



# Acute Lymphoblastic Leukemia in Children and Adolescents

# 72

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## 72.1 Introduction

Although the majority of children and adolescents with acute lymphoblastic leukemia (ALL) are curable with current chemotherapy regimens, poor outcome persists in some individuals (Eckert et al. 2011; von Stackelberg et al. 2011; Schrappe et al. 2012). Allo-HSCT is the most established treatment to control leukemia by means of the GVL effect. During the last decade, it was demonstrated in prospective trials that HSCT from HLA-MSD and from HLA-MURD results in similar outcomes.

Standardized MAC for paediatric patients with high relapse risk produced a low incidence of TRM and effective control of leukemia (Mann et al. 2010; Pulsipher et al. 2011; Peters et al.

2015). Currently, also HSCT from HLA haplo-identical family donors or mismatched CB gives promising results (Rocha et al. 2009; Luznik et al. 2012; Ruggeri et al. 2012; Berger et al. 2016; Klein et al. 2017; Locatelli et al. 2017).

To offer the patients the best available treatment options, a close collaboration between international therapy study groups and transplant consortia are necessary. This is realized within the big treatment consortia for childhood leukemia (e.g. IBFM-SG, IntReALL, NOPHO, UKALL, AIEOP, FRALLE and others) and the paediatric transplant community (e.g. EBMT-PD WG, IBFM-SC SCT, GETMON, GITMO). The study groups for ALL treatment evaluate outcome according to their chemotherapy protocols and stratify patients to relapse standard-risk, medium-risk and high-risk groups. In contrast to adult patients, only patients with high-relapse risk are eligible for allo-HSCT to protect children from the potential long-term consequences of myeloablation and GVHD.

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## 72.2 Prognostic Factors and Indications for HSCT

HSCT indications have to be defined prospectively and must be re-evaluated and reconfirmed at intervals dependent on modifications and improvements in non-transplant approaches for both front-line and relapse protocols. Some risk factors conveying a dismal prognosis in childhood

ALL can be identified even at diagnosis (Moorman 2016; O'Connor et al. 2018). Additionally, response to induction treatment measured by MRD has a strong predictive value and defines nowadays many indications or HSCT (Bader et al. 2009; Conter et al. 2010; Schrappe et al. 2011; Eckert et al. 2013).

### 72.2.1 Indications: CR1

Only patients with high-risk cytogenetic features or insufficient response to chemotherapy are eligible for HSCT in first remission. In contrast to earlier recommendations, for these patients a MSD and a MURD and for the highest relapse category also mismatched donors are an option (Table 72.1).

### 72.2.2 Indications: CR2 and Later

All patients with relapse of T-ALL and patients who relapse during or within 6 months of cessation of chemotherapy (very early and early relapse) have a dismal prognosis when treated with conventional chemotherapy. Allo-HSCT

from any donor type is the contemporary standard approach (Table 72.2).

If patients achieve a third or higher remission, allo-HSCT should be considered if the physical state allows such a procedure. Patient not in morphological remission should not receive allografts except in extraordinary experimental situations.

### 72.3 Donor Selection and Stem Cell Source

OS and incidence of NRM have constantly improved; however it has been shown that in children, a BMT from a HLA-identical sibling results in quicker myeloid engraftment, immunoreconstitution and less severe infections and should be therefore the preferred option (Peters et al. 2015). As only 25% of patients have a MSD, HSCT from other donors is the most applied method. Several groups have demonstrated that HSCT from unrelated donors, identified by HLA high-resolution typing and matching, has similar outcome results as MSD-HSCT (Zhang et al. 2012; Fagioli et al. 2013; Burke et al. 2015).

**Table 72.1** Indications for allogeneic HSCT in CR1 according to AIEOP-BFM ALL 2009-trial

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

PPR Prednisone Poor Response on day 8, *NRd33* No Remission day 33 *MRD* Minimal Residual Disease, *no* Allo HSCT not indicated, *MD* Permitted donor: HLA-matched sibling or non-sibling donor, *MMD* Permitted donor: HLA-matched or HLA-mismatched donor

<sup>a</sup>FCM-MRD results have no impact on the allo-HSCT indication

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

<sup>c</sup>Non-remission in patients with this rare constellation should be due to extramedullary disease. Allo-HSCT indication in these cases should be discussed with the national study coordinator

