCT, considering its less-clear role in these subgroups of children: patients affected by Down syndrome (DS) and patients with Philadelphia chromosome-positive (Ph+) ALL.

Children with DS are at 10 to 30% greater risk for developing acute leukemia than children with a normal constitutional karyotype; relapse and survival rates in case of ALL are worse than those of children without DS [73]. DS patients when transplanted require special consideration, because of possible pre-existing comorbidities and the potentially increased transplantation-related toxicity, resulting into increased TRM [74–76]. The main toxicity reported in studies of DS children undergoing HSCT involves respiratory complications, including infections, pulmonary hemorrhages, and upper airway obstruction following severe mucositis [75, 76]. Pulmonary vascular abnormalities and obstructive sleep apnea leading to pulmonary hypertension are common in children with DS and can predispose these patients to the development of the aforementioned complications. However, more recent reports suggest relapse, rather than TRM, as the most frequent cause of treatment failure and mortality in this population of patients, with a higher incidence of post-transplant relapse for children with DS (54%) than for non-DS patients [77, 78]. All these reports, however, are limited by the small sample size and the consequent impossibility of performing a subgroup analysis to define the role of conditioning regimens and GvHD prophylaxis on relapse and TRM incidence. It is important to note, however, that the risk of chemotherapy-induced toxicities accounts for a reduction of disease control before HSCT in this population of patients, with a higher proportion of children with DS receiving the transplantation

in a non-remission status that might affect the final patients' outcome. Concerning the risk of conditioning chemotherapy- or radiotherapy-associated toxicities, contrasting results have been published; indeed, three retrospective series showed that myeloablative doses of either TBI, Cy, or Bu did not impact the 100-day mortality [75, 77, 78]. Data on the risk of acute GvHD are also unclear, incidence ranging between 25% and 100% across different studies, whereas rates of chronic GvHD do not differ significantly from non-DS children [74, 77, 78]. Large controversies have been raised about the use of methotrexate as GvHD prophylaxis, given the well-known poor tolerance of these patients to the drug, although the reduced doses used in this setting as compared to those used in leukemia chemotherapy protocols might likely induce a lower toxicity [79]. So far, the limited data available do not allow drawing firm conclusions on the risk/benefit ratio associated with HSCT in patients with DS. Larger, prospective studies are necessary to define clear indications to HSCT and to identify the optimal conditioning regimens and GvHD prophylaxis approaches for this peculiar, fragile population.

Children and adolescents with Ph + ALL represent the second population of ALL patients deserving special consideration. Considered for a long time one of the poorest-prognosis subgroup of ALL, their prognostic perspective has been completely revolutionized by the introduction of imatinib and other tyrosine kinase inhibitors (TKIs) in front-line therapy. Through the blockade of the fusion protein associated with the characteristic t(9;22), TKIs significantly improved outcomes in pediatric Ph + ALL patients, with or without HSCT [80–82]. In 2014, COG reported outcomes of 91 children treated with the combination of imatinib and intensive chemotherapy, showing a 5-year DFS of 70% in the chemotherapy + imatinib group, 65% for patients receiving a MFD HSCT, and 59% for children transplanted from an UD, these results suggesting that many patients could be maintained on TKI treatment only, avoiding allo-HSCT [83]. A more recent study based on the use of the second-generation TKI dasatinib combined with intensive chemotherapy, reserving HSCT to high-risk patients with a MFD, showed comparable 5-year EFS between the two groups (61% versus 67%) [84]. Taken together, these data suggest the possibility of avoiding HSCT in a subgroup of pediatric patients with Ph + ALL in CR1, namely low-risk patients (i.e., those with low PCR-MRD at the end of induction). Identification of predictive factors influencing the outcome can further refine the selection of patients that can skip HSCT without impairing long-term survival. Whereas the role of MRD remains clear in predicting relapse also for these patients, the role of additional cytogenetic mutations needs to be further elucidated [85–87]. Lastly, the efficacy of the different TKIs available could also influence the outcome, as shown by studies comparing the last generation ponatinib with dasatinib and showing the superiority of the first one [88, 89].

What Is the Role of HSCT in the Immunotherapy Era?

In the last 15 years, novel treatment approaches aimed at exploiting the ability of the immune system to recognize and eliminate leukemia blasts have been developed and proved to be extremely effective in patients affected by refractory/relapsed (r/r) BCP-ALL [24•]. Different strategies have been developed, including BiTEs, CAR-expressing T cells, and the so-called antibody drug conjugates (ADCs).

