

# The Role of Hematopoietic Stem-Cell Transplantation in First Remission in Pediatric Acute Lymphoblastic Leukemia: A Narrative Review

Neel S. Bhatt,<sup>1</sup> Rachel Phelan,<sup>1</sup> and Michael J. Burke<sup>1\*</sup>

<sup>1</sup>Division of Pediatric Hematology-Oncology-Blood and Marrow Transplantation, Medical College of Wisconsin, Milwaukee, WI

\*Corresponding author: Michael J. Burke, MD, Associate Professor of Pediatric Hematology-Oncology-Blood and Marrow Transplantation, Department of Pediatrics, Division of Hematology/Oncology/BMT, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA. Tel: +1-4149554198, Fax: +98-4149556543, E-mail: mmburke@mcw.edu

Received 2017 February 03; Revised 2017 April 24; Accepted 2017 May 02.

## Abstract

**Context:** Survival after allogeneic hematopoietic stem-cell transplantation (HSCT) for children with hematologic malignancies including acute lymphoblastic leukemia (ALL) continues to improve in part due to advancement in HLA typing and enhanced supportive care. Despite improved outcomes with HSCT, the decision to offer it in first remission (CR1) in children with ALL remains a topic of debate and uncertainty. This review aims to discuss the role of HSCT in CR1 for children with high-risk subsets of ALL in the current era.

**Evidence Acquisition:** A thorough review of the literature was performed using electronic databases: PubMed, Google Scholar, and bibliographies. Studies focusing on high-risk subsets of ALL (Primary Induction Failure, Severe Hypodiploidy, Philadelphia-chromosome positive ALL, T-Cell ALL, Infant ALL, ALL with persistent minimal residual disease (MRD), and Philadelphia-like ALL) were included. Publications in non-English language were excluded.

**Results:** Based on our review of the current literature, HSCT should be considered in first remission for patients with primary induction failure, severe hypodiploidy, T-cell ALL with poor response, high-risk infant ALL, and persistently positive MRD. In contrast, HSCT in CR1 may not be warranted for patients with early T-cell progenitor ALL or Philadelphia-chromosome positive ALL. Further data are needed to make specific recommendations regarding Philadelphia-like ALL.

**Conclusions:** As our understanding of high-risk leukemia biology continues to develop, the role of HSCT in ALL CR1 will need to be revisited.

**Keywords:** Leukemia (lymphoid), Hematopoietic Stem-Cell Transplantation, Remission, Pediatrics, ALL, High-Risk

## 1. Context

Allogeneic hematopoietic stem-cell transplantation (HSCT) has been increasingly used as a curative option for both benign and malignant hematological conditions. In 2006, over 50,000 transplants were performed across the world (1). This number continues to increase as more than 40,000 transplants were reported in Europe alone in 2014 (2). In 2015, Bone marrow donors worldwide (BMDW) and the world marrow donor association (WMDA) reported 25 million active volunteer marrow donors (3). Because of better donor availability, usage of high resolution HLA typing, and improvement in supportive care during pre-and post-transplant periods, transplant outcomes have significantly improved over the years (4). In the last 25 years, transplant related mortality (TRM) has reached an all-time low with rates previously > 30% now dropping to 5% (5). Similarly, over the years, improvement in survival rates for pediatric patients with acute lymphoblastic leukemia (ALL) treated with chemotherapy alone has been achieved through therapy intensification and risk based stratifica-

tion. At the same time, new discoveries of high-risk (HR) ALL biology has been reported, for which conventional chemotherapy does not appear to cure. Examples of these new lesions with poor prognostic findings include deletions in IKZF1 (IKAROS), rearrangements of CRLF2, and ABL class fusions (6, 7). Taken together, these lesions in part comprise the new prognostic group of HR leukemia identified as Philadelphia-Like (Ph-Like) B-ALL (7).

Despite improved accessibility and outcomes, the role of HSCT for childhood ALL has remained controversial, particularly for patients in first remission (CR1) where survival rates are now greater than 90% (8). However, as HSCT outcomes continue to improve over time, its role should be re-assessed, particularly for patients with HR biology who have the poorest predicted response rates to chemotherapy alone (9). An expert panel of the American Society for Blood and Marrow Transplantation (ASBMT) has previously provided treatment recommendations through systematic evidence-based reviews (EBRs) every 5-year for various diseases including pediatric ALL (10). The latest up-

date, published in 2012, provided a position statement for HR subsets of pediatric ALL (11).

As a whole, the role of HSCT in CR1 for pediatric ALL has been a controversial topic for several decades (9, 12-15). Previous studies have been divided in recommending it for patients with certain high-risk leukemia subsets (16-18). A retrospective case control study performed in the Nordic countries found that ALL patients with very high-risk (VHR) features who received HSCT in CR1 had a DFS advantage at 10-years over patients who only received chemotherapy alone (73% vs. 50%;  $P = 0.02$ ) (19). VHR status was determined based on presence of a  $WBC \geq 50 \times 10^9/l$ , positive CNS status at diagnosis, T-ALL, t(9;22), t(4;11) and/or presence of a mediastinal mass. The authors concluded that HSCT should be considered in CR1 due to risk for unsuccessful salvage post-relapse and poor survival rates for HSCT in CR2. Over the years the paradigm appears to have shifted from HSCT in CR1 to more intensive multi-agent chemotherapy for previously considered HR patient groups (20-23). But at the same time, the definition of HR leukemia is changing given recent discoveries with new genomic lesions and continued MRD testing. HSCT in CR1 should still be considered when a patient's predicted EFS falls below 50% with conventional chemotherapy.

