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

Neel S. Bhatt,[1] Rachel Phelan,[1] and Michael J. Burke[1,*]

[1]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

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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 stratification. 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 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 multiagent 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.

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

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

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

3. Results

3.1. Primary Induction Failure

Primary Induction Failure (PIF) is rarely seen in pediatrics given current ALL therapy and is typically reported 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 ± 12% vs. 35 ± 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 ± 9% vs. 45 ± 8% vs. 26 ± 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 (≤ 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 + 12% for chemotherapy only patients in Cohort 5 (receiving continuous imatinib) compared to 65 + 11% for patients receiving related donor HSCT and 59 + 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 μL/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 multicenter 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 Valden 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.

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