Blinatumomab, the CD19-directed BiTE, was shown to be extremely effective in children with r/r CD19-positive BCP-ALL in an international, multicenter phase I–II study, showing 39% of CR within the first cycle and a median LFS of 4.4 months (increased to 7.5 months in the MRD-negative subpopulation) [90••]. Earlier use of blinatumomab is currently under investigation in the IntReALL consortium, as consolidation therapy before HSCT in children with high-risk first relapse, in order to reduce the pre-transplantation MRD levels. Promising results have been shown also by the ADC inotuzumab, a CD22-specific mAb conjugated with the cytotoxic agent calicheamicin, in a cohort of 51 children with r/r ALL treated on a compassionate use basis; 67% of patients achieved CR, this observation providing a strong basis for implementing a prospective, multicenter, phase I/II study [91]. Lastly, CD19-CAR T cells are currently the most advanced T cell therapy tested in clinical trials on patients with BCP-ALL. Initial clinical reports and clinical trials have demonstrated striking responses, with durable remissions obtained in patients with r/r ALL who were considered incurable [92••, 93]. These results led to the recent approval first by the Food and Drug Administration and subsequently by the European Medicines Agency of two CD19-directed CAR T cell therapies (Kymriah™ and Yescarta™), for treatment of children and young adults with r/r BCP-ALL and of adult patients with r/r large B cell lymphoma, respectively [94•].

In this scenario, the role of HSCT will likely have to be redefined. It must be noted, however, that, although effective, with durable responses in a subgroup of patients, CAR T therapy and other targeted therapies do not prevent the phenomenon of antigen escape, which renders leukemic blasts resistant to these approaches [95]. Well-designed RCTs will have to compare directly the long-term leukemia control offered by CAR T cell approaches versus HSCT, showing whether the former can substitute allogeneic HSCT. Interestingly, in the Memorial Sloan Kettering Cancer Center experience with CD19-CAR T cells, amongst the 32 patients obtaining MRD-negative CR, no significant difference in OS between patients who either did or did not subsequently undergo HSCT was found ($P = 0.89$) [93]. In the ELIANA trial, substantially identical OS was reported for patients who did not receive HSCT as compared to those who underwent HSCT, the persistence of tisagenlecleucel in peripheral blood being the main

factor associated with durable response [92••]. The limited and non-homogeneous data reported to date do not allow drawing firm conclusions, and the question remains to be properly addressed in future well-designed trials. Moreover, head-to-head comparisons of different immunotherapy strategies are lacking, precluding any definitive conclusion on the relative roles and merits of each approach. Future clinical trials and research developments will ultimately determine the best strategy to treat children with high-risk or r/r BCP-ALL.

Conclusions

For many years, allogeneic HSCT from an HLA-identical sibling has represented the treatment of choice for many children with high-risk features or r/r ALL. In the last two decades, results of transplantation from an UD have progressively improved over time, becoming similar to those obtained using a MFD when a highly compatible donor can be identified. More selective strategies of T cell depletion, such as those based on the physical removal of αβ T cells from the graft, have rendered HSCT from an HLA-haploidentical donor a suitable option to virtually transplant any child in need of an allograft. Several important questions are under investigation, including that of the advantage/limitations offered by a TBI-containing conditioning regimen in comparison to those based on the combination of cytotoxic agents. Through the conduction of well-designed trials based on the intention-to-treat approach analysis, the next few years will witness if allogeneic HSCT can be replaced by CAR T cells in BCP-ALL. Till these studies will be finalized, HSCT remains the standard-of-care treatment for every child with CR1 ALL carrying high-risk features predicting leukemia recurrence and for those experiencing high-risk first relapse or multiple recurrences.

Acknowledgments The authors would like to thank P.D.S. and F.M. for the critical revision of the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncol. 2012;30(14):1663–9. https://doi.org/10.1200/JCO.2011.37.8018.
2. Moorman AV. New and emerging prognostic and predictive genetic biomarkers in B-cell precursor acute lymphoblastic leukemia. Haematologica. 2016;101(4):407–16. https://doi.org/10.3324/haematol.2015.141101.
3. Iacobucci I, Mullighan CG. Genetic basis of acute lymphoblastic leukemia. J Clin Oncol. 2017;35(9):975–83. https://doi.org/10.1200/JCO.2016.70.7836.
4. Algeri M, Del Bufalo F, Galaverna F, Locatelli F. Current and future role of bispecific T-cell engagers in pediatric acute lymphoblastic leukemia. Expert Rev Hematol. 2018;11(12):945–56. https://doi.org/10.1080/17474086.2018.1540928.
5. Maus MV, Grupp SA, Porter DL, June CH. Antibody-modified T cells: CARs take the front seat for hematologic malignancies. Blood. 2014;123(17):2625–35. https://doi.org/10.1182/blood-2013-11-492231.
6. Jabbour E, O'Brien S, Ravandi F, Kantarjian H. Monoclonal antibodies in acute lymphoblastic leukemia. Blood. 2015;125(26):4010–6. https://doi.org/10.1182/blood-2014-08-596403.
7. Schrappe M, Hunger SP, Pui CH, Saha V, Gaynon PS, Baruchel A, et al. Outcomes after induction failure in childhood acute lymphoblastic leukemia. N Engl J Med. 2012;366(15):1371–81. https://doi.org/10.1056/NEJMoa1110169.
8.• Borowitz MJ, Devidas M, Hunger SP, Bowman WP, Carroll AJ, Carroll WL, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood. 2008;111(12):5477–85. https://doi.org/10.1182/blood-2008-01-132837 **First demonstration that end-induction MRD appears to predict disease relapse and long-term outcome in a multivariate analysis.**
9. van Dongen JJ, van der Velden VH, Bruggemann M, Orfao A. Minimal residual disease diagnostics in acute lymphoblastic leukemia: need for sensitive, fast, and standardized technologies. Blood. 2015;125(26):3996–4009. https://doi.org/10.1182/blood-2015-03-580027.
10.• Conter V, Bartram CR, Valsecchi MG, Schrauder A, Panzer-Grumayer R, Moricke A, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood. 2010;115(16):3206–14. https://doi.org/10.1182/blood-2009-10-248146 **Demonstration that PCR-MRD at the end of consolidation therapy is the major determinant of relapse risk.**
11. Schrappe M, Valsecchi MG, Bartram CR, Schrauder A, Panzer-Grumayer R, Moricke A, et al. Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study. Blood. 2011;118(8):2077–84. https://doi.org/10.1182/blood-2011-03-338707.
12. Nachman JB, Heerema NA, Sather H, Camitta B, Forestier E, Harrison CJ, et al. Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia. Blood. 2007;110(4):1112–5. https://doi.org/10.1182/blood-2006-07-038299.

