EVIDENCE-BASED MINIREVIEW

What is the role for HSCT or immunotherapy in pediatric hypodiploid B-cell acute lymphoblastic leukemia?

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LEARNING OBJECTIVES

- Understand the role of hematopoietic stem cell transplantation in pediatric patients with hypodiploid acute lymphoblastic leukemia (ALL)
- Understand the rationale for immunotherapy and the need for clinical trials of novel therapies in hypodiploid B-cell ALL

Clinical case

A 6-year-old boy was diagnosed with B-cell acute lymphoblastic leukemia and received induction chemotherapy on an institutional protocol. Cytogenetic analysis of the leukemic blasts revealed hypodiploidy (near haploid; 25 chromosomes); no other high-risk disease or patient characteristics were present. End-of-induction disease response showed complete remission, with minimal residual disease (MRD) by flow cytometry of 0.018%. The patient was risk stratified to high-risk therapy and received consolidation chemotherapy, after which MRD remained detectable at 0.039%. What is the role for hematopoietic stem cell transplantation or another immunotherapeutic approach for this patient?

Introduction

Pediatric hypodiploid acute lymphoblastic leukemia (ALL) is a rare subtype (<5% of B-cell ALLs [B-ALLs]) associated with adverse prognosis, with reported 5-year event-free-survival (EFS) of 50% to 55% overall.[1-4] Outcomes are increasingly dismal with decreasing modal chromosome number, with 5-year EFS as low as 30% in some subsets.[1-4] Subsets of hypodiploid ALL categorized by chromosome number carry distinct genetic lesions that may contribute to greater risk of treatment failure and/or toxicity, including mutations in *TP53*, *RB1*, and *IKZF2*, recurrent in low hypodiploid ALL with 32 to 39 chromosomes, and *IKZF3* and alterations in RAS and receptor tyrosine kinase signaling, recurrent in near-haploid ALL with 24 to 31 chromosomes.[5,6] Furthermore, increased incorporation of upfront response monitoring by minimal residual disease (MRD) testing has demonstrated that end-of-induction (EOI) MRD is more common and significantly decreases survival in hypodiploid ALL.[3-5] This suggests that chemotherapy resistance may play a role in poor outcomes, raising the question of whether immune-based approaches could improve responses and potentially avoid toxicity associated with *TP53* mutations, which can be germline in a significant fraction of pediatric patients. Because of its extremely poor prognosis, attempts to improve survival in hypodiploid ALL through empiric intensification of therapy have been employed, including allogeneic hematopoietic stem cell transplantation (HSCT) in first complete remission (CR1). We will review the evidence for HSCT and other immunotherapies in hypodiploid ALL.

Allogeneic HSCT for hypodiploid ALL

Randomized trials evaluating the efficacy of allogeneic HSCT compared with standard therapy for pediatric patients with hypodiploid ALL in CR1 are lacking, given the rarity of this disease subset and the poor outcomes with chemotherapy alone, making randomization undesirable. Using data submitted to the Center for International Blood and Marrow Transplant Research, Mehta et al[7] reported on 78 pediatric patients with hypodiploid B-ALL who underwent HSCT (CR1, 55%; CR2, 38%) between the years 1990

Table 1. Studies of empiric allogeneic HSCT in the treatment of pediatric hypodiploid ALL

