

Indications and Donor Selections for Allogeneic Stem Cell Transplantation in Children with Hematologic Malignancies

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Acute lymphoblastic leukemia

Pediatric acute lymphoblastic leukemia (ALL) is the most common malignant disease in childhood. International studies of childhood ALL, in developed countries between 1986 and 1998, have achieved 5-year event-free (EFS) survival rates, ranging from 63% to 83% [1] or even higher [2]. However, despite these impressive improvements in therapy and survival of patients with ALL, there are still a significant number of patients who will experience a relapse after initial treatment. Stem cell transplantation (SCT) may be the only curative approach in these patients. The goal of most therapeutic ALL studies is to identify patients at risk of relapse as early as possible during initial treatment, and then proceed with intensified chemotherapy. Subgroups of these patients with high-risk features of relapse will proceed to an allogeneic SCT while in first complete remission (CR1).

Although the strategy described above helps decrease the incidence of relapse after first-line therapy, a considerable number of children will still relapse. Relapsed ALL is the fourth most common malignant disease of childhood, with a higher incidence than many newly diagnosed pediatric malignancies [3].

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Various treatment strategies for patients with relapsed ALL are under study, including intensified chemotherapy and SCT. Because outcomes of SCT are best if performed in CR1 or second complete remission (CR2), the best strategy would be to identify patients in CR2 who would best benefit from allogeneic SCT, and in whom the risks of the procedure are justified.

Patients in third complete remission (CR3) and beyond have an extremely poor prognosis with conventional therapy alone, and can only be cured with SCT. However, the success of SCT in these patients with more advanced disease is not as favorable when compared with patients with earlier stage disease. This article discusses the indications for SCT in patients with ALL in CR1, CR2, and beyond.

Indications for stem cell transplantation in patients with high-risk features of acute lymphoblastic leukemia in first complete remission

The identification of patients at risk of relapse after CR1 is one of the major goals in most therapeutic studies. Patients identified with high-risk features require additional therapy after achieving CR1. High-risk features include the presence of chromosomal translocations such as t(4;11) or 11q23 (MLL)[4], Philadelphia chromosome t (9;22), hypodiploidy (fewer than 44 chromosomes) [5,6], and poor response to induction, such as induction failure (5% or more leukemic cells) or the presence of minimal residual disease (MRD) of more than 1% after 4 to 6 weeks of first-line therapy. Early clearance of blasts, as measured by morphology [7] or by flow cytometry [8], seems to be an important favorable prognostic factor. Once patients have been identified as being at high risk of relapse in CR1, optimal treatment might include an allogeneic SCT in CR1.

A recent study collecting data from 10 study groups of patients with Philadelphia chromosome-positive ALL, showed that SCT in CR1 with bone marrow from human leukocyte antigen (HLA)-matched related donors was associated with a significantly better outcome than with chemotherapy alone [9].

In another prospective study conducted in seven countries, the outcome of patients with very high risk ALL in CR1 was investigated. Subjects were either allocated to chemotherapy alone or chemotherapy followed by SCT, depending on the availability of a compatible related donor [10]. High risk features were defined by the presence of at least one of the following criteria: (1) failure to achieve complete remission after the first four-drug induction phase, (2) the presence of t(9;22) or t(4;11) clonal abnormalities, and (3) poor response to prednisone associated with T-immunophenotype, white blood count of greater than 100 times $10^9/L$, or both. The 5-year disease-free survival was 40.6% in children allocated to chemotherapy only, and 56.7% in those assigned to SCT ($P = .02$). In another study, the role of SCT versus chemotherapy alone was investigated in high-risk T-cell leukemia [11]. Very high-risk features were consistent with the presence T-cell

immunophenotype and a poor in vivo response to initial treatment (prednisone-poor response or nonresponse at day 33). The 5-year disease-free survival was 67% for 36 subjects who received SCT in CR1, and 42% for the 120 subjects treated with chemotherapy alone. The overall survival at 5 years was 67% for the SCT group and 47% for subjects receiving chemotherapy alone ($P = .01$). The Children's Cancer Study group (CCG-1921) investigated the role of SCT from HLA-matched family donors in patients with ultra-high risk features of ALL in CR1 [12]. Twenty-nine patients proceeded to SCT. The 5-year EFS was 58.6% for all patients, and 77.8% for patients without cytogenetic abnormalities. Patients with Philadelphia chromosome-positive ALL had a 5-year EFS of 66.7%.

Because the role of allogeneic SCT in patients with high-risk features in ALL is not yet clearly defined, the Berlin-Frankfurt-Münster (BFM) study group, the International BFM (IBFM) study group, and the Pediatric Disease Working Party of the European Group for Blood and Marrow Transplantation (EBMT) (PD-WP-EBMT) initiated a multicenter prospective trial enrolling patients with ALL in first, second, or subsequent remission, with a high risk of relapse as defined by cytogenetics, the response to the induction chemotherapy, and the time and site of relapse, respectively [13]. In addition, the levels of MRD at certain time points of the first-line therapy are used for risk stratification. In Table 1, the indications and type of transplants in patients with high risk ALL and CR1 according to the BFM criteria are shown. While all patients with the depicted high-risk features will receive a transplant from an available HLA-matched sibling donor, only subgroups of high-risk patients will proceed to an allogeneic

Table 1

List of indications for allogeneic stem cell transplantation in acute lymphoblastic leukemia in first complete remission according to the Berlin-Frankfurt-Munster criteria

Indication	Criteria	MSD	MD	MMD
Poor prednisone response	t(9;22)	+	+	+
	t(4;11)	+	+	—
	Pro-B-ALL	+	—	—
	M3 marrow d15	+	—	—
	WBC $\geq 10\,000$	+	—	—
Good prednisone response	t(9;22)	+	+	—
	t(4;11)	+	—	—
MRD level	R2 $\geq 10^{-2}$	+	+	+
	R2 $= 10^{-3}$	+	+	—
Remission	NR d + 33	+	+	+

Abbreviations: MD, matched donor; MMD, mismatched donor; MSD, matched sibling donor; R2 MRD level at time point 2 of induction; WBC, white blood cell count; + recommended; — not recommended.