13. Mullighan CG, Jeha S, Pei D, Payne-Turner D, Coustan-Smith E, Roberts KG, et al. Outcome of children with hypodiploid ALL treated with risk-directed therapy based on MRD levels. Blood. 2015;126(26):2896–9. https://doi.org/10.1182/blood-2015-09-671131.
14. McNeer J, Meenakshi D, Dai Y, Carroll AJ, Heerema NA, Gastier-Foster JM, et al. Hematopoietic stem cell transplantation does not improve the poor outcome of children with Hypodiploid Acute Lymphoblastic Leukemia: A report from Children's Oncology Group. J Clin Oncol. 2019. Epub ahead of print.
15. Biondi A, Cimino G, Pieters R, Pui CH. Biological and therapeutic aspects of infant leukemia. Blood. 2000;96(1):24–33.
16. Pieters R, Schrappe M, De Lorenzo P, Hann I, De Rossi G, Felice M, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. Lancet. 2007;370(9583):240–50. https://doi.org/10.1016/S0140-6736(07)61126-X.
17. Hilden JM, Dinndorf PA, Meerbaum SO, Sather H, Villaluna D, Heerema NA, et al. Analysis of prognostic factors of acute lymphoblastic leukemia in infants: report on CCG 1953 from the Children's Oncology Group. Blood. 2006;108(2):441–51. https://doi.org/10.1182/blood-2005-07-3011.
18. Dreyer ZE, Dinndorf PA, Camitta B, Sather H, La MK, Devidas M, et al. Analysis of the role of hematopoietic stem-cell transplantation in infants with acute lymphoblastic leukemia in first remission and MLL gene rearrangements: a report from the Children's Oncology Group. J Clin Oncol. 2011;29(2):214–22. https://doi.org/10.1200/JCO.2009.26.8938.
19.• Mann G, Attarbaschi A, Schrappe M, De Lorenzo P, Peters C, Hann I, et al. Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-lineage-leukemia (MLL)-rearranged acute lymphoblastic leukemia: results from the Interfant-99 Study. Blood. 2010;116(15):2644–50. https://doi.org/10.1182/blood-2010-03-273532 **Demonstration that HSCT in CR1 is superior to chemotherapy in infant MLL+ ALL carrying additional poor prognostic factors.**
20. Heerema NA, Carroll AJ, Devidas M, Loh ML, Borowitz MJ, Gastier-Foster JM, et al. Intrachromosomal amplification of chromosome 21 is associated with inferior outcomes in children with acute lymphoblastic leukemia treated in contemporary standard-risk children's oncology group studies: a report from the children's oncology group. J Clin Oncol. 2013;31(27):3397–402. https://doi.org/10.1200/JCO.2013.49.1308.
21. Moorman AV, Robinson H, Schwab C, Richards SM, Hancock J, Mitchell CD, et al. Risk-directed treatment intensification significantly reduces the risk of relapse among children and adolescents with acute lymphoblastic leukemia and intrachromosomal amplification of chromosome 21: a comparison of the MRC ALL97/99 and UKALL2003 trials. J Clin Oncol. 2013;31(27):3389–96. https://doi.org/10.1200/JCO.2013.48.9377.
22. Fischer U, Forster M, Rinaldi A, Risch T, Sungalee S, Warnatz HJ, et al. Genomics and drug profiling of fatal TCF3-HLF-positive acute lymphoblastic leukemia identifies recurrent mutation patterns and therapeutic options. Nat Genet. 2015;47(9):1020–9. https://doi.org/10.1038/ng.3362.
23. Locatelli F, Zugmaier G, Vora A, Rossig C, Peters C, Brethon B, et al. Blinatumomab use in pediatric patients (pts) with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL) from an open-label, multicenter, expanded access study. J Clin Oncol. 2017;35:10530. https://doi.org/10.1200/JCO.2017.35.15_suppl.10530.
24.• Locatelli F, Schrappe M, Bernardo ME, Rutella S. How I treat relapsed childhood acute lymphoblastic leukemia. Blood. 2012;120(14):2807–16. https://doi.org/10.1182/blood-2012-02-265884 **This is a comprehensive review on the pathophysiology and management of relapsed pediatric ALL.**