In the past, survival benefits of HSCT were offset by high rates of TRM, but as these rates continue to drop to well below 10% in children, (5) HSCT should remain an option to improve survival rates for these HR patients. Our review will focus on recommendations for HSCT for pediatric patients in CR1 with HR ALL building off of the last ASBMT EBR.

## 2. Evidence Acquisition

A review of the literature was conducted utilizing MEDLINE/PubMed and Google Scholar with the keywords "leukemia", "pediatric", "remission", "primary induction failure", "severe hypodiploidy", "Philadelphia-chromosome positive", "T-cell", "Infant ALL", "minimal residual disease", "Philadelphia-like" "allogeneic", "stem cell transplant", "ALL" and "bone marrow transplant". Reference lists of included articles were also reviewed. Studies in the English language up to June 2016 were included. A narrative review was undertaken to provide expert recommendations regarding HSCT in CR1 for pediatric patients with ALL. See Table 1 for a summary of this review.

## 3. Results

### 3.1. Primary Induction Failure

Primary Induction Failure (PIF) is rarely seen in pediatric patients given current ALL therapy and is typically reported

**Table 1.** Recommendation for HSCT in CR1 According to ALL Subtype

ALL Subtype	Recommendation for HSCT in CR1	Comments
<b>Induction failure</b>	Yes	Balduzzi et al. 2008 (24)
<b>Severe hypodiploidy</b>	Yes	EOI MRD negative may not need HSCT in CR1 (25)
<b>Ph + ALL</b>	No	Imatinib with chemotherapy has replaced HSCT in CR1 (26)
<b>T-Cell ALL</b>		
a) ETP-ALL	No	Consider for EOI/EOC MRD positive
b) Poor Response	Yes	Prednisone poor response, EOI M2 or EOI/EOC MRD positive
<b>Infant ALL (high-risk)</b>	Yes	MRD negative at EOI/EOC may not need HSCT in CR1 (27)
<b>Persistent MRD</b>	Yes	Borowitz et al. 2015 (28)
<b>Ph-Like B-ALL</b>	No	Consider for EOI/EOC MRD positive (28)

Abbreviations: EOC, end of Consolidation; EOI, end of Induction; ETP, early T-cell progenitor.

in < 3% of all pediatric patients (29). PIF is often defined as detection of 25% or more blasts in the bone marrow on day 29 of Induction therapy or 5% or more blasts in the bone marrow on day 33 of Induction (30). Several studies have assessed the role of HSCT for patients with B-ALL and PIF in CR1. A prospective international study by the Berlin-Frankfurt-Munster (BFM) and European bone marrow transplantation (EBMT) groups was performed in 2005 enrolling pediatric patients with ALL and very high-risk features including PIF (17). Patients were allocated to chemotherapy only versus HSCT with a related donor if such a donor was available. The study included PIF patients only if they achieved CR1 at the end of consolidation. A total of 357 patients were enrolled with 280 receiving chemotherapy only (PIF n = 58) and 77 HSCT in CR1 (PIF n = 25). Intent-to-treat analysis showed an advantage in 5-year disease-free survival (DFS) in patients who received a related HSCT compared to chemotherapy only (56% vs. 26.5%,  $P = 0.03$ ), but overall survival (OS) did not differ significantly (related HSCT vs. chemotherapy only; 56.4% vs. 50.1%,  $P = 0.12$ ). A recent large retrospective review by Schrappe et al. reported outcomes for pediatric patients with ALL and Induction failure (29). The rate of Induction failure was 2.4% (1041 out of 44,017 patients). As the patients were treated between 1985 and 2000, the ALL ther-

apy and HSCT conditioning varied significantly. Despite this variability, the results showed non-significant benefit of HSCT in OS for patients > 6 year of age with B-cell ALL who received matched related donor HSCT compared to chemotherapy ( $59 \pm 12\%$  vs.  $35 \pm 5\%$ ,  $P = 0.11$ ). The authors also reported a survival benefit of any type of HSCT over chemotherapy for patients with T-cell ALL (matched related donor HSCT vs. other types of HSCT vs. chemotherapy only:  $40 \pm 9\%$  vs.  $45 \pm 8\%$  vs.  $26 \pm 4\%$ ,  $P = 0.06$ ). Despite the results not being statistically significant, the HSCT outcomes include many patients transplanted prior to 2000 when TRM was much greater given the relative limitations in HLA-typing during that time.

Recommendation: these findings argue consideration of HSCT for patients with Primary Induction Failure (PIF) in CR1 as survival with chemotherapy alone appears to be < 40%.

