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Pediatric Clinics of North America: Hematopoietic Stem Cell Transplantation Stem Cell Transplantation for Leukemia

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Introduction

Leukemia represents the most common pediatric malignancy, accounting for approximately 30% of all cancers in children less than 20 years of age. Acute lymphoblastic leukemia (ALL) is the most frequent, comprising approximately 23% of childhood cancers. Acute myeloid leukemia (AML) accounts for approximately 4% of pediatric cancer diagnoses and 20% of childhood leukemia. Chronic myelogenous leukemia (CML) is rare and accounts for approximately 1% of all pediatric cancer, although it comprises 10% of leukemia in older adolescents. Juvenile myelomonocytic leukemia (JMML) is infrequent making up about 2% of leukemia and 25% of myelodysplastic syndrome in childhood [1]. Most children diagnosed with leukemia are cured without hematopoietic stem cell transplantation (HSCT), but for some, high-risk subgroups, allogeneic HSCT plays an important role in their therapeutic approach.

Acute Lymphoblastic Leukemia (ALL)

Prognostic Variables and Risk Stratification at Diagnosis

Clinical and biologic features are used to subtype, risk-stratify and assign therapy at diagnosis. Initial risk group assignment is made based on age, peripheral white blood cell count (WBC), central nervous system (CNS) involvement, and phenotype [2]. Phenotypic classification is determined by flow cytometry of lineage-associated cell surface markers. The majority of ALLs are of precursor B-cell (pre-B) phenotype (CD10, CD19, HLA-DR,

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TDT +), 10 to 20% are T-cell (CD2, CD3, CD5, and/or CD7 +), and <5% are mature B-cell or Burkitt-type (CD20, surface-IgM+).

Cytogenetic studies are subsequently used to further define the risk of relapse. The t(12;21) translocation, the most frequent recurrent chromosomal translocation associated with childhood ALL, is identified in approximately 25% of cases and this is associated with a favorable prognosis [3–6]. Gene rearrangements of the mixed-lineage leukemia (MLL) gene located at 11q23 is the most common cytogenetic finding in infants with ALL, which has an extremely poor prognosis [7–10]. The so called Philadelphia chromosome (Ph^+), which results from a translocation between chromosomes 9 and 22, t(9;22), also confers adverse risk [11]. The t(1;19) translocation is also associated with an increased risk of relapse, but this can be offset by therapy intensification [12,13]. Hyperdiploidy, which most often includes trisomies of chromosomes 4, 7, and/or 10, carries a favorable prognosis [14–18]. Hypodiploid cases are at higher risk of relapse [19–22]. Recently, gene expression analysis has been shown to allow further discrimination in regard to risk classification and treatment response prediction [23].

The initial response to therapy has important prognostic utility. A rapid early response (RER), defined as a marrow blast count below 5% within 7 to 14 days, or clearance of peripheral blasts within 7 to 10 days, has a better outcome than those whose response is slower (SER) [24–30]. Response to therapy can be further quantified by flow cytometric or molecular analysis of minimal residual disease (MRD), which has been shown to correlate with outcome [31,32]

Non-Transplant Therapy

Approximately 80% of children with ALL are cured with chemotherapy, the intensity of which is determined by risk-group assignment and treatment stratification. The majority of patients fall into the standard risk category characterized by age of 1 to 9 years, WBC <50,000/μL, B-precursor phenotype, and absence of high-risk chromosomal abnormalities. Therapy for B-precursor and T-cell ALL consists of induction, consolidation/intensification/re-induction, CNS sterilization, and maintenance for a total of 2 to 3 years [33] [34–40]. Individuals with mature B-cell phenotype are treated as per Burkitt lymphoma regimens, which most commonly employ dose and sequence intensive, short course combination chemotherapy [41–43].

The prognosis after relapsed ALL depends on the duration of the first remission (CR1) and the site of relapse [44–47]. Outcome after short CR1 duration (<12–18 months) is very poor, as is the prognosis for individuals who are unable to achieve a second remission. Those with isolated extramedullary relapse fair better than those with marrow relapse [48,49].

Transplantation

There have been no large prospective controlled clinical trials to evaluate the relative efficacy of allogeneic HSCT in comparison to chemotherapy for childhood ALL. However, multiple comparative studies suggest that relapse rates are lower after HSCT [50]. Some of the benefits in regard to relapse-free survival are offset by transplant-associated morbidity and mortality [51]. Consequently, HSCT is usually reserved for the management of relapse and it is rarely employed for children in CR1 except for those with extremely high-risk features (Table 1;]Figure 1). Results of recent trials of HSCT for children and adolescents with ALL in second remission (CR2) are presented in Table 2. For those with HLA-matched sibling donors, allogeneic HSCT in second remission is considered standard. Unrelated donor HSCT is usually reserved for those at high risk of relapse with chemotherapy (Figure 1,Figure 2). Importantly, the approach in individual cases will vary based on risk/benefit

analysis, donor options, and access to transplantation. The American Society for Blood and Marrow Transplantation (ASBMT) has published consensus guidelines for the use of HSCT in childhood ALL (Table 3) [50]. Suggested algorithms for HSCT in pediatric ALL are presented in Figure 1 and Figure 2.