Data from Peters C, Schrauder A, Schrappe M, et al. Allogeneic haematopoietic stem cell transplantation in children with acute lymphoblastic leukaemia: the BFM/IBFM/EBMT concepts. *Bone Marrow Transplant* 2005;35 (Suppl 1):S9-11.

SCT from an HLA-matched unrelated donor or an HLA-mismatched donor. The results of this study will hopefully help to better define the role of allogeneic SCT in patients with high risk ALL in CR1.

Indications for stem cell transplantation in patients with relapsed acute lymphoblastic leukemia, second complete remission and beyond

The most common reason for treatment failure in children with ALL is relapse. Although the disease-free survival with conventional chemotherapy has increased considerably over the decades [2,14], approximately 20% to 25% of children suffer a relapse following initial therapy. Relapsed ALL is as common as most pediatric tumors and more common than newly diagnosed acute myeloid leukemia (AML) [15]. In a retrospective analysis of the outcome of 505 patients with relapsed ALL in a single institution, 74% of the relapses occurred within 3 years from diagnosis, and most relapses involved the bone marrow alone or in combination with overt extramedullary involvement [16]. Early relapse, that is, relapse within 3 years after initial diagnosis, was more common in children with T-lineage ALL and in those with unfavorable cytogenetics. The German BFM relapse score (standard, intermediate, and high risk), which takes into account the time of relapse, site of relapse, and subsequent immunophenotype [17], was applied to these patients and was highly predictive of outcome. A retrospective comparison between patients treated with SCT and those that received chemotherapy only showed no difference in EFS for those assigned to the intermediate-risk group, but a possible advantage in the highest risk group [16].

A retrospective analysis of the United Kingdom ALL R2 protocol analyzed 150 children, of whom 139 achieved a CR2. Using the BFM risk score, the overall survival (OS) and EFS for standard, intermediate, and high-risk groups was 92% and 92%, 64% and 51%, and 14% and 15%, respectively [18]. In this study, children with a very early (ie, within 18 months after initial diagnosis) isolated extramedullary relapse were at higher risk for subsequent relapse.

In another study, the long-term outcome in children with relapsed ALL after risk-stratified salvage therapy was analyzed [19]. Of 207 registered patients, 183 were stratified into three groups: (A) early bone marrow relapse (relapse occurring on therapy or up to 6 months after cessation of front-line treatment), (B) late bone marrow relapse, and (C) isolated extramedullary relapse. The probability of EFS and OS of all registered patients at 15 years was 0.30 and 0.37, respectively. The differences of the probability of EFS between the groups were 0.18 and 0.20 for group A, 0.44 and 0.52 for group B, and 0.35 and 0.42 for group C. In a uni- and multivariate analysis, an early time point of relapse and T-lineage immunophenotype were significant predictors of inferior EFS.

The St. Jude group reported the clinical outcome of 106 children who developed a bone marrow recurrence as the first event after contemporary intensified therapy [20]. Bone marrow relapses were isolated in 79 patients,

and combined with extramedullary sites in 27 patients. The 5-year survival among all patients was 24.2%. On multivariate analysis, time to first disease recurrence and blast cell lineage were found to be independent predictors of a second EFS. The 5-year EFS estimate in patients with an initial disease remission of greater than or equal to 36 months was 42.6%, and only 12.5% for children with a short duration of remission (less than 36 months).

In a nonrandomized retrospective analysis, the outcome of patients with B-precursor ALL in CR2 was analyzed. Outcome was compared in 188 patients enrolled in chemotherapy trials and 186 HLA-matched sibling transplants [21]. For children with early first relapse (less than 36 months after diagnosis), the risk of a second relapse was significantly lower after a total body irradiation (TBI)-containing conditioning regimen than after chemotherapy regimens. In contrast, for children with late relapse (greater than or equal to 36 months after diagnosis), the risk of second relapse was similar after TBI-containing SCT and chemotherapy alone. These data support HLA-matched sibling SCT, using a TBI-containing preparative regimen in children with early relapse and those in CR2 or beyond.

In a Children's Oncology Group study (CCG-1941), the outcome for children with early first bone marrow relapse (within 12 months after completion of primary therapy) after matched sibling SCT, alternative donor bone marrow transplantation (BMT), and chemotherapy alone was compared [22]. In this study, 214 subjects received multiagent induction therapy, and 163 subjects with fewer than 25% marrow blasts and count recovery at the end of induction (CR2) were allocated by donor availability. Fifty subjects with sibling donors proceeded to SCT, and 72 subjects were randomly assigned to alternative donor SCT or chemotherapy, while 41 subjects refused allocation. The 3-year EFS from study entry was 19%. Thirty-two of the 50 subjects with a matched sibling donor and 19 of 37 subjects allocated to alternative donor SCT proceeded to SCT in CR2, with a 3-year disease-free survival (DFS) of 42% and 29%, respectively. The 3-year DFS for subjects allocated to matched sibling, alternative donor SCT, and chemotherapy was 29%, 21%, and 27%, respectively. More than half of the subjects died, failed reinduction, or relapsed again before 3 months after achieving CR2, which was the median time to BMT. Therefore, these investigators concluded that SCT is indisputably life-saving for some children, but not the whole answer to curing patients with ALL and early marrow relapse.