<sup>d</sup>Independent of prednisone response

<sup>e</sup>The finding of exactly 44 chromosomes qualifies for HR treatment but has no impact on allo-HSCT indication

<sup>f</sup>Including patients with 44 chromosomes

**Table 72.2** Indication for HSCT according to IntReALL SR 2010 and HR protocol criteria

Relapse risk group	Phenotype	Time of relapse	Site of relapse	MRD-status	Donor type
Very High	T-ALL	Any time	I-BM, C-BM, I-EM		MSD, MD, MMD
	Non-T-ALL	Very early	I-BM, C-BM, I-EM		
		Early	I-BM, C-BM	PR, ND	
High	Non-T-ALL	Late	I-BM, C-BM	PR, ND	MSD, MD
		Early	C-BM	GR	
			I-EM		
		Late	I-BM	PR, ND	
			C-BM	ND	

*I-BM* isolated bone marrow, *C-BM* combined bone marrow and extramedullary site, *I-EM* isolated extramedullary, *MRD*: GR good response as defined by the specific chemotherapy-protocol, PR poor response, ND not detectable.

**Table 72.3** Matching criteria according to HLA typing/matching and stem cell source for children and AYAs with ALL

MSD	HLA-genotypically matched sibling, or 10/10 allelic match (if parental haplotypes unknown)	BM, PBSC
MSD	6/6 or 8/8, 5/6 or 7/8 <sup>a</sup>	CB
MD	9/10 or 10/10 allelic matched related or unrelated	BM, PBSC
MD	5–6/6 unrelated or 6–7–8/8 unrelated	CB
MMD	Less than 9/10 matched	BM, PBSC
MMD	Less than 5/6 or 6/8 UCB	CB

MSD matched sibling donor, MD matched donor, MMD mismatched donor.

<sup>a</sup>4 digits high-resolution typing recommended also for CB matching definition.

Several methods were developed to overcome the HLA barriers. Today it is not clearly proven whether HSCT from HLA-mismatched CB, TCD (alpha-beta depleted, CD34+ selected or CD3/CD19 depleted) haplo-identical grafts or PT-CY approaches will result in the best outcome (Lang and Handgretinger 2008; Smith et al. 2009; Ruggeri et al. 2014; Locatelli et al. 2017) (Tables 72.3 and 72.4).

## 72.4 Conditioning Regimen

Most children receive a MAC. This consists either of TBI and VP and/or CY or—especially for children below 4 years of age—of BU-/FLU-

**Table 72.4** Donor hierarchy—further selection criteria

Variable/order	Priority
<i>CMV-status</i>	
Patient CMV IgG positive	
1	Donor CMV IgG positive
2	Donor CMV IgG negative
Patient CMV IgG negative	
1	Donor CMV IgG negative
2	Donor CMV IgG positive
<i>Gender</i>	
Female patient	
1	Male or female (preferentially not allo-immunized by prior pregnancy) donor
Male patient	
1	Male Donor
2	Female (preferentially not allo-immunized by prior pregnancy) donor
<i>Age</i>	
1	Younger donor if body weight enables sufficient SC harvest
2	Older donor
<i>Stem cell source</i>	
HSCT from MSD or MD	
1	Bone marrow
2	PPBSC (CAVE: adjust GvHD-prophylaxis for matched siblings)
2	Cord blood with sufficient cell number (>3 × 10 <sup>7</sup> NC/kg)
HSCT from MMD: possible options	
	BM, 8/10 matches, unmanipulated
	PBSC, haploidentical, CD3/CD19 depleted, α/β depleted
	CB, sufficient stem cell dose
	PBSC, haploidentical, CD34+ selection
	PT-CY

containing regimen, often combined with TT. An increasing use is recognized for TREO which results also in myeloablation but seems to have less toxic side effects (Wachowiak et al. 2011; Boztug et al. 2015; Lee et al. 2015; Peters et al. 2015).

To reduce acute organ toxicity, the interval between the end of the last chemotherapy and the start of conditioning is 3 or at most 6 weeks. If infection or toxicity requires a delay of conditioning, patients receive risk-adjusted chemotherapy to bridge the time until transplantation. Currently, a multinational trial comparing TBI/VP with either FLU/TT/BU or FLU/TT/TREO investigates in a randomized study the value of both conditioning regimens (FORUM study: allogeneic HSCT for children and AYAs with ALL comparing TBI with myeloablative chemotherapy) (Willasch et al. 2017).