A retrospective matched cohort analysis performed by the Children's Oncology Group (COG) and International Bone Marrow Transplant Registry (IBMTR) compared matched related HSCT to chemotherapy for children with ALL in CR2. Leukemia-free survival and relapse rates were better after HSCT in all patient groups regardless of the CR1 duration [51]. In a more recent study from the COG and IBMTR, overall survival, leukemia-free survival and treatment-related mortality were superior for patients with a short CR1 duration (< 36 months) who underwent HSCT with total body irradiation (TBI) based conditioning regimens (vs. chemotherapy and non-TBI transplant regimens). For those with a late relapse (≥36 months CR1 duration), outcomes were equivalent in the chemotherapy and TBI transplant group. Those treated with HSCT without TBI had inferior relapse and disease-free survival (DFS) rates regardless of CR1 duration [52].

Despite the lower relapse rates after HSCT, this approach carries the risk of transplant-associated mortality and morbidity (e.g., graft-versus-host disease [GVHD]). Further, chemotherapy alone can be effective. Approximately 30 – 40% of children who sustain a late relapse (> 36 months CR1 duration) may achieve long-term DFS with aggressive chemotherapy alone [45–47,51,53,54].

Decisions about the role for and timing of HSCT for children with relapsed ALL are commonly individualized based on biologic, clinical, treatment, and donor factors (Figure 2). Transplant is usually recommended for children with relapse who have HLA-matched sibling donors irrespective of other prognostic factors. An alternative approach for those with a long CR1 duration is to reserve HSCT in the event of another relapse. For individuals who sustain bone marrow relapse during front-line therapy or within 6 months of completion of therapy, the prognosis is poor with chemotherapy alone and HSCT with an alternative (i.e., unrelated or HLA-mismatched related) donor should be considered. HSCT is also often considered for T-cell ALL with marrow relapse. Additional factors that place an individual at high risk of subsequent relapse or that limit the ability to administer chemotherapy (e.g., allergy, organ toxicity) also warrant consideration of HSCT.

HSCT in first remission has no proven benefits for patients defined as high-risk by WBC count, gender, and age. However, transplantation is commonly considered for those at very high risk of relapse with standard therapy (e.g., hypodiploidy, induction failure) (Table 1; Figure 1). Although historically HSCT has been considered for children with Ph^+ ALL [11,55], the addition of the tyrosine kinase inhibitor imatinib mesylate to chemotherapy appears to have improved non-transplant outcome [56], diminishing the role of HSCT as upfront therapy. The role of HSCT for other very high-risk groups should be considered in the setting of a clinical trial [50]. HSCT in infants <18 months old, especially those with *MLL*-rearrangements remains controversial due to the high risk of adverse effects of transplant conditioning in such young patients [57]. Some series report outcomes following HSCT in CR1 that may be superior to chemotherapy [38,58–60]. However, others reveal no definitive benefit in comparison to intensive chemotherapy [61–63]. Results of an IBMTR database review indicate three-year probabilities of DFS of approximately 50% after HLA-matched sibling and unrelated donor transplantation in CR1 for infants with ALL [52].

Conditioning Regimens

Multiple studies indicate that TBI-based transplant conditioning regimens are associated with lower risk of relapse in comparison to chemotherapy-only regimens for children with

ALL [50,52,64,65]. Notably, second HSCT using TBI has been successful for children who have relapsed after a busulfan-based preparative regimen [66].

Disease Status

Individuals with ALL should be transplanted in complete remission and there is little to no role for HSCT in patients with ALL who are not in CR [67]. Further, recent data indicate that the MRD level at the time of HSCT correlates with outcome. Importantly, children with no detectable MRD (<1 leukemia cell in 10,000 bone marrow cells) have excellent post-transplant outcomes [68]. In addition, many series report that patients transplanted in earlier remissions fare better than those with a history of multiple relapses, although such studies are subject to significant selection bias.

Donor Selection

Outcomes of alternative donor transplantation have improved in recent years and a number of groups report equivalent outcomes to HLA-identical sibling donors using matched unrelated, partially matched related, partially mismatched unrelated cord blood, and haploidentical donors [69–76]. Donor T cell depletion and improvements in supportive care of infection and GVHD have improved the outcomes of such alternative donor transplants. However, T cell depletion is associated with increased risk of graft rejection, mixed chimerism, delayed immune reconstitution and infectious complications. Treatment-associated mortality remains high, exceeding 20% in published series of alternative donor transplants for ALL, due in part to the high-risk nature of patients treated with that approach. Rates of extensive chronic GVHD also remain high after alternative donor transplants [72–74].