### 3.2. Severe Hypodiploidy

Severe or extreme hypodiploidy has been defined as fewer than 44 chromosomes and/or a DNA index < 0.81 in leukemic blasts (30). Although previous studies have reported poor outcomes for this subgroup, there is a paucity of data and indications for HSCT in CR1 are unclear. Despite these limitations, the ASBMT EBR from 2012 recommended considering HSCT in CR1 based on expert opinion (11). A previous retrospective review of 130 patients with hypodiploid ALL was performed in 2007 (31). Both EFS and OS were significantly inferior in patients with less than 44 chromosomes compared to those with 44 chromosomes (8-year EFS: 30.1% vs. 50.2%,  $P = 0.01$ ; 8-year OS: 37.5% vs. 69.1%,  $P = 0.001$ ) identifying severe hypodiploidy as a poor prognostic biology. To determine whether HSCT may be beneficial for pediatric patients with severe hypodiploidy, a recent CIBMTR review reported on 78 children with severe hypodiploidy ALL ( $\leq 43$  chromosomes) who received a HSCT between 1990 and 2010 (32, 33). Forty-three patients received a HSCT in CR1 reporting an EFS and OS of 47% and 50%, respectively. Treatment failure and overall mortality were higher when transplants occurred prior to 2000 and patients were > CR1. This CIBMTR study, published after the latest ASBMT guidelines which did not recognize hypodiploidy as an indication for HSCT in CR1, reported relatively good outcomes for this HR ALL subgroup.

Recommendation: these findings argue consideration of HSCT for patients with Sever Hypodiploidy in CR1 as survival with chemotherapy alone appears to be < 40%.

### 3.3. Philadelphia-Positive ALL

Philadelphia-chromosome positive (Ph+) leukemia has been reported in 3% - 5% of childhood B-ALL (34). This subgroup has been associated with a very poor prognosis (EFS

< 40%), a higher rate of Induction failure (11% vs. 2% - 3% in Ph-negative ALL) and a greater likelihood of relapse with conventional chemotherapy (35, 36). Prior to the introduction of tyrosine kinase inhibitors (TKI), HSCT in CR1 was the accepted standard of care for patients with this HR biology (37). Arico et al. reported outcome data for 610 pediatric patients with Ph+ ALL who were diagnosed between 1995 and 2005 (35). Out of 542 patients who achieved CR after Induction chemotherapy, 217 received chemotherapy only (all prior to the TKI era) and 325 underwent HSCT. DFS was lower in patients who received chemotherapy only compared to HSCT (34.2% vs. 43.5%;  $P = 0.049$ ). As TKIs have since been introduced into the treatment of both adults and children with Ph+ leukemia, HSCT in CR1 is no longer the accepted standard of care as evidenced by results of the COG study AALL0031 investigating imatinib in children and young adults with Ph+ B-ALL (23). The long term results of this study reported 5-year EFS of  $70 \pm 12\%$  for chemotherapy only patients in Cohort 5 (receiving continuous imatinib) compared to  $65 \pm 11\%$  for patients receiving related donor HSCT and  $59 \pm 15\%$  for unrelated donor HSCT ( $P = 0.77$ ) (26).

Recommendation: Based on the dramatically improved outcomes with the introduction of imatinib to intensive chemotherapy, HSCT in CR1 is no longer recommended as standard of care for this subgroup and has been reported as such by the 2008 ASBMT guidelines (11).

### 3.4. T-Cell ALL (T-ALL)

Previously reported literature suggests that patients with T-ALL tend to have worse outcomes compared to B-ALL (38, 39). Historically, relapsed T-ALL has been identified as a poor prognostic disease, with 10-year EFS ~15% when treated with chemotherapy alone (40). A recent CIBMTR study reviewed HSCT outcomes in children and young adults with T-ALL in CR2 (41). Three year DFS was 46% (95% CI: 39% to 52%). Few studies have assessed the role of HSCT for T-ALL in CR1. In the BFM 90 and 95 studies, 36 patients with HR T-ALL underwent HSCT in CR1 (42). High-risk status was defined as prednisone poor response, day 33 non-response to Induction chemotherapy, and/or chromosomal translocations including t(9;22) or t(4;11). Five year DFS was significantly improved with HSCT compared to patients ( $n = 120$ ) who received chemotherapy only (67% vs. 42%,  $P = 0.01$ ). Over the years intensification with multi-agent chemotherapy has improved outcomes of children with newly diagnosed T-ALL, but patients with HR features continue to do poorly (20, 39). A subset of T-ALL, early T-cell progenitor (ETP), appears to have a poor prognosis with chemotherapy alone, but recently this association has become less clear (43, 44). T-ALL patients enrolled in AIEOP ALL-2000 and St. Jude study protocols were

retrospectively assessed for a distinct immunophenotype characteristic for ETP. Thirty patients were identified and were found to have a high rate of treatment failure or relapse (10-year cumulative risk of relapse: 72% vs. 10%; ETP ALL vs. non-ETP ALL) (44). However, in a more recent COG T-ALL study (AALL0434), patients with ETP and near-ETP (not meeting all criteria for ETP) were noted to have higher Induction failure rates but similar EFS at 5-years compared to non-ETP T-ALL (ETP vs. near ETP vs. non-ETP; 87% vs. 84.4% vs. 86.9%) (43). In addition, ETP patients who were reported as D29 of Induction MRD-positive did not have a significant difference in EFS.

Recommendation: while further studies are required for this subset, the role of HSCT currently is not justified.