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## 72.5 GVHD Prophylaxis

Children transplanted with BM from matched sibling donors might benefit from an augmented GVL effect if only single and short GVHD prophylaxis is given (Locatelli et al. 2000). However careful monitoring and rapid treatment intervention are crucial to prevent severe GVHD. After HSCT from non-sibling donors, a combination of CN1 and ATG with or without short MTX is given in most patients (Veys et al. 2012; Peters et al. 2015).

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## 72.6 Post-transplant Follow-Up and Interventions

### 72.6.1 Mixed Chimerism (MC) and MRD

*Mixed chimerism (MC) and MRD* strongly predict risk for relapse in children (Bader and Kreyenberg 2015).

Preemptive immunotherapy, e.g. withdrawal of IS or DLI guided by chimerism and MRD monitoring, can prevent impending relapse. However, the dynamic of leukaemic reappearance hampers the final success of these methods. Therefore, new post-transplant intervention strategies with less risk for severe complications like bi-specific antibodies or CAR-T-cell interventions may expedite the control of impending relapse (Handgretinger et al. 2011; Maude et al. 2018).

### 72.6.2 Children with Ph+

*Children with Ph+* should receive post-transplant TKIs: Whether the prophylactic approach (all Ph+ patients will receive TKIs) or a preemptive therapy (only patients with a Ph+ signal per HSCT) is more effective has to be prospectively proven (Schultz et al. 2010; Bernt and Hunger 2014). Both TKI options are currently under investigation.

#### 72.6.2.1 The Amended EsPhALL Recommendation

Administration of imatinib prophylaxis post HSCT when more than 50,000 platelets are reached. Duration, 365 days after HSCT.

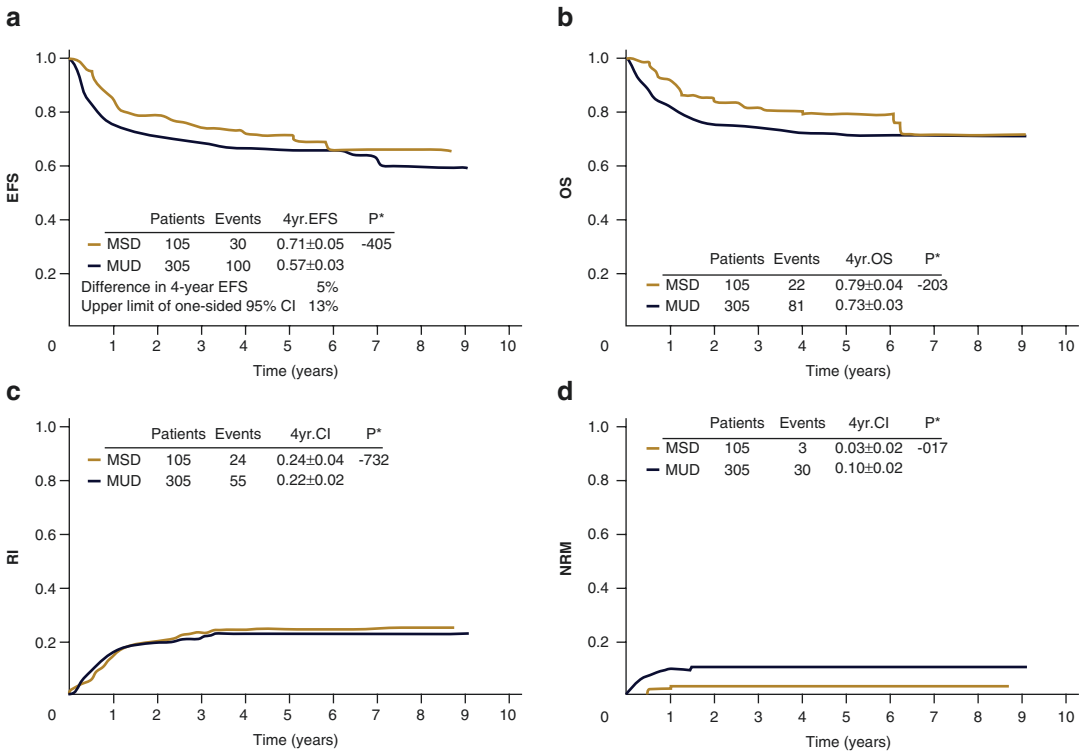
#### 72.6.2.2 TKI According to MRD Result

Administration of imatinib post HSCT for all MRD-positive patients until two negative results are achieved. FACS- and PCR-MRD analyses are accepted.