Second Transplantation

For patients who relapse following allogeneic HSCT for ALL, a second transplant may be possible, although the outlook is very poor [77]. This approach carries a high risk of mortality due to progressive disease and/or treatment-associated toxicity. Although remission can be obtained in as many as 50% to 70% of patients, the duration is typically short and only 10% to 30% achieve long-term event-free survival. The prognosis is better for those with longer remission duration after the first HSCT [71,78,79]. Donor leukocyte infusion (DLI) has a limited role in the setting of ALL and post-transplant relapse, although successful remission induction with withdrawal of immunosuppression and/or DLI has been reported in a small percentage of cases (discussed elsewhere in this edition) [80–84].

Acute Myelogenous Leukemia (AML)

Prognostic Variables and Risk Stratification at Diagnosis

The French-American-British (FAB) classification system categorizes AML into seven distinct subtypes based on morphology and phenotype. AML subtype and other clinical and biologic features that influence outcome have recently been used to stratify treatment [85].

Non-Transplant Therapy

In most cases AML treatment consists of intensive induction, consolidation, and CNS-directed chemotherapy. Approximately 75 to 90% of children with AML will achieve a CR and increasing the treatment intensity of induction improves DFS rates [86–88]. Post-remission consolidation chemotherapy is essential and can be delivered in standard doses or as high-dose therapy with autologous stem cell rescue with similar DFS rates [89–96] [97]. Despite treatment intensification the outcome is guarded for most children with AML, and only about 50% are cured with chemotherapy alone [98]. Individuals with acute

promyelocytic leukemia (FAB M3) have a better prognosis, with 80% DFS rates observed when all-*trans*-retinoic acid is added during induction and a maintenance phase [99–102]. Young children with trisomy 21 who develop AML also have excellent outcomes and require less intensive therapy [103–105].

Transplantation

Given the relative poor outcome for pediatric patients with AML, allogeneic HSCT has commonly been used as consolidation in CR1. There have been multiple "genetic randomization" studies of matched related allogeneic HSCT in which individuals who have matched sibling donors are assigned to transplantation. Allogeneic HSCT confers a lower risk of relapse and improves DFS in comparison to chemotherapy with or without autologous rescue (Table 4) [86–88,91,93–96,106–109]. However, clinical benefits can be offset by transplant-related morbidity and mortality, which may eliminate any overall survival advantage in low risk groups [87,110–113]. Consequently, there is some debate as to whether allogeneic HSCT should be employed in CR1 or CR2 for AML in childhood [113–115]. The ASBMT has published consensus guidelines for the use of HSCT in pediatric AML (Table 5) [91] and a suggested approach is presented in Figure 3.

In the U.S., matched related sibling donor HSCT is the most common consolidation therapy employed for children with AML in CR1 outside of specific low risk groups [91]. This approach is based largely on clinical trials conducted by the Pediatric Oncology Group (POG) and the Children's Cancer Group (CCG) [116,117]. Both groups reported superior outcomes for high and intermediate risk patients treated with HSCT in CR1. The 5-year overall survival for patients transplanted with a matched sibling donor in CR1 ranges from 52% to 72% (Table 4) [91] [117] [116] [86–88,95,109].

Long-term DFS can be achieved in approximately 30% of children with AML who are transplanted in CR2 with either matched unrelated or mismatched related donors [109]. Consequently, HSCT is sometimes reserved for management of patients who relapse after chemotherapy, especially for low risk groups [115] or those without sibling donors. ASBMT consensus guidelines recommend HSCT in CR2 only for patients with matched related donors, as evidence supporting unrelated donor HSCT is lacking [91].

Conditioning Regimens

Comparative clinical trials in adults reveal similar results with busulfan/cyclophosphamide in comparison to TBI/cyclophosphamide [118]. Pediatric studies are limited, although no obvious differences are apparent [119]. In general, busulfan/cyclophosphamide is the most commonly employed pre-transplant preparative regimen employed in pediatric AML.

Disease Status

In most of the published series of HSCT for pediatric AML, transplantation is performed for patients in remission [91]. Although some individuals with AML who undergo HSCT in relapse can achieve long-term DFS [67], small pediatric studies suggest that the percentage of pre-transplant blasts correlates with post-transplant relapse and that outcomes are improved when HSCT is performed in remission [120,121].

Donor Selection

Donors mismatched for natural killer cell killer (NK) immunoglobulin-like receptor (NK KIR) may improve post-transplant outcome in AML due to allogeneic NK-cell mediated anti-leukemic effects [122], an approach that is currently under study in pediatric AML (discussed elsewhere in this edition).

Second Transplants

As in ALL, the outcome of second transplants for children with AML varies based on the interval from prior transplantation [123].

Chronic Myelogenous Leukemia (CML)

Prognostic Variables and Risk Stratification at Diagnosis

CML is characterized by the presence of the Philadelphia chromosome and the associated translocation product *bcr/abl*. CML has three defined clinical phases: chronic, accelerated, and blast crisis, with most patients presenting with chronic phase. Response to treatment and survival correlate with phase of disease. Blast crisis is clinically indistinguishable from acute leukemia and treatment responses are short lived.