25. Bailey LC, Lange BJ, Rheingold SR, Bunin NJ. Bone-marrow relapse in paediatric acute lymphoblastic leukaemia. Lancet Oncol. 2008;9(9):873–83. https://doi.org/10.1016/S1470-2045(08)70229-8.
26. Einsiedel HG, von Stackelberg A, Hartmann R, Fengler R, Schrappe M, Janka-Schaub G, et al. Long-term outcome in children with relapsed ALL by risk-stratified salvage therapy: results of trial acute lymphoblastic leukemia-relapse study of the Berlin-Frankfurt-Munster Group 87. J Clin Oncol. 2005;23(31):7942–50. https://doi.org/10.1200/JCO.2005.01.1031.
27. Lawson SE, Harrison G, Richards S, Oakhill A, Stevens R, Eden OB, et al. The UK experience in treating relapsed childhood acute lymphoblastic leukaemia: a report on the medical research council UKALLR1 study. Br J Haematol. 2000;108(3):531–43.
28. Borgmann A, von Stackelberg A, Hartmann R, Ebell W, Klingebiel T, Peters C, et al. Unrelated donor stem cell transplantation compared with chemotherapy for children with acute lymphoblastic leukemia in a second remission: a matched-pair analysis. Blood. 2003;101(10):3835–9. https://doi.org/10.1182/blood.V101.10.3835.
29. Parker C, Waters R, Leighton C, Hancock J, Sutton R, Moorman AV, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. Lancet. 2010;376(9757):2009–17. https://doi.org/10.1016/S0140-6736(10)62002-8.
30. Paganin M, Zecca M, Fabbri G, Polato K, Biondi A, Rizzari C, et al. Minimal residual disease is an important predictive factor of outcome in children with relapsed 'high-risk' acute lymphoblastic leukemia. Leukemia. 2008;22(12):2193–200. https://doi.org/10.1038/leu.2008.227.
31. Eckert C, Biondi A, Seeger K, Cazzaniga G, Hartmann R, Beyermann B, et al. Prognostic value of minimal residual disease in relapsed childhood acute lymphoblastic leukaemia. Lancet. 2001;358(9289):1239–41. https://doi.org/10.1016/S0140-6736(01)06355-3.
32. Coustan-Smith E, Gajjar A, Hijiya N, Razzouk BI, Ribeiro RC, Rivera GK, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia after first relapse. Leukemia. 2004;18(3):499–504. https://doi.org/10.1038/sj.leu.2403283.
33. Eckert C, von Stackelberg A, Seeger K, Groeneveld TW, Peters C, Klingebiel T, et al. Minimal residual disease after induction is the strongest predictor of prognosis in intermediate risk relapsed acute lymphoblastic leukaemia—long-term results of trial ALL-REZ BFM P95/96. Eur J Cancer. 2013;49(6):1346–55. https://doi.org/10.1016/j.ejca.2012.11.010.
34. Krentz S, Hof J, Mendioroz A, Vaggopoulou R, Dorge P, Lottaz C, et al. Prognostic value of genetic alterations in children with first bone marrow relapse of childhood B-cell precursor acute lymphoblastic leukemia. Leukemia. 2013;27(2):295–304. https://doi.org/10.1038/leu.2012.155.
35. Besse K, Maiers M, Confer D, Albrecht M. On modeling human leukocyte antigen-identical sibling match probability for allogeneic hematopoietic cell transplantation: estimating the need for an unrelated donor source. Biol Blood Marrow Transplant. 2016;22(3):410–7. https://doi.org/10.1016/j.bbmt.2015.09.012.
36. Locatelli F, Zecca M, Messina C, Rondelli R, Lanino E, Sacchi N, et al. Improvement over time in outcome for children with acute lymphoblastic leukemia in second remission given hematopoietic stem cell transplantation from unrelated donors. Leukemia. 2002;16(11):2228–37. https://doi.org/10.1038/sj.leu.2402690.
37. Zhang MJ, Davies SM, Camitta BM, Logan B, Tiedemann K, Eapen M, et al. Comparison of outcomes after HLA-matched sibling and unrelated donor transplantation for children with high-risk acute lymphoblastic leukemia. Biol Blood Marrow Transplant. 2012;18(8):1204–10. https://doi.org/10.1016/j.bbmt.2012.01.007.