### 3.5. Infant ALL

Despite ongoing advances in ALL treatment leading to improved outcomes for pediatric ALL, (8) prognosis for our youngest patients, infants with ALL, remains incredibly poor (45, 46). Previous studies have identified younger age at diagnosis (< 6 months of age), MLL (mixed lineage leukemia) rearrangement, high presenting WBC (> 300,000  $\mu\text{L}/\text{mL}$ ) and poor prednisone response as poor prognostic factors for infants (21, 45, 47). Historical data would suggest transplant in CR1 is advantageous for infants with MLL-R ALL. Sanders et al. reported a 3-year DFS of 76% for patients who underwent HSCT in CR1 (n = 17) compared to 45% and 8% for patients in CR2/CR3 (n = 7) and relapse (n = 16), respectively (48). However, recent multi-center studies have reported contrary results with no apparent benefit of HSCT over chemotherapy alone (21, 22). The children's cancer group (CCG) study 1953 and Pediatric Oncology Group (POG) study 9407 enrolled 189 combined patients with infant ALL, out of which 53 underwent HSCT in CR1 (22). Five year EFS was not significantly different between the chemotherapy only vs. HSCT group (48.7% vs. 48.8%,  $P = 0.60$ ). The results of the Interfant-99 study reported by Mann et al. also did not show a DFS advantage in most of the patients except those with HR features (21). Van der Valken et al. reported further on Interfant-99 and identified a prognostic significance of MRD in infants (27). Based on MRD at end of Induction (EOI) and end of Consolidation (EOC), patients were divided into 3 risk groups: low-risk (MRD <  $10^{-4}$  at both time-points), high-risk (EOC  $\geq 10^{-4}$ ), and medium risk (all remaining patients). The study noted that all patients in the high-risk MRD group relapsed, and therefore recommended a change in treatment for this population.

Recommendation: based on results of Interfant-99, infants with High-Risk ALL should be considered for HSCT in CR1.

### 3.6. Persistence of Minimal Residual Disease (MRD) Leukemia

Historically, the presence of MRD at EOI has been considered an independent poor prognostic factor (49) with outcomes comparable to patients with Induction failure (50, 51). Persistently positive MRD (EOI and EOC MRD-positive) has been associated with various high-risk cytogenetic subgroups such as MLL-R leukemia (27). Recently the COG published results from their HR B-ALL trial AALL0232 showing the prognostic significance of both EOI and EOC MRD on EFS (28). Patients who were initially MRD-positive at EOI (> 0.01%) and continued with persistent MRD ( $\geq 0.01$ ) at EOC had a  $39 \pm 7\%$  5-year DFS, compared to  $79 \pm 5\%$  if MRD negative at EOC. Shrappe et al. published results from the AIEOP-BFM-ALL 2000 study for pediatric T-ALL (52). Risk stratification was performed based on Day 33 and Day 78 MRD using polymerase chain reaction (PCR) of the complete and incomplete T-cell receptors. Standard-risk (SR) was defined as negative MRD at both time points, intermediate-risk (IR) if either one MRD time-point was positive but <  $10^{-3}$ , and HR if MRD was  $\geq 10^{-3}$  at day 78. The 7-year EFS differed significantly between risk groups (91.1% for SR, 80.6% for IR, and 49.8% for HR). MRD at EOC was identified as the most important prognostic factor predicting disease relapse and together with EOI MRD, could be used to stratify patients to chemotherapy alone or HSCT in CR1.

Recommendation: for patients with persistent MRD identified at EOI and EOC, independent of their underlying leukemia biology, HSCT in CR1 should be considered given the very poor predicted EFS for this patient subgroup.

### 3.7. Philadelphia-Like ALL (Ph-Like)

A number of recently published articles have focused on various HR ALL biologies that have been associated with poor outcomes with conventional chemotherapy. Mullighan et al. first documented the role of IKZF1 in pediatric ALL which encodes the lymphoid transcription factor IKAROS where a deletion of IKZF1 was found in 15% of pediatric B-ALL patients and close to 80% of Ph+ ALL cases (53, 54). In addition it has been strongly associated with MRD-positivity at EOI (23.9%) and high-risk of relapse. Similarly, cases of Philadelphia-like (Ph-like) B-ALL, originally reported by Den Boer et al. (55) and Mullighan et al. (53), and further described by Loh et al. based on CRLF2 overexpression, JAK1/JAK2 mutations and/or ABL-class kinase fusions, have identified a new subgroup of HR patients with very poor EFS (56). The 5-year EFS for HR patients with Ph-like B-ALL treated on contemporary children's oncology group (COG) protocols compared to patients without Ph-like mutations was  $62.9 \pm 0.06\%$  vs.  $83.9 \pm 0.02\%$  ( $P < 0.0001$ ). Currently, there are no recommendations regarding HSCT in CR1 for these patients but following their EOI

and EOC MRD and determining treatment based on therapy response would be a reasonable approach until more data is reported for this new HR subgroup. As leukemia biology is a constantly evolving field with new discoveries of high-risk lesions associated with poor outcomes, the role of HSCT in CR1 for such patients as a means to improve survival remains unclear.

**Recommendation:** While we await data to support specific recommendations for these subgroups, using EOI and EOC MRD assessment likely provides the best guide to making treatment decisions regarding HSCT in CR1 for patients with Ph-like disease.