Non-Transplant Therapy

The kinase activity of the *bcr/abl* fusion protein is inhibited by imatinib mesylate (Gleevec) and related kinase inhibitors, and these agents have transformed the approach to treatment with CML [124]. Imatinib induces complete remissions in most patients with chronic phase CML, although continuous treatment appears to be required and resistance may develop [125,126]. Thus, there is as of yet no evidence that this new class of kinase inhibitors will be curative and they cannot be recommended as a replacement for allogeneic HSCT in children who have an HLA-matched donor [127]. A number of criteria have been proposed for deciding when to proceed from kinase inhibitor therapy to HSCT, including loss of therapeutic response or failure to achieve a complete hematologic response by 3 months or a substantial cytogenetic response by 3 to 6 months of treatment [128].

Transplantation

Allogeneic HSCT is the only proven cure for CML and donor availability should be considered soon after diagnosis for all children with this disorder. Post-transplant DFS rates are inversely related to age and exceed 80% for young children with matched sibling donors in first chronic phase.

Conditioning Regimens

Busulfan/cyclophosphamide is the most common preparative regimen used for pediatric patients with CML undergoing SCT.

Disease Status

Results are best when HSCT is performed in first chronic phase and with a shorter diagnosis-to-transplant interval. Success is substantially diminished for the accelerated phase or blast crisis and attempts should be made to induce a second chronic phase prior to transplant [129,130].

Donor Selection

In general, pediatric patients have relatively low risk of transplant-related mortality and results are similar with matched unrelated and related donors. Thus, unrelated donor HSCT is usually recommended for those who lack sibling donors [124,127,130–133].

Second Transplants

DLIs have been well demonstrated in adult studies and in a small pediatric series to be effective in the management of post-transplant relapse of chronic phase CML [82]. When

DLI is unsuccessful, second transplants should be considered, especially in cases where there was no prior development of GVHD [84].

Juvenile Myelomonocytic Leukemia (JMML) and Myelodysplastic Syndromes (MDS)

Prognostic Variables and Risk Stratification at Diagnosis

The myelodysplastic syndromes represent a heterogeneous group of disorders characterized by ineffective hematopoiesis, impaired maturation of myeloid progenitors, cytopenias, dysplastic changes, and a propensity for the development of AML [134,135]. The major diagnostic groups within MDS encountered in pediatric patients include JMML, myeloid leukemia of Down syndrome, and MDS occurring *de novo* and secondary to previous therapy or pre-existing disorders [136–138]. In general, pediatric MDS carries a poor prognosis and clinical variables have little practical utility in guiding therapy [139–142].

Non-Transplant Therapy

In general, therapeutic options are limited in MDS and outcome is guarded. Some patients with MDS initially have an indolent course without therapy [141]. AML-type chemotherapy is associated with low response and high relapse rates [135,142]. JMML is resistant to therapy. Although chemotherapy may reduce disease burden, responses are usually short lived and the disease rapidly progresses with a median survival of approximately 1 year [143]. The European Working Group of MDS (EWOG-MDS) in Childhood reported a retrospective analysis of 110 cases of JMML. The probability of survival at 10 years was 6% for the non-transplant group vs. 39% after transplantation [140].

Transplantation

HSCT is considered the only curative treatment for childhood MDS and JMML.

Given the low response rates to non-transplant therapies, and because failure rates after HSCT appear lower when HSCT is performed soon after diagnosis, strong consideration should be given for early transplantation, especially when a matched sibling donor is available. DFS rates of 50 to 64% are reported with HSCT. Results of the largest published transplant series for children with MDS and JMML are summarized in Table 6 [144–150]. Individuals with JMML who develop GVHD have a lower incidence of relapse [134,151].

Conditioning Regimens

Busulfan- and TBI- based pre-transplant preparative regimens have both been employed for pediatric MDS and JMML, and neither has been shown to be superior. Results with second transplants suggest that radiation may be advantageous (see below). Given the risks of radiation in young children, however, busulfan-based regimens are most commonly employed for children with JMML.

Disease Status

Outcome may be improved for individuals transplanted with lower blast percentage and induction chemotherapy is commonly employed for patients with elevated bone marrow blasts to induce a CR prior to HSCT [142] [152]. However, definitive recommendations cannot be made given the paucity of data.

Donor Selection

Given the poor prognosis without transplant and the favorable results of matched unrelated donor HSCT in pediatrics, transplantation is usually recommended for children with JMML and MDS without regard to the donor type (Table 6) [135,145,146,149,150].

Second Transplants

Initial management of post-transplant relapse should include withdrawal of immunosuppression and/or DLI, although this is frequently ineffective. In contrast to other types of leukemia, children with JMML have outcomes after second HSCT that are comparable to results of first transplant [147]. The EWOG-MDS observed a number of important factors in regard to second transplants for JMML. Most patients received transplants from the same donor, but with reduced GVHD prophylaxis and using TBI-based regimens (vs. busulfan-based conditioning) in comparison to the first transplant. Chronic GVHD was significantly associated with improved DFS after second HSCT. Notably, there was no apparent impact of the interval between transplants [145].