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## 72.7 Results

Figure 72.1 shows the event-free survival (EFS), overall survival (OS), relapse incidence (RI) and non-relapse mortality (NRM) of the prospective international multicentre trial comparing MSD with MURD (Peters et al. 2015).



**Fig. 7.2.1** Four-year event-free survival (EFS), overall survival (OS), relapse incidence (RI) and non-relapse mortality (NRM) of the prospective international multi-centre trial comparing sibling donors with matched unre-

lated donors – the ALL-SCT-BFM-2003 trial on behalf of the BFM Study Group, the IBFM Study Group and the EBMT Paediatric Diseases Working Party (Peters et al. 2015)

### Key Points

- Only children and adolescents with very high or high relapse risk should be candidates for allo-HSCT. The definition of relapse risk depends on the leukaemic phenotype, response to chemotherapy and—if applicable—time and site of relapse.
- MRD levels during chemotherapy but also pre- and post-HSCT are powerful predictors for outcome after HSCT.
- Patients who are not in morphological remission before conditioning should not undergo allogeneic HSCT except in extraordinary situations.
- MAC is recommended for children with ALL. Whether TBI is necessary to control leukemia is subject of a prospective randomized EBMT/IBFM trial.

### References

- Bader P, Kreyenberg H, Henze GH, et al. Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group. *J Clin Oncol.* 2009;27:377–84.
- Bader P, Kreyenberg H, von Stackelberg A, et al. Monitoring of minimal residual disease after allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia allows for the identification of impending relapse: results of the ALL-BFM-SCT 2003 trial. *J Clin Oncol.* 2015;33:1275–84.
- Berger M, Lanino E, Cesaro S, 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;22:902–9.
- Bernt KM, Hunger SP. Current concepts in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia. *Front Oncol.* 2014;4:54.