In a retrospective matched-pair analysis of the BFM-relapse group, matched unrelated SCT was compared with chemotherapy alone in patients with ALL in second remission and without an HLA-matched family donor [17]. Altogether, 81 pairs could be matched exactly for site of relapse and immunophenotype, and as closely as possible for duration of first remission, age, diagnosis date, and peripheral blast count at relapse. No significant difference in the probability of EFS between SCT and chemotherapy was seen in 28 pairs with an intermediate risk (0.39 versus 0.49, $P = .105$), whereas the probability of the EFS was significantly different in the 53 pairs

of the high-risk group, with an EFS of 0.44 for the SCT group and 0.00 for the chemotherapy-alone group. In another study, the impact of allogeneic SCT was investigated in 117 subjects who experienced relapse from ALL. CR2 was attained in 90 subjects, and 30 are in remission with an EFS of 25.1% [23]. The significant prognostic factors in a multivariate analysis were time of relapse and the treatment after relapse. Subjects proceeding to SCT had an EFS of 60.2%, as compared with 25.7% in the subjects receiving chemotherapy alone.

The outcome of children with very late relapse of ALL was investigated in patients who relapsed greater than or equal to 60 months after attainment of CR1 [24]. In this study, 93 children had a first relapse at a median time of 6.1 years (range 5.8–13.7 years) after initial diagnosis. After a median follow-up, the 5-year EFS and OS was 39.5% and 55.6%, respectively. In a multivariate analysis, the site of relapse was the only significant predictor of duration of the CR2, as patients with isolated bone marrow relapse fared worse (5-year EFS 24.5%) than those with combined or isolated extramedullary relapse (5-year EFS 68.4%). All of the seven children who received SCT from a matched-related donor following a late relapse are alive in CR2. SCT should therefore be considered for subgroups of patients.

Another prognostic feature in patients with relapsed ALL is their MRD status after initiation of relapse chemotherapy. In a retrospective study of 30 children, all of whom were treated according to the relapsed ALL BFM trials, the MRD status during the first stages of treatment was monitored [25]. In subjects with MRD less than 10^{-3} at day 36, the probability of event-free survival was 0.86 (or 86%), whereas none of the patients with MRD of greater than or equal to 10^{-3} survived. In another study, similar results were obtained in 41 subjects using flow cytometry techniques for determination of MRD levels at the end of remission reinduction [26]. Thirty-five subjects were in morphologic remission. Of these 35 subjects, 19 had MRD greater than or equal to 0.01% with a 2-year cumulative incidence of second relapse of 70.2%, whereas it was only 27.9% for subjects with negative MRD. The time of relapse and MRD status were the only two significant predictors of outcome in a multivariate analysis.

To decide which patients in CR2 would benefit most from SCT, the BFM study group, IBFM study group, and the PD-WP-EBMT initiated a prospective cooperative multicenter trial to better define risk groups according to time to relapse, site of relapse, immunophenotype, and MRD status [13]. In this study, patients with relapsed ALL are subdivided into risk groups according to the parameters mentioned above. High-risk group patients (early isolated or very early isolated combined bone marrow relapse of a B-cell precursor ALL, and any bone marrow involving relapse of a T-lineage ALL) will proceed to a transplant with any allogeneic donor. Intermediate-risk patients (early or late combined bone marrow relapse, late isolated bone marrow relapse of B-cell precursor ALL) and patients with a MRD level greater than or equal to 10^{-3} will proceed to a matched sibling or matched unrelated

donor SCT, and patients with intermediate-risk features and MRD less than 10^{-3} will receive SCT only if a matched sibling donor is available (Table 2).

The MRD status before SCT has also been shown an important prognostic factor for assessing which patients might be at risk of relapse after SCT. Patients with high MRD burden before transplant had a significant poorer outcome when compared with MRD-negative subgroups [27–30]. These data were challenged by another study, which found no correlation between the pretransplant MRD burden and the posttransplant relapse [31]. In a more recent study, detectable levels of MRD before SCT predicted an extremely poor prognosis because of the high rate of relapses in the MRD-positive group [32]. Further prospective studies will hopefully lead to better use of MRD detection for risk-adapted stratification and treatment.

Patients with CR3 and beyond have a very high risk for subsequent relapse with chemotherapy alone, and allogeneic SCT from any donor source might offer the only chance of cure.

The role of allogeneic SCT in infant ALL is controversial. Most infants have rearrangements of the MLL gene on chromosome 11q23, which is associated with a poor outcome [33]. SCT with matched sibling donors does not seem to improve the prognosis for this patient group [34]. Clinical studies are needed to further evaluate innovative strategies in this disease [35].