General Considerations in the Use of HSCT for Childhood Leukemia

Graft-vs.-Host Disease and the Graft-vs.-Leukemia Effect

As noted above, an allogeneic graft versus leukemia (GVL) effect is an important component of the curative potential of HSCT for certain leukemias. Thus, interventions designed to decrease the incidence and severity of GVHD must be balanced against the risk of leukemic relapse.

Late Effects

Leukemia remains the leading indication for HSCT in pediatrics and with improvements in post-transplant DFS rates, acute and long-term toxicities have assumed an increasing impact on organ function, quality of life, and overall survival. The risks of conditioning regimens on the developing child should be closely considered during pre-transplant planning.

Reduced Intensity Conditioning Regimens

Reduced intensity pre-transplant regimens have been developed in order to decrease the toxicity associated with myeloablative conditioning. Based on positive results in adults with hematologic malignancies, pilot studies of reduced intensity conditioning regimens have been conducted in pediatric populations [153]. Due to the potency of the GVL effect in CML, this approach is particularly appealing in that disorder. However, safety and efficacy in the more common acute leukemias of childhood have yet to be demonstrated.

The Future of HSCT for Pediatric Leukemias

Allogeneic HSCT will likely continue to play a part in the curative treatment of childhood leukemias well into the future. Scientific discovery and technological advances in transplant immunology, cancer biology, and supportive care will continue to transform the approach to HSCT. As is discussed elsewhere in this edition, novel approaches to donor selection, graft source and manipulation, immunotherapy, and tumor-directed targeted treatment with applications in hematologic malignancies are being developed and advanced in the pediatric setting. Alternative donors have assumed an increasing role in HSCT for pediatric leukemias, especially umbilical cord blood in the U.S. and haplo-identical donors in Europe. It is hoped that such strategies will lead to continued decreases in transplant-associated toxicities as well as improvements in relapse-free and overall survival for children with leukemia.

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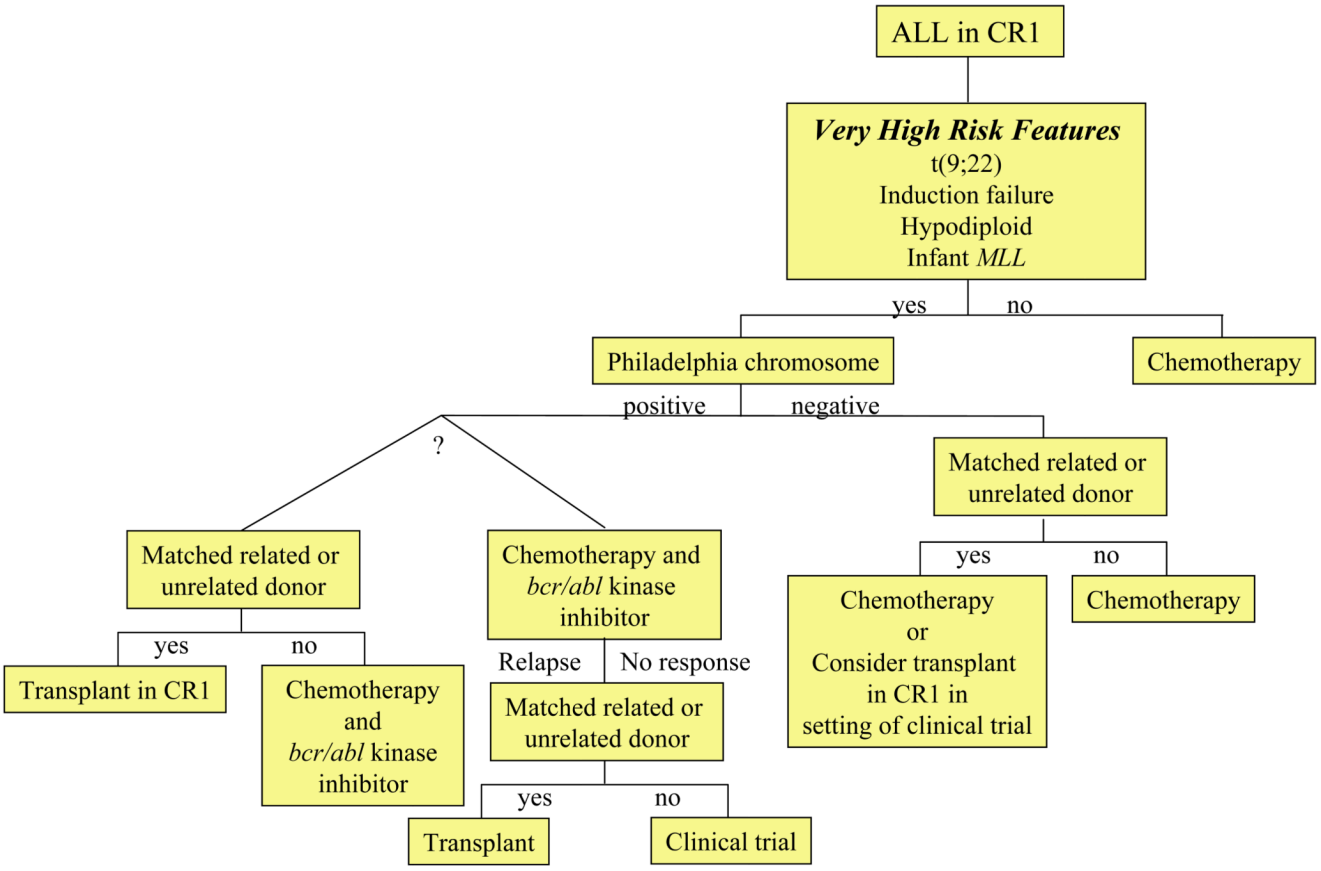