#### 4. Conclusions

As our understanding of HR leukemia biology continues to develop and change as well as improvements in HSCT care and outcomes be made, the role of HSCT in CR1 for children and young adults with ALL will need to be revisited. However, based on the current data and the most recent ASBMT 2012 position statement, patients with Primary Induction Failure, Severe Hypodiploidy, T-ALL with poor response, HR Infant ALL and persistent MRD should be considered for HSCT in CR1. Future research efforts will be needed regarding the continued role of HSCT in pediatric ALL particularly in the current era of immune and cellular therapies.

#### Acknowledgments

Midwest athletes against cancer (MACC) fund and the children's hospital of Wisconsin pediatric leukemia & lymphoma program supported this work.

#### Footnotes

**Financial Disclosure:** None.

**Funding/Support:** None.

#### References

1. Gratwohl A, Baldomero H, Aljurf M, Pasquini MC, Bouzas LF, Yoshimi A, et al. Hematopoietic stem cell transplantation: a global perspective. *JAMA*. 2010;**303**(16):1617-24. doi: [10.1001/jama.2010.491](https://doi.org/10.1001/jama.2010.491). [PubMed: 20424252].
2. Passweg JR, Baldomero H, Bader P, Bonini C, Cesaro S, Dreger P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. *Bone Marrow Transplant*. 2016;**51**(6):786-92. doi: [10.1038/bmt.2016.20](https://doi.org/10.1038/bmt.2016.20). [PubMed: 26901709].
3. International Marrow Donor . Registries Reach 25 Million Potential Donors, Give Hope to Searching Blood Cancer Patients Around the World 2016. Available from: <https://bethematch.org/news/news-releases/international-marrow-donor-registries-reach-25-million-potential-donors--give-hope-to-searching-blood-cancer-patients-around-the-world/>.
4. Horowitz MM. Uses and growth of hematopoietic cell transplantation. Thomas' hematopoietic cell transplantation. ;2004.
5. Mateos MK, O'Brien TA, Oswald C, Gabriel M, Ziegler DS, Cohn RJ, et al. Transplant-related mortality following allogeneic hematopoietic stem cell transplantation for pediatric acute lymphoblastic leukemia: 25-year retrospective review. *Pediatr Blood Cancer*. 2013;**60**(9):1520-7. doi: [10.1002/pbc.24559](https://doi.org/10.1002/pbc.24559). [PubMed: 23733511].
6. Harvey RC, Mullighan CG, Chen IM, Wharton W, Mikhail FM, Carroll AJ, et al. Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. *Blood*. 2010;**115**(26):5312-21. doi: [10.1182/blood-2009-09-245944](https://doi.org/10.1182/blood-2009-09-245944). [PubMed: 20139093].
7. Hunger SP, Mullighan CG. Redefining ALL classification: toward detecting high-risk ALL and implementing precision medicine. *Blood*. 2015;**125**(26):3977-87. doi: [10.1182/blood-2015-02-580043](https://doi.org/10.1182/blood-2015-02-580043). [PubMed: 25999453].
8. Hunger SP, Loh ML, Whitlock JA, Winick NJ, Carroll WL, Devidas M, et al. Children's Oncology Group's 2013 blueprint for research: acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2013;**60**(6):957-63. doi: [10.1002/pbc.24420](https://doi.org/10.1002/pbc.24420). [PubMed: 23255467].
9. Pulsipher MA, Peters C, Pui CH. High-risk pediatric acute lymphoblastic leukemia: to transplant or not to transplant?. *Biol Blood Marrow Transplant*. 2011;**17**(1 Suppl):S137-48. doi: [10.1016/j.bbmt.2010.10.005](https://doi.org/10.1016/j.bbmt.2010.10.005). [PubMed: 21195303].
10. Hahn T, Wall D, Camitta B, Davies S, Dillon H, Gaynon P, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in children: an evidence-based review. *Biol Blood Marrow Transplant*. 2005;**11**(11):823-61. doi: [10.1016/j.bbmt.2005.08.035](https://doi.org/10.1016/j.bbmt.2005.08.035). [PubMed: 16275588].
11. Oliansky DM, Camitta B, Gaynon P, Nieder ML, Parsons SK, Pulsipher MA, et al. Role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of pediatric acute lymphoblastic leukemia: update of the 2005 evidence-based review. *Biol Blood Marrow Transplant*. 2012;**18**(4):505-22. doi: [10.1016/j.bbmt.2011.12.585](https://doi.org/10.1016/j.bbmt.2011.12.585). [PubMed: 22209888].
12. Pinkel D. Allogeneic bone marrow transplantation in children with acute leukemia: a practice whose time has gone. *Leukemia*. 1989;**3**(3):242-4. [PubMed: 2645474].
13. Pinkel D. 'Allogeneic marrow transplantation in children with acute leukemia: a practice whose time has gone': twenty years later. *Leukemia*. 2009;**23**(12):2189-96. doi: [10.1038/leu.2009.132](https://doi.org/10.1038/leu.2009.132). [PubMed: 20016481].
14. Pulsipher MA, Hunger SP, Gamis AS, Wall DA, Grupp SA. Allogeneic marrow transplantation in children with acute leukemia: careful comparison with chemotherapy alternatives required. *Leukemia*. 2010;**24**(6):1212-6. doi: [10.1038/leu.2010.72](https://doi.org/10.1038/leu.2010.72). [PubMed: 20428198].
15. Pinkel D. Response to letter by Pulsipher et al. *Leukemia*. 2010;**24**(8):1532-3. doi: [10.1038/leu.2010.125](https://doi.org/10.1038/leu.2010.125). [PubMed: 20535154].
16. Ribera JM, Ortega JJ, Oriol A, Bastida P, Calvo C, Perez-Hurtado JM, et al. Comparison of intensive chemotherapy, allogeneic, or autologous stem-cell transplantation as postremission treatment for children with very high risk acute lymphoblastic leukemia: PETHEMA ALL-93 Trial. *J Clin Oncol*. 2007;**25**(1):16-24. doi: [10.1200/JCO.2006.06.8312](https://doi.org/10.1200/JCO.2006.06.8312). [PubMed: 17194902].
17. Balduzzi A, Valsecchi MG, Uderzo C, De Lorenzo P, Klingebiel T, Peters C, et al. Chemotherapy versus allogeneic transplantation for very-high-risk childhood acute lymphoblastic leukaemia in first complete remission: comparison by genetic randomisation in an international prospective study. *Lancet*. 2005;**366**(9486):635-42. doi: [10.1016/S0140-6736\(05\)66998-X](https://doi.org/10.1016/S0140-6736(05)66998-X). [PubMed: 16112299].