- Boztug H, Zecca M, Sykora KW, et al. EBMT paediatric diseases working party. Treosulfan-based conditioning regimens for allogeneic HSCT in children with acute lymphoblastic leukemia. *Ann Hematol*. 2015;94:297–306.
- Burke MJ, Verneris MR, Le Rademacher J, et al. Transplant outcomes for children with t cell acute lymphoblastic leukemia in second remission: a report from the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant*. 2015;21:2154–9.
- Conter V, Bartram CR, Valsecchi MG, 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;115:3206–14.
- Eckert C, Flohr T, Koehler R, et al. Very early/early relapses of acute lymphoblastic leukemia show unexpected changes of clonal markers and high heterogeneity in response to initial and relapse treatment. *Leukemia*. 2011;25:1305–13.
- Eckert C, von Stackelberg A, Seeger K, et al. Minimal residual disease after induction is the strongest predictor of prognosis in intermediate risk relapsed acute lymphoblastic leukemia - long-term results of trial ALL-REZ BFM P95/96. *Eur J Cancer*. 2013;49:1346–55.
- Fagioli F, Quarello P, Zecca M, et al. Hematopoietic stem cell transplantation for children with high-risk acute lymphoblastic leukemia in first complete remission: a report from the AIEOP registry. *Haematologica*. 2013;98:1273–81.
- Handgretinger R, Zugmaier G, Henze G, et al. Complete remission after blinatumomab-induced donor T-cell activation in three pediatric patients with post-transplant relapsed acute lymphoblastic leukemia. *Leukemia*. 2011;25:181–4.
- Klein OR, Buddenbaum J, Tucker N, et al. Nonmyeloablative haploidentical bone marrow transplantation with post-transplantation cyclophosphamide for pediatric and young adult patients with high-risk hematologic malignancies. *Biol Blood Marrow Transplant*. 2017;23:325–32.
- Lang P, Handgretinger R. Haploidentical SCT in children: an update and future perspectives. *Bone Marrow Transplant*. 2008;42(Suppl 2):S54–9.
- Lee JW, Kang HJ, Kim S, et al. Favorable outcome of hematopoietic stem cell transplantation using a targeted once-daily intravenous busulfan-fludarabine-etoposide regimen in pediatric and infant acute lymphoblastic leukemia patients. *Biol Blood Marrow Transplant*. 2015;21:190–5.
- Locatelli F, Bruno B, Zecca M, et al. Cyclosporin A and short-term methotrexate versus cyclosporin A as graft versus host disease prophylaxis in patients with severe aplastic anemia given allogeneic bone marrow transplantation from an HLA-identical sibling: results of a GITMO/EBMT randomized trial. *Blood*. 2000;96:1690–7.
- Locatelli F, Merli P, Pagliara D, et al. Outcome of children with acute leukemia given HLA-haploidentical HSCT after alphabeta T-cell and B-cell depletion. *Blood*. 2017;130:677–85.
- Luznik L, O'Donnell PV, Fuchs EJ. Post-transplantation cyclophosphamide for tolerance induction in HLA-haploidentical bone marrow transplantation. *Semin Oncol*. 2012;39:683–93.
- Mann G, Attarbaschi A, Schrappe M, 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;116:2644–50.
- Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with b-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378:439–48.
- Moorman AV. New and emerging prognostic and predictive genetic biomarkers in B-cell precursor acute lymphoblastic leukemia. *Haematologica*. 2016;101:407–16.
- O'Connor D, Enshaei A, Bartram J, et al. Genotype-specific minimal residual disease interpretation improves stratification in pediatric acute lymphoblastic leukemia. *J Clin Oncol*. 2018;36:34–43.
- Peters C, Schrappe M, von Stackelberg A, 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;33:1265–74.
- Pulsipher MA, Peters C, Pui CH. High-risk pediatric acute lymphoblastic leukemia: to transplant or not to transplant? *Biol Blood Marrow Transplant*. 2011;17(Suppl 1):S137–48.
- Rocha V, Kabbara N, Ionescu I, et al. Pediatric related and unrelated cord blood transplantation for malignant diseases. *Bone Marrow Transplant*. 2009;44:653–9.
- Ruggeri A, Michel G, Dalle JH, et al. Impact of pretransplant minimal residual disease after cord blood transplantation for childhood acute lymphoblastic leukemia in remission: an Eurocord, PDWP-EBMT analysis. *Leukemia*. 2012;26:2455–61.
- Ruggeri A, Labopin M, Sormani MP, et al. Engraftment kinetics and graft failure after single umbilical cord blood transplantation using a myeloablative conditioning regimen. *Haematologica*. 2014;99:1509–15.
- Schrappe M, Valsecchi MG, Bartram CR, 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;118:2077–84.
- Schrappe M, Hunger SP, Pui CH, et al. Outcomes after induction failure in childhood acute lymphoblastic leukemia. *N Engl J Med*. 2012;366:1371–81.
- Schultz KR, Prestidge T, Camitta B. Philadelphia chromosome-positive acute lymphoblastic leukemia in children: new and emerging treatment options. *Expert Rev Hematol*. 2010;3:731–42.
- Smith AR, Baker KS, Defor TE, et al. Hematopoietic cell transplantation for children with acute lymphoblastic leukemia in second complete remission:

- similar outcomes in recipients of unrelated marrow and umbilical cord blood versus marrow from HLA matched sibling donors. *Biol Blood Marrow Transplant.* 2009;15:1086–93.
- Veys P, Wynn RF, Ahn KW, et al. Impact of immune modulation with in vivo T-cell depletion and myeloablative total body irradiation conditioning on outcomes after unrelated donor transplantation for childhood acute lymphoblastic leukemia. *Blood.* 2012;119:6155–61.
- von Stackelberg A, Volzke E, Kuhl JS, et al. Outcome of children and adolescents with relapsed acute lymphoblastic leukemia and non-response to salvage protocol therapy: a retrospective analysis of the ALL-REZ BFM Study Group. *Eur J Cancer.* 2011;47:90–7.
- Wachowiak J, Sykora KW, Cornish J, et al. Treosulfan-based preparative regimens for allo-HSCT in childhood hematological malignancies: a retrospective study on behalf of the EBMT pediatric diseases working party. *Bone Marrow Transplant.* 2011;46:1510–8.
- Willasch A, Peters C, Sedlacek P, et al. Myeloablative conditioning for first allogeneic hematopoietic stem cell transplantation in children with all: total body irradiation or chemotherapy? - a multicenter EBMT-PDWP Study. *Blood.* 2017;130:911.
- Zhang MJ, Davies SM, Camitta BM, 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;18:1204–10.

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