Figure 1.
ALL: Algorithm for transplantation in first remission.

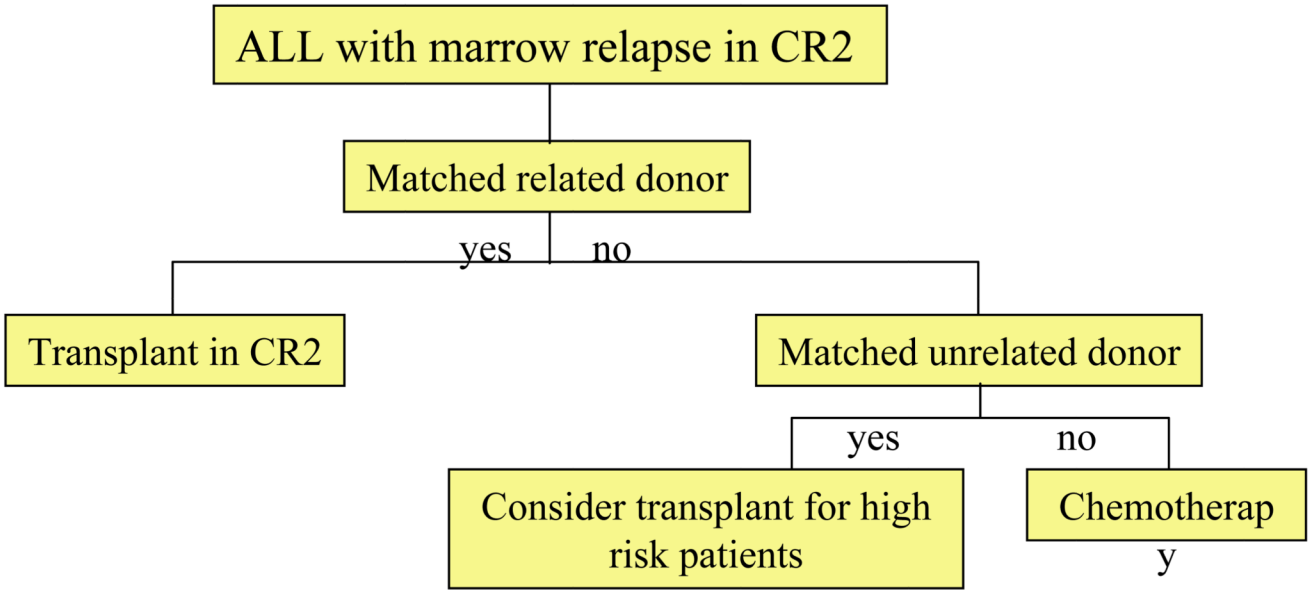

Figure 2.
ALL: Algorithm for transplantation in second remission.