18. Uderzo C, Valsecchi MG, Balduzzi A, Dini G, Miniero R, Locatelli F, et al. Allogeneic bone marrow transplantation versus chemotherapy in high-risk childhood acute lymphoblastic leukaemia in first remission. *Associazione Italiana di Ematologia ed Oncologia Pediatrica (AIEOP) and the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Br J Haematol.* 1997;**96**(2):387-94. [PubMed: 9029031].
19. Saarinen UM, Mellander L, Nysom K, Ringden O, Schroeder H, Glomstein A, et al. Allogeneic bone marrow transplantation in first remission for children with very high-risk acute lymphoblastic leukemia: a retrospective case-control study in the Nordic countries. *Nordic Society for Pediatric Hematology and Oncology (NOPHO). Bone Marrow Transplant.* 1996;**17**(3):357-63. [PubMed: 8704687].
20. Silverman LB, Stevenson KE, O'Brien JE, Asselin BL, Barr RD, Clavell L, et al. Long-term results of Dana-Farber Cancer Institute ALL Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1985-2000). *Leukemia.* 2010;**24**(2):320-34. doi: 10.1038/leu.2009.253. [PubMed: 20016537].
21. Mann G, Attarbaschi A, Schrappe M, De Lorenzo P, Peters C, Hann I, et al. Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-lineage-leukemia (MLL)-rearranged acute lymphoblastic leukemia: results from the Interfant-99 Study. *Blood.* 2010;**116**(15):2644-50. doi: 10.1182/blood-2010-03-273532. [PubMed: 20592248].
22. Dreyer ZE, Dinndorf PA, Camitta B, Sather H, La MK, Devidas M, et al. Analysis of the role of hematopoietic stem-cell transplantation in infants with acute lymphoblastic leukemia in first remission and MLL gene rearrangements: a report from the Children's Oncology Group. *J Clin Oncol.* 2011;**29**(2):214-22. doi: 10.1200/JCO.2009.26.8938. [PubMed: 21135279].
23. Schultz KR, Bowman WP, Aledo A, Slayton WB, Sather H, Devidas M, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. *J Clin Oncol.* 2009;**27**(31):5175-81. doi: 10.1200/JCO.2008.21.2514. [PubMed: 19805687].
24. Balduzzi A, De Lorenzo P, Schrauder A, Conter V, Uderzo C, Peters C, et al. Eligibility for allogeneic transplantation in very high risk childhood acute lymphoblastic leukemia: the impact of the waiting time. *Haematologica.* 2008;**93**(6):925-9. doi: 10.3324/haematol.12291. [PubMed: 18413892].
25. Mullighan CG, Jeha S, Pei D, Payne-Turner D, Coustan-Smith E, Roberts KG, et al. Outcome of children with hypodiploid ALL treated with risk-directed therapy based on MRD levels. *Blood.* 2015;**126**(26):2896-9. doi: 10.1182/blood-2015-09-671131. [PubMed: 26527677].
26. Schultz KR, Carroll A, Heerema NA, Bowman WP, Aledo A, Slayton WB, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. *Leukemia.* 2014;**28**(7):1467-71. doi: 10.1038/leu.2014.30. [PubMed: 24441288].
27. Van der Velden VH, Corral L, Valsecchi MG, Jansen MW, De Lorenzo P, Cazzaniga G, et al. Prognostic significance of minimal residual disease in infants with acute lymphoblastic leukemia treated within the Interfant-99 protocol. *Leukemia.* 2009;**23**(6):1073-9. doi: 10.1038/leu.2009.17. [PubMed: 19212338].
28. Borowitz MJ, Wood BL, Devidas M, Loh ML, Raetz EA, Salzer WL, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. *Blood.* 2015;**126**(8):964-71. doi: 10.1182/blood-2015-03-633685. [PubMed: 26124497].
29. Schrappe M, Hunger SP, Pui CH, Saha V, Gaynon PS, Baruchel A, et al. Outcomes after induction failure in childhood acute lymphoblastic leukemia. *N Engl J Med.* 2012;**366**(15):1371-81. doi: 10.1056/NEJMoai10169. [PubMed: 22494120].