Study	Design	Study years	Population, N (n with HSCT)	CR (% of patients)	Median age (range), y	N of chromosomes (% of patients)	EOI MRD (% of patients)	Outcomes (95% CI)
Mehta et al[7] (CIBMTR)	Retrospective, nonrandomized, multicenter	1990-2010	78 (78)	CR1 (55)	10 (3-18)	≤43 (50)	NR	5-y LFS: 51% ≤43 ch, 37% (23-51) vs 44-45, 64% (48-76); *P* = .01
				CR2 (38)		44 (15)		5-y OS: 56% ≤43 ch, 38% (24-52) vs 44-45, 71% (56-82); *P* = .001
				CR3 (7)		45 (35)		
Pui et al[4] (Ponte di Legno)	Retrospective, nonrandomized, multicenter	1997-2013	272 (42 of 228)*	CR1 (100)	9.8 (0.6-19.5)	25-29 (37) 30-39 (43) 40-43 (5) 44 (15)	$<10^{-4}$ (54)	5-y EFS: 55.1% (49.3-61.5)
							10^{-4}-10^{-3} (16)	Favorable: 44 ch, 74% (61-89); *P* = .021
							$\geq 10^{-3}$ (30)	MRD $<10^{-4}$, 75% (66-85); *P* = .003
								5-y DFS: HSCT vs no HSCT*: 59.8% (45.7-78.2) vs 53% (45.9-61.2); *P* = .47 MRD $<10^{-4}$: 70% (46.7-100) vs 73.6% (63.3-85.7); *P* = .81 MRD $\geq 10^{-3}$: 55.9% (37.2-84) vs 40.3% (27.2-59.7); *P* = .29 30-39 ch, 63.5 (43.2-93.3) vs 61.6 (51.8-73.1); *P* = .89 25-29 ch, 50.8 (32.5-79.4) vs 44 (34.2-56.6); *P* = .60
								5-y OS: HSCT vs no HSCT*: 68.9% (55.8-85.2) vs 57.7% (50.7-65.7); *P* = .21
McNeer et al[2] (COG)	Retrospective, nonrandomized, multicenter	2003-2011	131 (61 of 113)	CR1 (100)	10 (1-30)†	25-29 (42) 30-39 (36) 40-43 (2) Masked (20)	<0.01% (68)	5-y EFS: 52.2% ± 4.9%
							≥0.01%, 32%	HSCT vs no HSCT: 56.4% ± 7.3% vs 48.8% ± 7.8%; *P* = .62 NCI SR: 68.8% ± 10.3% vs 57.1% ± 13.2%; *P* = .64 NCI HR: 48.3% ± 9.0% vs 44.4% ± 9.2%; *P* = .75 MRD <0.01%: 66.3% ± 7.9% vs 60.3 ± 9.2%; *P* = .77 MRD ≥0.01%: 29.4% ± 14.3% vs 16.7% ± 10.8%; *P* = .67
								5-y OS: 58.9% ± 4.8% HSCT vs no HSCT: 65.6% ± 6.9% vs 53.8% ± 7.8%; *P* = .32

ch, chromosomes; CI, confidence interval; CIBMTR, Center for International Blood and Marrow Transplant Research; COG, Children's Oncology Group; DFS, disease-free survival; HR, high risk (age ≥10 y or white blood cell count ≥50,000/μL); LFS, leukemia-free survival; NCI, National Cancer Institute; NR, not reported; SR, standard risk (age 1 to <10 y and white blood cell count <50 x 10^3/μL).
*HSCT analyses limited to patients with <44 chromosomes.
†Age range eligible for study (actual age range not reported).

and 2010. Overall survival (OS) for the entire cohort was similar to that in prior reports (Table 1), and modal number of chromosomes significantly affected both 5-year OS (≤43: 38%; 95% CI, 24-52 vs 44-45: 71%; 95% CI, 56-82; *P* = .001) and leukemia-free survival (≤43: 37%; 95% CI, 23-51 vs 44-45: 64%; 95% CI, 48-76; *P* = .01), when adjusting for both CR number and transplantation era.[7] Although these data suggest those with higher modal number of chromosomes fare well with HSCT, this subset also fares better with chemotherapy alone. Therefore, improved survival post-HSCT may not be attributable to HSCT.

Relapsed hypodiploid ALL portended a significantly worse prognosis (mortality hazard ratio for CR2/3 vs CR1, 2.28; 95% CI, 1.02-5.10; *P* = .04); while expected, this suggests hypodiploid ALL is exceedingly difficult to salvage. The authors acknowledged the limitations of modest sample size, only including patients who achieved CR and were candidates for HSCT, and lack of EOI MRD response risk stratification. Conclusions regarding superiority of undergoing consolidative HSCT compared with receiving chemotherapy alone cannot be drawn from this study.

Does HSCT improve outcomes over chemotherapy alone?

More recently, reports on 2 larger cohorts of pediatric patients with hypodiploid ALL included comparative analyses of consolidative HSCT in CR1 or chemotherapy alone. The first included 272 evaluable patients treated among 16 cooperative groups/institutions between the years 1997 and 2013 (Ponte di Legno Childhood ALL Working Group).[4] Among 228 patients with <44 chromosomes, 18% underwent HSCT in CR1, and the remainder received chemotherapy alone. Between these 2 cohorts, no significant difference was seen in adjusted 5-year DFS or OS (Table 1). Importantly, HSCT did not significantly affect DFS, regardless of high-risk features, including EOI MRD and ploidy. However, MRD-stratified protocols were associated with improved EFS and OS.[4] The COG reported on 131 patients with hypodiploid ALL treated from 2003 to 2011, 113 of whom were evaluable for impact of consolidative HSCT in CR1 (n = 61) vs chemotherapy alone (n = 52).[2] HSCT did not confer a survival advantage (Table 1), including in subgroup analyses using National Cancer Institute risk group and EOI MRD. Notably, patients in the HSCT cohort had a higher incidence of secondary malignant neoplasms.[2] Although germline *TP53* mutations were not evaluated in this study, >90% of patients with low hypodiploid ALL harbor *TP53* mutations, nearly half of which may be germline, underscoring the importance of critically evaluating the role of HSCT in populations that may have higher toxicity risk.[6] Both studies adjusted for time to HSCT to partially mitigate the selection bias inherent to nonrandomized studies of HCST, which necessitate patients achieving and maintaining CR.