Acute myeloid leukemia

As in ALL, the prognosis of childhood AML has improved over the decades [36]. With current aggressive induction chemotherapy protocols, approximately 80% to 90% of children with AML achieve remission and

Table 2

Indication for allogeneic stem cell transplantation according to Berlin-Frankfurt-Munster criteria for patients after first relapse

Risk status	Donor selection		
High risk T-lineage: any BM involvement	MSD	MD	MMD
BCP-ALL: very early BM involving relapse, early isolated BM relapse (> CR 2: according to risk for TRM)	MSD	MD	MMD
Intermediate-risk, MRD $\geq 10^{-3}$ after 2 nd induction BCP-ALL: early combined BM MSD relapse, late BM involving relapse (all t(9;22) with IR feature)	MSD	MD	
Intermediate-risk, MRD $< 10^{-3}$ after 2 nd induction BCP-ALL: early combined BM relapse	MSD		

Groups are defined by immunophenotype, site of relapse and time point of relapse (very early, < 18 months after primary diagnosis; early, ≥ 18 months after primary diagnosis and < 6 months of cessation of front-line therapy; late, ≥ 6 months after cessation of front-line therapy).

Abbreviations: BCP, B-cell precursor; BM, bone marrow; IR feature, intermediate risk feature; TRM, transplant-related mortality.

Data from Peters C, Schrauder A, Schrappe M, et al. Allogeneic haematopoietic stem cell transplantation in children with acute lymphoblastic leukaemia: the BFM/IBFM/EBMT concepts. Bone Marrow Transplant 2005;35 (Suppl 1):S9–11.

nearly 50% remain in remission and are long-term survivors [37,38]. Given the improvements of survival with chemotherapy alone, the role of SCT—especially in patients in CR1—has not yet been clearly defined by prospective randomized trials. The survival of patients with relapsed AML in CR2 or beyond and patients with refractory AML is poor, and allogeneic SCT is for most patients the only change for long-term cure.

Indications for stem cell transplantation in patients with acute myeloid leukemia in first complete remission

The best therapy for patients with AML in first remission remains controversial. The definition of risk factors for subsequent therapy failure might help to decide which patients should proceed to SCT in CR1. Patients with AML associated with the t(8;21), t(15;17), or inv(16) have a favorable prognosis, whereas those with complex karyotypes, such as -5, del(5q), -7, or 3q abnormalities might benefit from SCT [39]. Hyperleucocytosis indicates a high risk, especially for early failure. Multivariate analysis showed a high correlation of hyperleucocytosis with other parameters, such as blast cell count greater than or equal to 5% in the bone marrow on day 15 of induction chemotherapy [40]. Favorable or low-risk groups can be defined by morphologic and response criteria or cytogenetic and molecular findings. Morphology includes French-American-British (FAB) subtypes with granulocytic differentiation (FAB M1 to M4) and additional features, such as Auer rods or eosinophils with a blast cell reduction in the bone marrow at day 15 [40]. Favourable cytogenetic features [41] correlate with the FAB types M1 and M2 with Auer rods, M3, and M4eo [40,42,43].

While the North American study groups seem to favor SCT from a matched related family donor (MSD-SCT) in all patients in CR1 [44], European groups take a more conservative approach, and MSD-SCT is limited in some European studies to patients at high risk of relapse [45]. The North Americans derive their preference from results obtained in studies that compared allogeneic with autologous SCT [36,46–49]. Because these studies all show fewer relapses in the allogeneic groups, this approach is supported in the United States and Canada. Moreover, studies have shown a role for graft-versus-leukemia in the maintenance of disease-free survival in AML patients [50].

In a large analysis of the postremission outcome of 1,464 children under 21 years old, enrolled between 1979 and 1996 in five consecutive Children's Cancer Group AML trials, 373 children were allocated to SCT in CR1 if a matched family donor was available [51]. The remaining children were assigned to chemotherapy (n = 688), autologous purged SCT (n = 217), withdrawn from the study without assignment, or had unknown data (n = 186). The overall and disease-free survival was superior for children assigned to allogeneic SCT. In this analysis, a high diagnostic white blood cell (WBC) count (greater than $50,000 \times 10^9/l$) was prognostic for inferior outcome, whereas the FAB subtypes were not. Benefit from allogeneic SCT was

evident in most children, including those with high or low diagnostic WBC count, each FAB subtype, and the presence of t(8;21). The benefit was not seen in patients with inv(16). Because the North American studies have demonstrated that the best relapse-free and OS for pediatric patients with AML is achieved in those receiving family donor SCT, MSD-SCT is routinely performed in patients in CR1, except for patients with inv(16).

The reasoning for the more conservative European approach is that several cooperative groups, including the Medical Research Council and BFM, have shown that patients with good-risk AML can be effectively treated with chemotherapy alone, and that SCT can therefore be reserved for patients who relapse [45,52]. While most of the European study groups recommend SCT from a matched family donor in patients with high-risk AML in CR1, the German cooperative AML-BFM study group has completely abandoned SCT in CR1 following their 2006 amendment, independent of the risk features and even if a matched family donor is available (Ursula Creutzig, MD, Hannover, Germany, personal communication, August 2007). In the current AML-BFM trial, allogeneic SCT is reserved for patients with de-novo refractory AML (persistent blasts after second induction or continuous aplasia after 6 weeks after second induction).

One of the main reasons leading the German investigators to abandon SCT in all patients with AML in CR1, besides long-term effects, is the high treatment-related mortality (TRM) associated with this approach. However, similar to the more aggressive chemotherapeutic regimens, the improved supportive care of patients undergoing SCT and the optimization of conditioning regimens, has significantly decreased TRM in matched sibling, matched unrelated, and even in haploidentical transplantation [53]. The enormous advances in the field of allogeneic SCT with a decrease of TRM, improved prevention and treatment of graft-versus-host disease (GVHD), and increase of overall survival must be taken into account, and the benefit might outweigh the reduced risk with better supportive care.