30. Schultz KR, Devidas M, Bowman WP, Aledo A, Slayton WB, Sather H, et al. Philadelphia chromosome-negative very high-risk acute lymphoblastic leukemia in children and adolescents: results from Children's Oncology Group Study AALL0031. *Leukemia.* 2014;**28**(4):964-7. doi: 10.1038/leu.2014.29. [PubMed: 24434862].
31. Nachman JB, Heerema NA, Sather H, Camitta B, Forestier E, Harrison CJ, et al. Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia. *Blood.* 2007;**110**(4):1112-5. doi: 10.1182/blood-2006-07-038299. [PubMed: 17473063].
32. Mehta PA, Eapen M, Zhang MJ, He W, Seber A, Kitko CL, et al. Transplant Outcomes for Children with Hypodiploid Acute Lymphoblastic Leukemia: The Cibmtr Experience. *Biol Blood Marrow Transplant.* 2014;**20**(2):S87. doi: 10.1016/j.bbmt.2013.12.110.
33. Mehta PA, Zhang MJ, Eapen M, He W, Seber A, Gibson B, et al. Transplantation Outcomes for Children with Hypodiploid Acute Lymphoblastic Leukemia. *Biol Blood Marrow Transplant.* 2015;**21**(7):1273-7. doi: 10.1016/j.bbmt.2015.04.008. [PubMed: 25865650].
34. Schlieben S, Borkhardt A, Reinisch I, Ritterbach J, Janssen JW, Ratei R, et al. Incidence and clinical outcome of children with BCR/ABL-positive acute lymphoblastic leukemia (ALL). A prospective RT-PCR study based on 673 patients enrolled in the German pediatric multicenter therapy trials ALL-BFM-90 and CoALL-05-92. *Leukemia.* 1996;**10**(6):957-63. [PubMed: 8667652].
35. Arico M, Schrappe M, Hunger SP, Carroll WL, Conter V, Galimberti S, et al. Clinical outcome of children with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia treated between 1995 and 2005. *J Clin Oncol.* 2010;**28**(31):4755-61. doi: 10.1200/JCO.2010.30.1325. [PubMed: 20876426].
36. Arico M, Valsecchi MG, Camitta B, Schrappe M, Chesselis J, Baruchel A, et al. Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. *N Engl J Med.* 2000;**342**(14):998-1006. doi: 10.1056/NEJM200004063421402. [PubMed: 10749961].
37. Pulsipher MA, Bader P, Klingebiel T, Cooper LJ. Allogeneic transplantation for pediatric acute lymphoblastic leukemia: the emerging role of peritransplantation minimal residual disease/chimerism monitoring and novel chemotherapeutic, molecular, and immune approaches aimed at preventing relapse. *Biol Blood Marrow Transplant.* 2009;**15**(1 Suppl):62-71. doi: 10.1016/j.bbmt.2008.11.009. [PubMed: 19147081].
38. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol.* 2012;**30**(14):1663-9. doi: 10.1200/JCO.2011.37.8018. [PubMed: 22412151].
39. Goldberg JM, Silverman LB, Levy DE, Dalton VK, Gelber RD, Lehmann L, et al. Childhood T-cell acute lymphoblastic leukemia: the Dana-Farber Cancer Institute acute lymphoblastic leukemia consortium experience. *J Clin Oncol.* 2003;**21**(19):3616-22. doi: 10.1200/JCO.2003.10.116. [PubMed: 14512392].
40. Einsiedel HG, von Stackelberg A, Hartmann R, Fengler R, Schrappe M, Janka-Schaub G, et al. Long-term outcome in children with relapsed ALL by risk-stratified salvage therapy: results of trial acute lymphoblastic leukemia-relapse study of the Berlin-Frankfurt-Munster Group 87. *J Clin Oncol.* 2005;**23**(31):7942-50. doi: 10.1200/JCO.2005.01.1031. [PubMed: 16258094].
41. Burke MJ, Verneris MR, Le Rademacher J, He W, Abdel-Azim H, Abraham AA, 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**(12):2154-9. doi: 10.1016/j.bbmt.2015.08.023. [PubMed: 26327632].
42. Schrauder A, Reiter A, Gadner H, Niethammer D, Klingebiel T, Kremens B, et al. Superiority of allogeneic hematopoietic stem-cell transplantation compared with chemotherapy alone in high-risk childhood T-cell acute lymphoblastic leukemia: results from ALL-BFM 90 and 95. *J Clin Oncol.* 2006;**24**(36):5742-9. doi: 10.1200/JCO.2006.06.2679. [PubMed: 17179108].
43. Wood BL, Winter SS, Dunsmore KP, Devidas M, Chen S, Asselin BL, et