38.• Peters C, Schrappe M, von Stackelberg A, Schrauder A, Bader P, Ebell W, et al. Stem-cell transplantation in children with acute lymphoblastic leukemia: a prospective international multicenter trial comparing sibling donors with matched unrelated donors-the ALL-SCT-BFM-2003 trial. J Clin Oncol. 2015;33(11):1265–74. https://doi.org/10.1200/JCO.2014.58.9747 **The first prospective study to compare HSCT from unrelated donors and matched family donors in well-defined cohorts of children with high-risk ALL.**

39. Gragert L, Eapen M, Williams E, Freeman J, Spellman S, Baitty R, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. N Engl J Med. 2014;371(4):339–48. https://doi.org/10.1056/NEJMsa1311707.

40.• Locatelli F, Merli P, Pagliara D, Li Pira G, Falco M, Pende D, et al. Outcome of children with acute leukemia given HLA-haploidentical HSCT after alphabeta T-cell and B-cell depletion. Blood. 2017;130(5):677–85. https://doi.org/10.1182/blood-2017-04-779769 **A large single-center study on TCRαβ-depleted haploidentical HSCT demonstrating similar outcomes when haploidentical, unrelated and matched-family donors were used.**

41. Bertaina A, Zecca M, Buldini B, Sacchi N, Algeri M, Saglio F, et al. Unrelated donor vs HLA-haploidentical alpha/beta T-cell- and B-cell-depleted HSCT in children with acute leukemia. Blood. 2018;132(24):2594–607. https://doi.org/10.1182/blood-2018-07-861575.

42. Bashey A, Solomon SR. T-cell replete haploidentical donor transplantation using post-transplant CY: an emerging standard-of-care option for patients who lack an HLA-identical sibling donor. Bone Marrow Transplant. 2014;49(8):999–1008. https://doi.org/10.1038/bmt.2014.62.

43. Srour SA, Milton DR, Bashey A, Karduss-Urueta A, Al Malki MM, Romee R, et al. Haploidentical transplantation with post-transplantation cyclophosphamide for high-risk acute lymphoblastic leukemia. Biol Blood Marrow Transplant. 2017;23(2):318–24. https://doi.org/10.1016/j.bbmt.2016.11.008.

44. Santoro N, Ruggeri A, Labopin M, Bacigalupo A, Ciceri F, Gulbas Z, et al. Unmanipulated haploidentical stem cell transplantation in adults with acute lymphoblastic leukemia: a study on behalf of the Acute Leukemia Working Party of the EBMT. J Hematol Oncol. 2017;10(1):113. https://doi.org/10.1186/s13045-017-0480-5.

45. Berger M, Lanino E, Cesaro S, Zecca M, Vassallo E, Faraci M, et al. Feasibility and outcome of haploidentical hematopoietic stem cell transplantation with post-transplant high-dose cyclophosphamide for children and adolescents with hematologic malignancies: an AIEOP-GITMO retrospective multicenter study. Biol Blood Marrow Transplant. 2016;22(5):902–9. https://doi.org/10.1016/j.bbmt.2016.02.002.

46. Hong KT, Kang HJ, Choi JY, Hong CR, Cheon JE, Park JD, et al. Favorable outcome of post-transplantation cyclophosphamide haploidentical peripheral blood stem cell transplantation with targeted busulfan-based myeloablative conditioning using intensive pharmacokinetic monitoring in pediatric patients. Biol Blood Marrow Transplant. 2018;24(11):2239–44. https://doi.org/10.1016/j.bbmt.2018.06.034.

47. Rocha V, Cornish J, Sievers EL, Filipovich A, Locatelli F, Peters C, et al. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. Blood. 2001;97(10):2962–71.

48. Eapen M, Rubinstein P, Zhang MJ, Stevens C, Kurtzberg J, Scaradavou A, et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. Lancet. 2007;369(9577):1947–54. https://doi.org/10.1016/S0140-6736(07)60915-5.

49. Passweg JR, Baldomero H, Bader P, Basak GW, Bonini C, Duarte R, et al. Is the use of unrelated donor transplantation leveling off in Europe? The 2016 European Society for Blood and Marrow Transplant activity survey report. Bone Marrow Transplant. 2018;53(9):1139–48. https://doi.org/10.1038/s41409-018-0153-1.

50. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. Blood. 2014;124(3):344–53. https://doi.org/10.1182/blood-2014-02-514778.

51. Davies SM, Ramsay NK, Klein JP, Weisdorf DJ, Bolwell B, Cahn JY, et al. Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia. J Clin Oncol. 2000;18(2):340–7. https://doi.org/10.1200/JCO.2000.18.2.340.

52. Shi-Xia X, Xian-Hua T, Hai-Qin X, Bo F, Xiang-Feng T. Total body irradiation plus cyclophosphamide versus busulphan with cyclophosphamide as conditioning regimen for patients with leukemia undergoing allogeneic stem cell transplantation: a meta-analysis. Leuk Lymphoma. 2010;51(1):50–60. https://doi.org/10.3109/10428190903419130.