A low TRM of 6% was reported in a recent study in children receiving allogeneic transplantation from a matched sibling donor for acute leukemia [54]. In this study, 55 subjects with AML in CR1 received allogeneic SCT. The 5-year OS was 74%. Relapse was not seen in subjects with AML developing acute GVHD, thus corroborating the previously published graft-versus-leukemia effect in AML. In a recent update of the Children's Cancer group (CCG 2891), the clinical outcome of those patients with no available HLA-matched family donor was reported. Patients were randomized to receive either an autologous SCT or consolidation chemotherapy [55]. DFS, relapse-free-survival, and OS at 8 years were 47%, 50%, and 55%, respectively, thus confirming previous studies that autologous SCT might be an effective post remission therapy for patients with AML in first remission.

The definition of patients at risk of relapse will remain a major goal for future research, and it remains to be seen whether, similar to patients with ALL, the determination of minimal residual disease and MRD-directed

therapy will improve the outcome of patients with AML [56]. Further clinical prospective and ideally randomized trials in patients with AML in CR1 will be necessary to define the best therapy for these patients.

Indications for stem cell transplantation in patients with acute myeloid leukemia in second complete remission and beyond

While with contemporary treatment, 80% to 90% of patients achieve remission, 30% to 40% of these patients subsequently suffer recurrence. After recurrence, the likelihood of survival is poor, ranging from 21% to 33% [57–61]. In these studies, the length of first remission was the best predictor of survival.

Allogeneic SCT in CR2 is associated with improved outcome after relapse. The survival of 64 children undergoing SCT as part of their relapse therapy was 62% [62]. In another retrospective analysis, the outcome in 58 children with advanced AML after allogeneic SCT was analyzed. At time of SCT, 12 children were in CR2, 11 in untreated first relapse, and 35 had refractory disease. Estimates of 5-year DFS for patients in CR2, untreated first relapse, and refractory disease were 58%, 36%, and 9%, respectively [63]. In this analysis, advanced disease phase and cytogenetic abnormalities at time of transplantation were each associated with decreased EFS and increased risk of relapse. The survival of children transplanted in CR2 or untreated first relapse in this study was higher than previously reported [64]. In another study, survival for 25 patients who relapsed after autologous SCT (n = 11) or allogeneic SCT (n = 14) was analyzed in patients who then underwent a second allogeneic SCT from either a matched related, mismatched related, or unrelated donor [65]. Patients who received their second transplant less than or equal to 6 months after the first transplantation were at higher risk of relapse. The disease-free survival at 10 years was 44%.

Outcome of patients with relapsed AML has been shown to be dependent on the length of initial remission, and those patients with CR1 longer than 12 months had a better survival than patients with CR1 less than 12 months [59]. In contrast to patients in CR1, there is less controversy over the indication for SCT in patients with AML in CR2 or with refractory disease (less than 20% bone marrow blasts). In patients with a short CR1, SCT is the only chance for long-term cure.

Myelodysplastic syndromes

The prognosis of most children with a myelodysplastic syndrome (MDS) is poor. SCT is currently the therapy of choice for most of these patients. MDS can be divided into refractory cytopenia, high-grade MDS, and secondary MDS.

Stem cell transplantation in patients with refractory cytopenias

Patients with lesser risk of life-threatening complications secondary to cytopenias, or lesser risk of progression to leukemia, will respond best to

allogeneic transplantation [66]. This group includes patients with refractory anemia, refractory anemia with ringed sideroblasts, and those with normal cytogenetics. In the patients with refractory cytopenia, the karyotype is the most important factor for progression to high grade MDS and survival. Patients with trisomy 8 or chromosomal abnormalities other than monosomy 7 may experience a longer stable course of the disease [67]. Patients with monosomy 7, 7q-, or complex karyotypes should proceed to SCT as soon as the diagnosis has been established and a donor has been identified. In patients with all other karyotypes, an absolute neutrophil count (ANC) greater than 1,000/ μ l, and no need for transfusions, a watch-and-wait strategy can be adopted. In patients with a karyotype other than monosomy 7 and in the absence of complex karyotype abnormalities, who have an ANC less than 1,000/ μ l, or those that are transfusion-dependent, SCT from a matched related or unrelated donor is indicated. More recently, immunosuppressive therapy in selected patients, with hypoplastic refractory cytopenia and normal karyotype or trisomy 8, has been shown to induce complete or partial remissions [68].

The role of conditioning, that is, myeloablative versus reduced-intensity conditioning (RIC), still needs to be established in clinical trials. In a pilot trial of the European Working Group (EWOG) study, 19 patients with hypocellular refractory cytopenia and normal karyotypes were transplanted from a matched (n = 14) or mismatched (n = 5) unrelated donor using a RIC regimen consisting of thiotepe, fludarabine, and antithymocyte globuline. The Kaplan-Meier estimate for EFS and OS at 3 years was 74% and 84%, respectively [69].

High-grade myelodysplastic syndrome

MDS with increased blast counts comprises the MDS subtype refractory anemia with excess blasts (RAEB) and refractory anemia with excess blasts in transformation (RAEB-t). The distinction between high-grade MDS and de novo AML is difficult and important, because de novo AML is chemosensitive, while MDS is resistant to chemotherapy. Patients with cytogenetic abnormalities normally associated with AML should be treated as de novo AML independent of the blast count [70]. Myelodysplasia-related AML (MDR-AML) is associated with MDS progressing to disease, with bone marrow blasts greater than 30%. It is currently not clear whether MDS with monosomy 7 and progression to MDR-AML is biologically the same as de novo AML with monosomy 7. Patients diagnosed with AML and monosomy 7 have a poorer outcome when compared with patients with AML without monosomy 7 [71–73].