- al. T-lymphoblastic leukemia (T-ALL) shows excellent outcome, lack of significance of the early thymic precursor (ETP) immunophenotype, and validation of the prognostic value of end-induction minimal residual disease (MRD) in Children's Oncology Group (COG) Study AALL0434. *Blood*. 2014;**124**(21):1.
44. Coustan-Smith E, Mullighan CG, Onciu M, Behm FG, Raimondi SC, Pei D, et al. Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia. *Lancet Oncol*. 2009;**10**(2):147-56. doi: [10.1016/S1470-2045\(08\)70314-0](https://doi.org/10.1016/S1470-2045(08)70314-0). [PubMed: [19147408](https://pubmed.ncbi.nlm.nih.gov/19147408/)].
  45. Pui CH, Gaynon PS, Boyett JM, Chessells JM, Baruchel A, Kamps W, et al. Outcome of treatment in childhood acute lymphoblastic leukaemia with rearrangements of the 11q23 chromosomal region. *Lancet*. 2002;**359**(9321):1909-15. doi: [10.1016/S0140-6736\(02\)08782-2](https://doi.org/10.1016/S0140-6736(02)08782-2). [PubMed: [12057554](https://pubmed.ncbi.nlm.nih.gov/12057554/)].
  46. Biondi A, Cimino G, Pieters R, Pui CH. Biological and therapeutic aspects of infant leukemia. *Blood*. 2000;**96**(1):24-33. [PubMed: [10891426](https://pubmed.ncbi.nlm.nih.gov/10891426/)].
  47. Hilden JM, Dinndorf PA, Meerbaum SO, Sather H, Villaluna D, Heerema NA, et al. Analysis of prognostic factors of acute lymphoblastic leukemia in infants: report on CCG 1953 from the Children's Oncology Group. *Blood*. 2006;**108**(2):441-51. doi: [10.1182/blood-2005-07-3011](https://doi.org/10.1182/blood-2005-07-3011). [PubMed: [16556894](https://pubmed.ncbi.nlm.nih.gov/16556894/)].
  48. Sanders JE, Im HJ, Hoffmeister PA, Gooley TA, Woolfrey AE, Carpenter PA, et al. Allogeneic hematopoietic cell transplantation for infants with acute lymphoblastic leukemia. *Blood*. 2005;**105**(9):3749-56. doi: [10.1182/blood-2004-08-3312](https://doi.org/10.1182/blood-2004-08-3312). [PubMed: [15637143](https://pubmed.ncbi.nlm.nih.gov/15637143/)].
  49. Borowitz MJ, Devidas M, Hunger SP, Bowman WP, Carroll AJ, Carroll WL, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood*. 2008;**111**(12):5477-85. doi: [10.1182/blood-2008-01-132837](https://doi.org/10.1182/blood-2008-01-132837). [PubMed: [18388178](https://pubmed.ncbi.nlm.nih.gov/18388178/)].
  50. Pui CH, Campana D, Evans WE. Childhood acute lymphoblastic leukaemia-current status and future perspectives. *Lancet Oncol*. 2001;**2**(10):597-607. doi: [10.1016/S1470-2045\(01\)00516-2](https://doi.org/10.1016/S1470-2045(01)00516-2). [PubMed: [11902549](https://pubmed.ncbi.nlm.nih.gov/11902549/)].
  51. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med*. 2006;**354**(2):166-78. doi: [10.1056/NEJMra052603](https://doi.org/10.1056/NEJMra052603). [PubMed: [16407512](https://pubmed.ncbi.nlm.nih.gov/16407512/)].
  52. Schrappe M, Valsecchi MG, Bartram CR, Schrauder A, Panzer-Grumayer R, Moricke A, et al. Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study. *Blood*. 2011;**118**(8):2077-84. doi: [10.1182/blood-2011-03-338707](https://doi.org/10.1182/blood-2011-03-338707). [PubMed: [21795999](https://pubmed.ncbi.nlm.nih.gov/21795999/)].
  53. Mullighan CG, Su X, Zhang J, Radtke I, Phillips LA, Miller CB, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. *N Engl J Med*. 2009;**360**(5):470-80. doi: [10.1056/NEJMoa0808253](https://doi.org/10.1056/NEJMoa0808253). [PubMed: [19129520](https://pubmed.ncbi.nlm.nih.gov/19129520/)].
  54. Mullighan CG. Genomic profiling of B-progenitor acute lymphoblastic leukemia. *Best Pract Res Clin Haematol*. 2011;**24**(4):489-503. doi: [10.1016/j.beha.2011.09.004](https://doi.org/10.1016/j.beha.2011.09.004). [PubMed: [22127311](https://pubmed.ncbi.nlm.nih.gov/22127311/)].
  55. Den Boer ML, van Slegtenhorst M, De Menezes RX, Cheok MH, Buijs-Gladdines JG, Peters ST, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. *Lancet Oncol*. 2009;**10**(2):125-34. doi: [10.1016/S1470-2045\(08\)70339-5](https://doi.org/10.1016/S1470-2045(08)70339-5). [PubMed: [19138562](https://pubmed.ncbi.nlm.nih.gov/19138562/)].
  56. Loh ML, Zhang J, Harvey RC, Roberts K, Payne-Turner D, Kang H, et al. Tyrosine kinome sequencing of pediatric acute lymphoblastic leukemia: a report from the Children's Oncology Group TARGET Project. *Blood*. 2013;**121**(3):485-8. doi: [10.1182/blood-2012-04-422691](https://doi.org/10.1182/blood-2012-04-422691). [PubMed: [23212523](https://pubmed.ncbi.nlm.nih.gov/23212523/)].