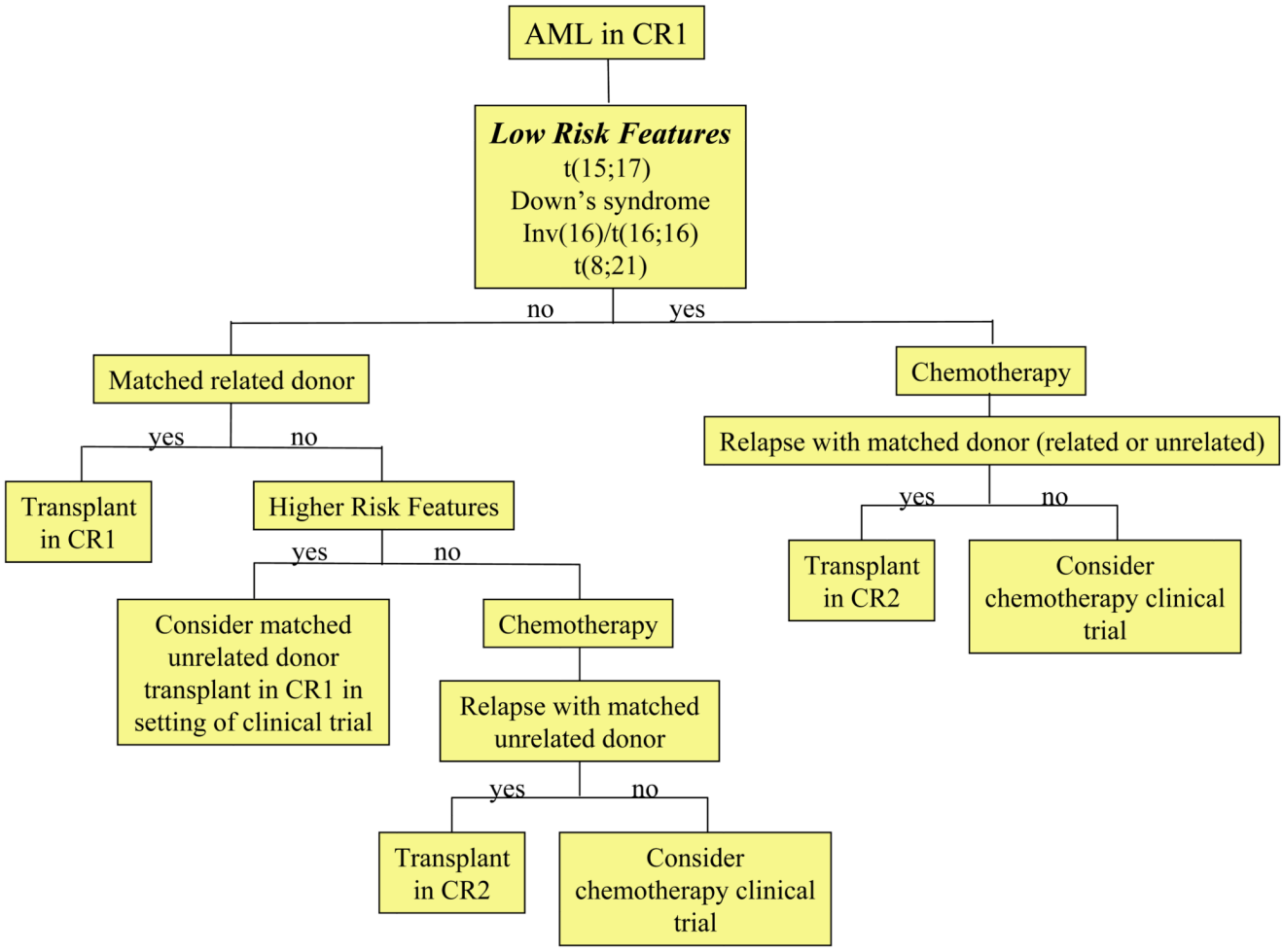

Figure 3.
AML: Algorithm for transplantation.

Table 1

Results of SCT for Pediatric Patients with ALL in First Remission

Study Group	Dates of Study	High risk indicator	Patients (n)	Outcome (years)	Reference
Toronto	1985–2001	t(9;22)	11 MRD, MUD 10 chemo	53% EFS (4)	Sharathkumar 2004 [154]
UKALL -X UKALL -XI	1985–90 1990–97	WBC >100,000/μL +/− t(9;22), Near-haploid, Induction failure	76 MRD, 25 MUD 351 chemo	45% EFS (10) 39% EFS (10)	Wheeler 2000 [155]
AIEOP/ GITMO	1986–94	WBC >100,000/μL BFM risk index >1.7 t(9;22), t(8;11) Steroid resistance T-cell disease Induction failure	30 MRD 130 chemo	58% DFS (4) 48% DFS (4)	Uderzo 1997 [156]
NOPHO	1981–91	WBC >100,000/μL	22 MRD 44 chemo* 405chemo†	73% DFS (10) 50% DFS (10) 59% DFS (10)	Saarinen 1996 [157]
IBMTR	1978–90	t(9;22)	33 MRD	38% DFS (2)	Barrett 1992 [158]
Groupe d'Etude de la Greffe de Moelle Osseuse	1980–87	t(9;22) WBC >100,000/μL Induction failure	32 MRD	84% DFS (2.5)	Bordigoni 1989 [159]