Although HSCT has been shown to improve outcomes for subsets of patients with ALL with poor-risk features, the large international, multicenter studies demonstrate that HSCT in CR1 does not significantly improve outcomes for pediatric patients with hypodiploid ALL.[2,4] Despite these 2 larger patient cohorts, analyses regarding the role of empiric HSCT are likely still underpowered as a result of the rarity of this disease subtype. Collectively, these data highlight that EOI MRD may be a useful indicator of leukemic chemosensitivity. Therefore, empiric intensification of existing therapies is likely not needed for patients who achieve MRD^- status nor effective for MRD^+ patients; alternative approaches with distinct mechanisms of action are needed.

Immunotherapy: beyond HSCT

Although allogeneic HSCT is an effective immunotherapy for many patients, it is not curative for all, particularly subgroups of patients with persistent MRD at the time of HSCT. Chemorefractory leukemias may be responsive to the immune surveillance provided by allogeneic HSCT, but aggressive leukemias with detectable disease at the time of HSCT may not tolerate the delay in immune surveillance before donor T-cell engraftment. Increased resistance to HSCT may also be in part due to increased inherent capability of mutagenesis and acquisition of immune escape mechanisms. As we strive to improve outcomes for hypodiploid ALL, targeted immunotherapeutic approaches could provide an alternative treatment strategy with increased benefit in these high-risk patients. More contemporary immunotherapeutic strategies specifically target leukemic cells, often through recognition of tumor-associated antigens in conjunction with an effector cell–mediated response. Many of these therapies have seen great success, particularly CD19-specific chimeric antigen receptor (CAR) T-cell therapy for the treatment of pediatric $CD19^+$ B-ALL.[8-10] Although data are limited in rare subsets, an analysis of outcomes with the CD19 CAR T-cell therapies CTL019 and CTL119 demonstrated similar outcomes for ALL with high-risk cytogenetics, including hypodiploidy, which accounted for 3.5% of the cohort of 231 patients, relative to other cytogenetic subgroups.[11] Similarly, a retrospective study of the CD22 antibody-drug conjugate inotuzumab in relapsed/refractory pediatric ALL included hypodiploidy (6% of the cohort of 51) and found no predictive effect of cytogenetic subtype on response.[12] However, as with chemotherapy and HSCT, remission is not attainable or durable for all patients, likely in part due to inherent leukemic resistance and/or mutagenicity. Mutagenic leukemic clones may have a higher risk of developing immune escape after antigen-directed therapy. With current data, it is impossible to draw conclusions yet regarding the role of these newer immunotherapeutic modalities for hypodiploid ALL, because the number of reported patients treated thus far is quite limited. Both strategies are being studied in the frontline setting in clinical trials that include hypodiploid ALL. A single-center single-arm trial is investigating CTL019 for indications not previously studied, including hypodiploid ALL (registered at www.clinicaltrials.gov as #NCT04276870). The current frontline COG trial for de novo high-risk B-ALL, AALL1732 (registered at www.clinicaltrials.gov as #NCT03959085), is randomly assigning patients to standard chemotherapy or the intercalation of inotuzumab into the chemotherapy backbone. Although sample size is likely to remain limiting, by offering therapies with mechanisms of action distinct from those of cytotoxic chemotherapy, these studies have the potential to provide improved outcomes and valuable insights into the resistance of hypodiploid ALL to current standard therapies.

Conclusion

Pediatric hypodiploid ALL is a high-risk disease subtype, with continued poor outcomes despite intensification of both upfront and relapse therapies. The use of empiric allogeneic HSCT in CR1 has not proven to add a survival benefit for this patient population. However, improvements have been reported with risk-stratified protocols based on EOI MRD response, which remains highly predictive of outcome in this subtype. Using modal chromosome number, genomics, and EOI MRD, patients with hypodiploid ALL can be categorized into distinct biologic subsets with different responses to traditional therapies. This may allow for the opportunity to evaluate the role of newer treatment strategies, including immunotherapy, for patients with the worst predicted outcomes. The rarity of such subgroups necessitates continued collaboration and prospective study to sufficiently power analyses and gain further biologic insight into this difficult-to-treat patient population.

Recommendations

1. MRD response is prognostic and can guide treatment considerations in pediatric hypodiploid ALL (grade 1A).
2. There is insufficient evidence to recommend HSCT for all children with hypodiploid ALL in CR1 (grade 2C).
3. Novel immunotherapies, such as CD19 CAR T cells and inotuzumab, with strong evidence of efficacy in the relapsed/refractory setting can be considered for hypodiploid ALL with poor MRD response in the context of a clinical trial (grade 2D).

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Off-label drug use

CTL019 and inotuzumab are investigational in the frontline setting.

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