There is no controversy at all that allogeneic SCT is the treatment of choice for patients with high-grade MDS. The children who will most likely benefit from SCT are those with RAEB, RAEB-t, an age younger than 2 years, and a hemoglobin F level of 10% or higher [74,75]. Because of

the rarity of these diseases in children, international studies by cooperative groups, such as the EWO of MDS in Childhood, are required to find out the best treatment strategies.

There is controversy, however, whether or not intensive chemotherapy before SCT should routinely be performed. Patients with RAEB-t might have a high relapse rate if transplanted without preceding chemotherapy, whereas those with less than 5% blasts do better with SCT performed in the absence of induction chemotherapy [76,77]. A large prospective study of children with MDS found that patients with RAEB-t often do as well as those with AML when treated with AML therapy at diagnosis, including SCT when an HLA-matched sibling is available [72]. On the other hand, children with refractory anemia or RAEB do very poorly with standard AML therapy, and should be considered for SCT without preceding chemotherapy [78,79].

Juvenile myelomonocytic leukemia

The optimal treatment for juvenile myelomonocytic leukemia (JMML) is not clearly established, but there are no drugs known to be curative in the absence of SCT. Pretransplant therapy might be useful to control tumor burden [80]. Other approaches, such as isoretinoin, have shown nonconclusive results [81,82]. In a recent European Working Group MDS/EBMT trial, intensive chemotherapy before SCT had no influence on the outcome [83]. The survival of patients with JMML is very poor without SCT [84], and SCT offers the greatest likelihood for cure [80,84–86]. In the analysis of the EWO-MDS/EBMT trial of 100 patients with JMML, the 5-year EFS was 52%, and there was no difference in the EFS of patients receiving a transplant from a matched related or matched unrelated donor [83]. In this study, age greater than 4 years and female sex predicted a poorer outcome, whereas cytogenetic abnormalities were not associated with a worse prognosis. Another study reported that monosomy 7 was associated with an outcome comparable to or even better than that of patients with normal karyotypes [87].

The role of GVHD on the rate of relapse is not clear. One study showed that chronic GVHD was associated with a lower risk of relapse and better survival, and acute GVHD (greater than or equal to grade III) with a poor survival [88]. The success of SCT is limited primarily by the tendency of this disease to relapse, generally within the first year after transplant [89]. Therefore, additional posttransplant interventions, such as alpha-interferon, biologic differentiation agents, such as retinoic acids or farnesyltransferase inhibitors, are under investigation [90]. Following relapse, a substantial number of patients might still be cured by a second SCT [91].

Therapy-related myelodysplastic syndrome and acute myeloid leukemia

Therapy-related MDS (t-MDS) and AML (t-AML) are defined as clonal malignant disorders that arise after exposure to cytotoxic agents. While many

of the clinical and biologic features of t-MDS and t-AML are similar to those of de novo disorders, patients with t-MDS and t-AML often have a rapidly progressive disease, and their neoplastic clones usually have distinct chromosomal abnormalities [92]. Most likely as a result of the high frequency of poor prognostic factors, including unfavorable cytogenetic abnormalities characteristic of secondary disorders, chemotherapy yields fewer and shorter complete remissions [93]. Patients with favorable karyotypes, such as the t(8:21), inv(16) or t(15:17) translocations might be treated as any other case of de novo AML [92]. SCT seems to be a potential curative treatment, especially for patients who lack poor-risk cytogenetic features [94], and might be the only curative option for a small number of patients with primary refractory disease [95]. However, outcome in these children is negatively impacted by high TRM rates [96].

Chronic myeloid leukemia

Allogeneic transplantation from an MSD or matched unrelated donor offers long-term disease-free survival in patients with chronic phase, and is the only proven curative approach [97]. The survival in children after SCT ranges from 70% to 80% with matched related donors to 40% to 60% with unrelated donors [98–101]. A shorter time between diagnosis and transplantation resulted in a better outcome [102]. One study comparing the use of peripheral blood SCT with bone marrow as a stem cell source found the former method to have a significant survival advantage (1,000-day overall survival of 94% versus 66%) [103]. Conversely, a retrospective analysis by the Center for International Blood and Marrow Transplant Research (CIBMTR) showed a significantly poorer EFS for children transplanted with peripheral blood precursor cells, as compared with bone marrow [104]. In children, a 3-year OS of 65% after matched unrelated donor transplants with a myeloablative conditioning regimen has been described [98]. In this study, however, 55% of the matched unrelated donor transplants were performed 1 year after diagnosis and were associated with a higher TRM (31% in chronic phase 1 and 46% in advanced phase). Relapse rates were higher in advanced phase patients, especially after MSD transplants. The outcomes for patients in advanced phase were 3-year OS of 46% for MSD, and 39% for matched unrelated donor transplants. In an early pediatric study, the 12-year OS for patients transplanted within 3 years of diagnosis with MSD and matched unrelated donors was 62% [105]. In all of these studies, TRM has limited the success rate, especially after SCT from unrelated donors. In a study including pediatric patients, however, it was indicated that comparable survival after related and unrelated SCT can be obtained [106].

The use of RIC conditioning regimens and the known sensitivity of chronic myelogenous leukemia (CML) to immunologic approaches, like donor lymphocyte infusions, might decrease TRM and long-term side effects

of SCT [107] and increase long-term survival [108,109]. However, the efficacy of RIC needs to be confirmed in larger pediatric studies comparing RIC and myeloablative approaches.