53. Brochstein JA, Kernan NA, Groshen S, Cirrincione C, Shank B, Emanuel D, et al. Allogeneic bone marrow transplantation after hyperfractionated total-body irradiation and cyclophosphamide in children with acute leukemia. N Engl J Med. 1987;317(26):1618–24. https://doi.org/10.1056/NEJM198712243172602.

54. Kato M, Ishida H, Koh K, Inagaki J, Kato K, Goto H, et al. Comparison of chemotherapeutic agents as a myeloablative conditioning with total body irradiation for pediatric acute lymphoblastic leukemia: a study from the pediatric ALL working group of the Japan Society for Hematopoietic Cell Transplantation. Pediatr Blood Cancer. 2015;62(10):1844–50. https://doi.org/10.1002/pbc.25602.

55. Zecca M, Pession A, Messina C, Bonetti F, Favre C, Prete A, et al. Total body irradiation, thiotepa, and cyclophosphamide as a conditioning regimen for children with acute lymphoblastic leukemia in first or second remission undergoing bone marrow transplantation with HLA-identical siblings. J Clin Oncol. 1999;17(6):1838–46. https://doi.org/10.1200/JCO.1999.17.6.1838.

56. Blume KG, Forman SJ, O'Donnell MR, Doroshow JH, Krance RA, Nademanee AP, et al. Total body irradiation and high-dose etoposide: a new preparatory regimen for bone marrow transplantation in patients with advanced hematologic malignancies. Blood. 1987;69(4):1015–20.

57. Snyder DS, Chao NJ, Amylon MD, Taguchi J, Long GD, Negrin RS, et al. Fractionated total body irradiation and high-dose etoposide as a preparatory regimen for bone marrow transplantation for 99 patients with acute leukemia in first complete remission. Blood. 1993;82(9):2920–8.

58. Marks DI, Forman SJ, Blume KG, Perez WS, Weisdorf DJ, Keating A, et al. A comparison of cyclophosphamide and total body irradiation with etoposide and total body irradiation as conditioning regimens for patients undergoing sibling allografting for acute lymphoblastic leukemia in first or second complete remission. Biol Blood Marrow Transplant. 2006;12(4):438–53. https://doi.org/10.1016/j.bbmt.2005.12.029.

59. Giorgiani G, Bozzola M, Locatelli F, Picco P, Zecca M, Cisternino M, et al. Role of busulfan and total body irradiation on growth of prepubertal children receiving bone marrow transplantation and results of treatment with recombinant human growth hormone. Blood. 1995;86(2):825–31.

60. Willard VW, Leung W, Huang Q, Zhang H, Phipps S. Cognitive outcome after pediatric stem-cell transplantation: impact of age and total-body irradiation. J Clin Oncol. 2014;32(35):3982–8. https://doi.org/10.1200/JCO.2014.56.2223.

61. Bunin N, Aplenc R, Kamani N, Shaw K, Cnaan A, Simms S. Randomized trial of busulfan vs total body irradiation containing conditioning regimens for children with acute lymphoblastic leukemia: a Pediatric Blood and Marrow Transplant Consortium study.

Bone Marrow Transplant. 2003;32(6):543–8. https://doi.org/10.1038/sj.bmt.1704198.