chemo = chemotherapy, EFS = event free survival, DFS = disease free survival

*matched control patients

†unmatched patients

Table 2

Results of SCT for Pediatric Patients with ALL in Second Remission

Study Group	Dates of Study	Patients (n)	Outcome (years)	Reference
BFM	1985–91	51 MRD	52% EFS (5)	Dopfer 1991 [160]
IBMTR/POG	1983–91	255 MRD	40% DFS (5)	Barrett 1994 [51]
		255 chemo	17% DFS (5)	
Leiden	1982–91	25 MRD	44% DFS (4)	Hoogerbrugge 1995 [161]
		97 chemo	24% DFS (4)	
AIEOP/GITMO	1980–90	57 MRD	41% DFS (5)	Uderzo 1995 [162]
		230 chemo	21% DFS (5)	
Paris	1983–93	42 MRD	53% (4)	Moussalem 1995 [163]
UKALL-X	1985–90	83 MRD, 27 MUD	40% EFS(5)	Wheeler 1998 [164]
		61 ABMT	34% EFS	
		261 chemo	(5) 26% EFS (5)	
UKALL-R1	1991–95	63 MRD	46% EFS (5)	Harrison 2000 [165]
		41 MUD	54% EFS (5)	
		15 ABMT, 89 chemo	43% EFS (5)	
IBMTR/COG	1991–97	CR1 < 36 months		Eapen 2006 [52]
		92 MRD + TBI	32% OS (8)	
		19 MRD no TBI	44% OS (8)	
		110 Chemo	(8)18% OS	
		CR1 ≥ 36 months		
		61 MRD + TBI	66% OS (8)	
		14 MRD no TBI	63% OS (8)	
		78 Chemo	32% OS (8)	
COG	1995–98	32 MRD	42% DFS (3)	Gaynon 2006 [45]
		19 MUD	29% DFS (3)	
		23 chemo	30% DFS (3)	

chemo = chemotherapy, MUD = matched unrelated donor, MRD = matched related donor, EFS = event free survival, DFS = disease free survival, OS = overall survival, ABMT = autologous bone marrow transplant, TBI = total body irradiation

Table 3

Stem Cell Transplantation for Pediatric ALL - *2005 American Society for Blood and Marrow Transplantation Expert Panel Consensus* [Hahn BBMT 2005]

Recommendation	Indication	References
SCT in CR1	Benefit demonstrated for matched related donor SCT for Philadelphia chromosome + only. Not recommended for other high-risk patients, except in the setting of a clinical trial.	Wheeler 2000 [155] Chessells 1992 [166] Arico 2000 [11] Uderzo 1997 [156]
SCT in CR2 with prior bone marrow relapse	Recommended for those with matched related donors. Evidence insufficient to recommend unrelated donor SCT.	Barrett 1994 [51] Wheeler 1998 [164] Uderzo 1995 [162] Harrison 2000 [165]

Table 4

Results of SCT as Post-Remission Therapy for Childhood AML in First Remission

Study Group	Disease Free Survival			Median Follow-Up	Reference
	Matched Related Donor SCT	Chemotherapy	Autologous SCT		
AML-80	43%	31%	-	6 years	Dahl 1990 [106]
AIEOP LAM-87	51%*	27%	21%	5 years	Amadori 1993 [94]
CCG-213	54%*	37%	-	5 years	Wells 1994 [108]
CCG-251	45%*	32%	-	8 years	Nesbit 1994 [107]
POG-8821	52%*	36%	38%	3 years	Ravindranath 1996 [93]
MRC AML-10	61%*	46%	68%^	7 years	Stevens 1998 [87]
AML BFM-93	64%	61%	-	5 years	Creutzig 2001 [86]
CCG-2891	55%*	47%	42%	8 years	Woods 2001 [95]
LAME-89/91	72%*	48%	-	6 years	Perel 2002 [88] Aladjidi 2003 [109]

Key: * p≤0.05 allogeneic vs. others;

^ p≤0.05 autologous vs. chemotherapy

Table 5

Stem Cell Transplantation for Pediatric AML 2007 American Society for Blood and Marrow Transplantation Expert Panel Consensus [Oliansky BBMT 2007]

Recommendation	Indication	References
SCT in CR1	Benefit demonstrated for matched related donor SCT.	Alonzo 2005 [167] Woods 2001 [95] Ravindranath 1996 [93] Wells 1994 [108] Nesbit 1994 [107] Amadori 1993 [94]
SCT in CR2	Recommended for those with matched related donors. Evidence insufficient to recommend unrelated donor SCT, except in the setting of a clinical trial.	Aladjidi 2003 [109] Pession 2000 [168] Gorin 1996 [169]

Table 6

Results of SCT for Pediatric Patients with MDS and JMML

Patients (n)	Survival (years)					Reference
	RA/RARS	RAEB	RAEB/T	MDS/AML	JMML	
48 MRD 52 MUD					55% EFS (5) 49% EFS (5)	Locatelli 2005 [145]
30 MRD, 27 MMRD, 30 MUD, 7 MMUD	59% EFS (3) 74% OS (3)	58%EFS (3) 68%OS (3)	18% EFS (3) 18% OS (3)		27% EFS (3) 33% OS (3)	Yusuf 2004 [144]
46 MUD					24% DFS (2)	Smith 2002 [150]
9 MUD 3 MMRD					64% EFS (3)	Bunin 1999 [149]
131 MRD	52% DFS (5) 57% OS (5)	34% DFS (5) 42% OS (5)	19% DFS (5) 24% OS (5)	26% DFS (5) 28% OS (5)		Runde 1998 [148]
60 MRD 19 MUD					36% OS (4) 31% OS (4)	Arico* 1997 [146]
14 MRD, 1 MMRD, 7 MUD, 2 MMUD (2nd SCT)					32% DFS (5)	Yoshimi 2007 [147]

MRD = matched related donor, MMRD = mismatched related donor, MUD = matched unrelated donor, MMUD = mismatched unrelated donor

* review article