There is no broad consensus on the use of imatinib mesylate as front-line therapy in children with CML [110]. While imatinib might be chosen as primary therapy to bridge the time until a suitable donor has been identified, it should be kept in mind that the delay of transplant more than 1 year after diagnosis was associated in the pre-imatinib era with a higher TRM, especially after SCT from unrelated donors. It must be anticipated that patients treated with imatinib and not proceeding to transplant before developing accelerated phase or blast phase, will have a poor outcome with transplant [111]. Because the goal of therapy in children is cure rather than palliation, all new nontransplant approaches must aim for long-term cure. The risk of the gradual emergence of resistance in patients continuing imatinib [112] should be kept in mind when abandoning SCT, and only carefully planned, controlled clinical studies comparing these different approaches should be performed, especially when the transplantation is delayed beyond 1 year after diagnosis.

Together, the information available suggests that pediatric patients with chronic phase 1 or advanced phase, who have an MSD or a matched unrelated donor, should proceed to an allogeneic SCT after initial therapy with imatinib.

Preparative regimens

The most commonly used preparative regimes before allogeneic transplantation for leukemia include various doses (12 gray–15.75 gray) of fractionated total-body irradiation (TBI) and cyclophosphamide or melphalan, with or without the addition of etoposide, cytarabine, thiotepla, or fludarabine. Non-TBI-based regimens with busulfan or cyclophosphamide, with or without additional cytotoxic drugs such as melphalan, etoposide, thiotepla, and fludarabine, are also used, but no conclusive studies to support either TBI- or non-TBI-based regimens have been reported for children. The preparative regimen should have a cytotoxic antileukemic effect, but should also provide adequate immunosuppression to ensure engraftment. Other non-TBI-based myeloablative regimens based on melphalan, fludarabine, and thiotepla have been reported to facilitate safe engraftment in three-loci mismatched haploidentical transplants with low TRM [53]. For patients with ALL, the use of TBI-containing regimens was associated with better survival, compared with busulfan-containing regimens [113,114]. From these data, TBI-based regimens should be recommended for preparative regimens in patients with ALL undergoing matched sibling or matched unrelated donor transplantation.

Less aggressive so-called nonmyeloablative SCT regimens are attracting increasing interest, especially for patients who otherwise cannot tolerate a conventional myeloablative regimen. Such regimens range from minimal,

to facilitate engraftment (fludarabine plus low-dose TBI) [115], to more intensive but still not myeloablative (reduced intensity conditioning), such as reduced doses of fludarabine plus busulfan [116]. The rationale behind nonmyeloablative stem cell transplantation is to induce an optimal graft-versus-leukemia effect by donor-alloreactive effector cells [117]. While this form of transplantation is mostly applied in adult and elderly patients, the data in children with leukemia remains insufficient to conclude that the reduced cytotoxic antileukemic effect of the preparative regimen is counterbalanced by an increased antileukemic effect of the allograft. Furthermore, children have a healthier immune system and a greater capacity to reject grafts in the setting of reduced intensity conditioning; hence, these regimens should be used only in the context of controlled clinical trials.

Donor selection for stem cell transplantation

There are several types of allogeneic donors for SCT in children. These include related or unrelated donors, cells from bone marrow, umbilical cord blood or mobilized peripheral blood, unmanipulated or T-cell depleted, or CD34 or CD133 selected grafts. Donor selection is influenced by donor availability, the size and age of the patient, and the underlying diagnosis and risk for relapse.

In case of the rather unlikely availability of more than one HLA-matched related donor, additional selection criteria will include the donor's cytomegalovirus (CMV) status (negative preferred), donor age (younger preferred), and donor health or social issues. If more than one adult unrelated donor is available, the age of the donor (younger), donor sex (male preferred), and donor CMV status (negative preferred) are factored into the selection of the optimal donor.

The most important selection factor in donor selection is HLA matching. Identification of an HLA-matched donor at the DNA level is prioritized. DNA typing for HLA antigens has identified disparities between patients and serologically matched donors [118], and high resolution HLA matching at one or more alleles is associated with decreased mortality after SCT from unrelated donors [119]. While the role of high resolution matching at HLA-A, HLA-B, and HLA-DRB1 is clearly established, the significance of the other loci, including HLA-C, HLA-DQ, HLA-DRB3 and DRB5, and HLA-DPB1 is less clear and under current investigation. It has been shown that HLA-C mismatching is associated with increased rejection and strong adverse effects on transplantation outcome [120].

Some transplant centers consider 6 out of 6 matched (A, B, DR) donor-recipient pair a match, others require 8 out of 8 (A, B, C, DR), whereas the majority of centers would consider a 10 out of 10 (HLA-A, -B, -C, -DRB1, and -DQB1) recipient-donor pair as best match for adult donors [121–123]. For most centers, a single allele-mismatch (9 out of 10) would be acceptable.

A low mortality was reported in children after SCT from 7 out of 10 or 8 out of 10 HLA allele-matched unrelated donors with the use of antithymocyte globulin [124]. Therefore, the decision to proceed with a mismatch unrelated transplant needs to be made in the context of the experience of the preparative regimens, the use of in vivo or in vitro T-cell depletion strategies, GVHD prophylaxis regimens, the probability to identify a better matched donor within a reasonable time, and the availability of alternative transplant strategies. If there are more than one HLA-matched donor, other non-HLA donor characteristics have to be taken into account, such as CMV status, donor age, donor gender, parity for female donors, and ABO blood group.