62. Pulsipher MA, Boucher KM, Wall D, Frangoul H, Duval M, Goyal RK, et al. Reduced-intensity allogeneic transplantation in pediatric patients ineligible for myeloablative therapy: results of the Pediatric Blood and Marrow Transplant Consortium Study ONC0313. Blood. 2009;114(7):1429–36. https://doi.org/10.1182/blood-2009-01-196303.
63. Locatelli F, Merli P, Bertaina A. Rabbit anti-human T-lymphocyte globulin and hematopoietic transplantation. Oncotarget. 2017;8(57):96460–1. https://doi.org/10.18632/oncotarget.20878.
64. Soiffer RJ, Kim HT, McGuirk J, Horwitz ME, Johnston L, Patnaik MM, et al. Prospective, randomized, double-blind, phase III clinical trial of anti-T-lymphocyte globulin to assess impact on chronic graft-versus-host disease-free survival in patients undergoing HLA-matched unrelated Myeloablative hematopoietic cell transplantation. J Clin Oncol. 2017;35(36):4003–11. https://doi.org/10.1200/JCO.2017.75.8177.
65.•• Locatelli F, Bernardo ME, Bertaina A, Rognoni C, Comoli P, Rovelli A, et al. Efficacy of two different doses of rabbit anti-T-lymphocyte globulin to prevent graft-versus-host disease in children with haematological malignancies transplanted from an unrelated donor: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(8):1126–36. https://doi.org/10.1016/S1470-2045(17)30417-5 **Multicenter randomized-controlled study demonstrating that a lower dose of ATLG determines a better outcome as compared to the use of an higher dose. This was due to a lower incidence of infectious complications, while the incidence of acute and chronic GvHD, as well as that of recurrence of the original disease was not significantly affected.**
66. Pulsipher MA, Langholz B, Wall DA, Schultz KR, Bunin N, Carroll W, et al. Risk factors and timing of relapse after allogeneic transplantation in pediatric ALL: for whom and when should interventions be tested? Bone Marrow Transplant. 2015;50(9):1173–9. https://doi.org/10.1038/bmt.2015.103.
67. Pulsipher MA, Langholz B, Wall DA, Schultz KR, Bunin N, Carroll WL, et al. The addition of sirolimus to tacrolimus/methotrexate GVHD prophylaxis in children with ALL: a phase 3 Children's Oncology Group/Pediatric Blood and Marrow Transplant Consortium trial. Blood. 2014;123(13):2017–25. https://doi.org/10.1182/blood-2013-10-534297.
68. Lucarelli B, Merli P, Bertaina V, Locatelli F. Strategies to accelerate immune recovery after allogeneic hematopoietic stem cell transplantation. Expert Rev Clin Immunol. 2016;12(3):343–58. https://doi.org/10.1586/1744666X.2016.1123091.
69. Zecca M, Prete A, Rondelli R, Lanino E, Balduzzi A, Messina C, et al. Chronic graft-versus-host disease in children: incidence, risk factors, and impact on outcome. Blood. 2002;100(4):1192–200. https://doi.org/10.1182/blood-2001-11-0059.
70. Bosi A, Laszlo D, Labopin M, Reffeirs J, Michallet M, Gluckman E, et al. Second allogeneic bone marrow transplantation in acute leukemia: results of a survey by the European Cooperative Group for Blood and Marrow Transplantation. J Clin Oncol. 2001;19(16):3675–84. https://doi.org/10.1200/JCO.2001.19.16.3675.
71. Yaniv I, Krauss AC, Beohou E, Dalissier A, Corbacioglu S, Zecca M, et al. Second hematopoietic stem cell transplantation for post-transplantation relapsed acute leukemia in children: a retrospective EBMT-PDWP study. Biol Blood Marrow Transplant. 2018;24(8):1629–42. https://doi.org/10.1016/j.bbmt.2018.03.002.
72. Willasch AM, Salzmann-Manrique E, Krenn T, Duerken M, Faber J, Opper J, et al. Treatment of relapse after allogeneic stem cell transplantation in children and adolescents with ALL: the Frankfurt experience. Bone Marrow Transplant. 2017;52(2):201–8. https://doi.org/10.1038/bmt.2016.224.
73. Maloney KW, Carroll WL, Carroll AJ, Devidas M, Borowitz MJ, Martin PL, et al. Down syndrome childhood acute lymphoblastic leukemia has a unique spectrum of sentinel cytogenetic lesions that influences treatment outcome: a report from the Children's Oncology Group. Blood. 2010;116(7):1045–50. https://doi.org/10.1182/blood-2009-07-235291.
74. Ragab AH, Abdel-Mageed A, Shuster JJ, Frankel LS, Pullen J, van Eys J, et al. Clinical characteristics and treatment outcome of children with acute lymphocytic leukemia and Down's syndrome. A Pediatric Oncology Group study. Cancer. 1991;67(4):1057–63.
75. Rubin CM, Mick R, Johnson FL. Bone marrow transplantation for the treatment of haematological disorders in Down's syndrome: toxicity and outcome. Bone Marrow Transplant. 1996;18(3):533–40.
76. Goto H, Kaneko T, Shioda Y, Kajiwara M, Sakashita K, Kitoh T, et al. Hematopoietic stem cell transplantation for patients with acute lymphoblastic leukemia and down syndrome. Pediatr Blood Cancer. 2015;62(1):148–52. https://doi.org/10.1002/pbc.25245.
77. Meissner B, Borkhardt A, Dilloo D, Fuchs D, Friedrich W, Handgretinger R, et al. Relapse, not regimen-related toxicity, was the major cause of treatment failure in 11 children with Down syndrome undergoing haematopoietic stem cell transplantation for acute leukaemia. Bone Marrow Transplant. 2007;40(10):945–9. https://doi.org/10.1038/sj.bmt.1705844.
78. Hitzler JK, He W, Doyle J, Cairo M, Camitta BM, Chan KW, et al. Outcome of transplantation for acute lymphoblastic leukemia in children with Down syndrome. Pediatr Blood Cancer. 2014;61(6):1126–8. https://doi.org/10.1002/pbc.24918.
79. Duncan CN, Clark JJ, Silverman LB. Hematopoietic stem cell transplantation in unique pediatric populations: adolescents, infants, and children with down syndrome. Biol Blood Marrow Transplant. 2013;19(1 Suppl):S52–7. https://doi.org/10.1016/j.bbmt.2012.10.018.
80. Schultz KR, Bowman WP, Aledo A, Slayton WB, Sather H, Devidas M, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol. 2009;27(31):5175–81. https://doi.org/10.1200/JCO.2008.21.2514.
81. Biondi A, Schrappe M, De Lorenzo P, Castor A, Lucchini G, Gandemer V, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. Lancet Oncol. 2012;13(9):936–45. https://doi.org/10.1016/S1470-2045(12)70377-7.
82. Rives S, Estella J, Gomez P, Lopez-Duarte M, de Miguel PG, Verdeguer A, et al. Intermediate dose of imatinib in combination with chemotherapy followed by allogeneic stem cell transplantation improves early outcome in paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia (ALL): results of the Spanish Cooperative Group SHOP studies ALL-94, ALL-99 and ALL-2005. Br J Haematol. 2011;154(5):600–11. https://doi.org/10.1111/j.1365-2141.2011.08783.x.
83. Schultz KR, Carroll A, Heerema NA, Bowman WP, Aledo A, Slayton WB, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia. 2014;28(7):1467–71. https://doi.org/10.1038/leu.2014.30.
84. Slayton WB, Schultz KR, Kairalla JA, Devidas M, Mi X, Pulsipher MA, et al. Dasatinib plus intensive chemotherapy in children, adolescents, and young adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: results of Children's Oncology Group Trial AALL0622. J Clin Oncol. 2018;36(22):2306–14. https://doi.org/10.1200/JCO.2017.76.7228.
85. Litzow MR. Allogeneic transplantation for patients with Philadelphia chromosome positive acute lymphoblastic leukemia: is it imperative in the tyrosine kinase inhibitor era? Best Pract Res Clin Haematol. 2018;31(4):357–60. https://doi.org/10.1016/j.beha.2018.09.004.