In a large retrospective analysis, the influence of various donor characteristics on the overall and disease-free survival was analyzed [125]. In this analysis, age was the only donor trait significantly associated with overall and disease-free survival. The 5-year overall survival rates for recipients were 33%, 29%, and 25%, respectively, with donors aged 18 to 30 years, 31 to 45 years, and more than 45 years ($P = .0002$). A similar effect was observed among HLA-mismatched cases. Patients with older donors had a higher incidence of acute GVHD, and recipients with female donors who had undergone multiple pregnancies had a higher rate of chronic GVHD. Therefore, the use of younger, male donors may lower the incidence of GVHD and improve survival. In this analysis, the donor serologic CMV status did not affect the survival of either seropositive or seronegative recipients, and a race mismatch also did not affect the outcome. Other studies have demonstrated a distinct survival advantage when the donor is CMV seronegative [126,127]. If there is a choice among several matched donors, a CMV-negative donor would be preferred for a CMV-negative patient. The most optimal donor would be a young male who shares the same blood type with the patient and is HLA-matched at 10 out of 10 loci.

With the higher degree of HLA-matching of unrelated donors and improved supportive care strategies, the differences in the outcome between matched sibling donors and matched unrelated donors have become small, and comparable outcomes after unrelated and HLA-matched sibling SCTs have been reported [128,129].

Despite the availability of matched sibling donor or a 10 out of 10 allele-matched unrelated donor, transplant-related complications, especially GVHD, can still be observed, and further research will be necessary to determine factors that influence the outcome after transplantation. Such factors might be minor histocompatibility antigens [130], genetic single nucleotide polymorphisms within the promoter regulatory regions of non-HLA encoded genes, such as those for cytokines and cytokines receptors [131,132], or killer immunoglobulin-like receptor polymorphisms of the donors [133]. Additional research will be necessary to determine the influence of these factors on the overall outcome after allogeneic SCT.

Given the improvements of HLA typing and matching, and the further evaluation of the role on non-HLA donor characteristics, it is questionable

whether it is beneficial to a patient to proceed to SCT only if an HLA-matched sibling is available, and not to proceed to allogeneic transplant even if a 10 out of 10 allele-matched donor would be available. In fact, the incidence of posttransplant leukemic relapse might be lower in patients undergoing unrelated donor transplantation, as compared with those transplanted with matched siblings. The promising outcome after matched unrelated donor SCT does not support such an approach, and further clinical studies are needed to demonstrate whether transplantations from matched sibling donors can continue to be considered as the gold standard superior to all other transplant approaches.

The time to identify an HLA-matched unrelated donor negatively influences the outcome. Because of the lack of prospective “intend-to-transplant” studies, the number of patients progressing and succumbing from disease during donor search is not clear, but up to 50% of the patients might progress during donor search before transplantation [134]. Therefore, this factor has to be taken into account in each individual patient for whom a donor search is initiated. Probability estimates to identify a 10 out of 10 allele-matched donor might be helpful to decide the best treatment strategy for patients [135], so that alternative strategies can be planned. The chance of survival in patients who are at high risk for rapid progression might be better if they proceed with a lesser matched unrelated donor transplant or with an alternative transplant strategy, such as matched or mismatched umbilical cord blood (UCB) or haploidentical SCT before disease progression.

Alternative transplantations: umbilical cord blood and haploidentical transplantation

A distinct advantage of unrelated donor UCB or haploidentical related donors is their rapid availability. Promising results have been reported with matched and mismatched unrelated UCB transplants from a single donor [136], or from two partially HLA-matched donors [137]. Important predictors of success after UCB transplant are the number of cells in the UCB graft and the degree of HLA disparity [138]. In a recent pediatric study, patients who received a cell dose of less than 3 times $10^7/\text{kg}$ had a much lower survival when compared with patients who received more than 3 times $10^7/\text{kg}$ [139]. Other studies have also reported promising results in children [140,141], and transplantation with UCB might be a reasonable option for children lacking a matched related donor. A recent review of outcomes data reported to the CIBMTR showed a hierarchy of success, with the best survival in recipients of fully matched (6 out of 6) UCB donors. Outcomes using 5 out of 6 matched UCB donors were equivalent to those with matched bone marrow [136].

Initial experiences with haploidentical transplantation using bone marrow and less effective T-cell depletion methods resulted in a higher rate of GVHD [142]. However, newer, more efficient methods for T-cell depletion,

using CD34+ positive selection from mobilized peripheral stem cells, has allowed for successful haploidentical transplantation without GVHD in adults [143] and children [144], with comparable outcomes as compared with matched unrelated donor transplantation [145]. More recent developed T-cell depletion techniques and the use of less intensive conditioning regimens were associated with a very low TRM and improved immune reconstitution [53]. Because of the further availability of haploidentical donors posttransplant, adoptive transfer of additional cells, such as stem cell boosts [146], virus-specific T-cells [147], or natural killer [35,148] cells can be systematically investigated in clinical protocols.

For each patient, an individual risk-benefit analysis based on the disease status, the risk of progression, patient age and the likelihood to identify an HLA-suitable donor within a reasonable time (less than or equal to 3–4 months) has to be performed to determine the best treatment options. With the inclusion of matched or partially matched UCBs and haploidentical donors into the donor pool, almost every child with a high-risk hematologic malignancy should be able to find a suitable donor and can proceed to an allogeneic transplantation, if the benefit outweighs the risk.

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