86. Akahoshi Y, Mizuta S, Shimizu H, Uchida N, Fukuda T, Kanamori H, et al. Additional cytogenetic abnormalities with Philadelphia chromosome-positive acute lymphoblastic leukemia on allogeneic stem cell transplantation in the tyrosine kinase inhibitor era. Biol Blood Marrow Transplant. 2018;24(10):2009–16. https://doi.org/10.1016/j.bbmt.2018.06.006.
87. Pfeifer H, Raum K, Markovic S, Nowak V, Fey S, Oblander J, et al. Genomic CDKN2A/2B deletions in adult Ph(+) ALL are adverse despite allogeneic stem cell transplantation. Blood. 2018;131(13):1464–75. https://doi.org/10.1182/blood-2017-07-796862.
88. Sasaki K, Jabbour EJ, Ravandi F, Short NJ, Thomas DA, Garcia-Manero G, et al. Hyper-CVAD plus ponatinib versus hyper-CVAD plus dasatinib as frontline therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: a propensity score analysis. Cancer. 2016;122(23):3650–6. https://doi.org/10.1002/cncr.30231.
89. Jabbour E, DerSarkissian M, Duh MS, McCormick N, Cheng WY, McGarry LJ, et al. Efficacy of ponatinib versus earlier generation tyrosine kinase inhibitors for front-line treatment of newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk. 2018;18(4):257–65. https://doi.org/10.1016/j.clml.2018.02.010.
90.•• von Stackelberg A, Locatelli F, Zugmaier G, Handgretinger R, Trippett TM, Rizzari C, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol. 2016;34(36):4381–9. https://doi.org/10.1200/JCO.2016.67.3301 **This study reports the results of a large phase I/phase II trial of blinatumomab in pediatric patients with relapsed/refractory ALL.**
91. Bhojwani D, Sposto R, Shah NN, Rodriguez V, Yuan C, Stetler-Stevenson M, et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. Leukemia. 2018. https://doi.org/10.1038/s41375-018-0265-z.
92.•• Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with b-cell lymphoblastic leukemia. N Engl J Med. 2018;378(5):439–48. https://doi.org/10.1056/NEJMoa1709866 **Large, updated, multicenter, phase II study proving the efficacy of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory CD19+−ALL.**
93. Park JH, Riviere I, Gonen M, Wang X, Senechal B, Curran KJ, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med. 2018;378(5):449–59. https://doi.org/10.1056/NEJMoa1709919.
94.• Kansagra AJ, Frey NV, Bar M, Laetsch TW, Carpenter PA, Savani BN, et al. Clinical utilization of chimeric antigen receptors T-cells (CAR-T) in B-cell acute lymphoblastic leukemia (ALL)—an expert opinion from the European Society for Blood and Marrow Transplantation (EBMT) and the American Society for Blood and Marrow Transplantation (ASBMT). Biol Blood Marrow Transplant. 2018. https://doi.org/10.1016/j.bbmt.2018.12.068 **A comprehensive expert opinion on the use of CD19 CAR T cells for ALL, including a commentary on the role of HSCT.**
95. Orlando EJ, Han X, Tribouley C, Wood PA, Leary RJ, Riester M, et al. Genetic mechanisms of target antigen loss in CAR19 therapy of acute lymphoblastic leukemia. Nat Med. 2018;24(10):1504–6. https://doi.org/10.1038/s41591-018-0146-z.