EVIDENCE-BASED MINIREVIEW

Should posttransplant cyclophosphamide be considered standard of care for pediatric transplantation of acute leukemia?

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LEARNING OBJECTIVES

- Examine the adult experience for haploidentical stem cell transplant with PTCy and how it informs its application to pediatric patients
- Compare survival outcomes and incidence of GVHD in pediatric regimens using PTCy to the current standard or care for GVHD prophylaxis

CLINICAL CASE

A 7-year-old female diagnosed with CRLF2-positive pre-B acute lymphoblastic leukemia showed persistent disease at the end of consolidation. Complete remission followed treatment with blinatumomab, and the patient is referred for stem cell transplant. There are no siblings. Donor registry search identifies a single 10/10 human leukocyte antigen matched unrelated donor (MUD), but the donor is unavailable for 2 months. Both parents are healthy and in their thirties. Who is the preferred donor? Select the unrelated donor but risk disease recurrence while waiting, or select a haploidentical parent and proceed to transplant immediately using posttransplant cyclophosphamide (PTCy)?

Introduction

Hematopoietic stem cell transplantation (HSCT) can be a curative option for pediatric high-risk hematologic malignancies. Its use, however, still poses considerable logistical concerns and risks. Prompt identification and availability of a suitable donor can determine whether the patient undergoes transplantation free of minimal residual disease, a state recognized to impact posttransplant relapse. No less important, the HLA match between donor and patient influences the risk for severe acute and chronic graft-versus-host disease (GVHD). The need to address the dual mandate for timely donor access and prevention of GVHD has led to clinical trials utilizing haploidentical donors and incorporating PTCy for GVHD prophylaxis.

The Children's Oncology Group in clinical trials has favored a calcineurin inhibitor and methotrexate (CNI+MTX) for GVHD prevention. Now, with the emergence of haploidentical transplants using PTCy, the value of this treatment for children in need of transplantation must be determined. In this evidence-based mini-review, we assess the clinical experience and outcomes for PTCy and how this approach may relate to future transplantation in pediatric patients with hematologic malignancies.

What can we learn about PTCy from adult HSCT trials?

Reports suggest that the outcomes for adults with hematologic malignancies transplanted from haploidentical donors utilizing PTCy are comparable to MRD/MUD or mismatched donor transplants using CNI-based GVHD prophylaxis. The seminal randomized trial, BMT CTN 1101, compared outcomes for adult patients with lymphoma or acute leukemia following reduced intensity conditioning (RIC) and either a double umbilical cord blood with cyclosporine and mycophenolate mofetil (MMF) for GVHD prophylaxis or a haploidentical transplant with PTCy, tacrolimus, and MMF. GVHD outcomes were comparable, but overall survival (OS) was superior in the haplo-PTCy group (46% OS with double umbilical cord blood vs 57% OS with haplo-PTCy, $P = 0.037$).[1]

PTCy has not been limited to transplantation from haplo-donors. For example, in the BMT CTN 1703 trial, adults with high-risk hematologic malignancy with a matched related/unrelated or 7/8 mismatched unrelated donor underwent RIC and peripheral blood stem cell

(PBSC) infusion and were randomized to either CNI+MTX or PTCy, tacrolimus, and MMF. There was no difference in relapse or OS at 1 year, but the PTCy group experienced significantly superior GVHD-free, relapse-free survival (GRFS) (52.7% vs 34.5%), largely due to less acute and chronic GVHD.[2] Following a similar design, the HOVON-96 trial prospectively analyzed adult patients, receiving nonmyeloablative conditioning for hematologic malignancies with 8/8 MUDs or matched sibling donors (MSDs). One-year GRFS was 45% vs 21% in favor of PTCy[3] over cyclosporine and MMF as prophylaxis. Again, superior GRFS was attributed to the lower incidence of acute and chronic GVHD. The BMT CTN 1301 trial for adults with hematologic malignancies and MRD/MUD donors showed similar OS and chronic GVHD following myeloablative conditioning with either PTCy+tacrolimus+MMF or CNI+MTX, as GVHD prophylaxis.[4] When comparing outcomes of haplo-transplant to MUD transplant following myeloablative conditioning (MAC) with PTCy, CIBMTR registry data found no difference for OS, disease-free survival, or relapse rate, but a higher incidence of acute and chronic GVHD for patients transplanted from haploidentical donors.[5]

What are the strategies to decrease GVHD in pediatric HSCT?

The likelihood of identifying a matched related donor is less than 25%, and the focus for pediatric patients in emergent need of transplant has been on selecting the best alternative donor and proceeding immediately to transplant. Keating et al reported that for pediatric patients with acute myeloid leukemia the OS, leukemia free survival, and relapse rate (63%, 57%, and 22%, respectively) were similar whether selecting an matched related donor, an MUD, or a umbilical cord blood.[6] Chronic GRFS following umbilical cord blood and MRD transplantation was superior to MUD transplant, but the use of cord blood may be limited by other transplant considerations. Locatelli et al reported OS, LFS, and relapse rates (72% [68% for acute myeloid leukemia], 71% and 24%, respectively) for pediatric patients with acute leukemia receiving haploidentical transplants utilizing the GVHD prevention strategy of αβ T-cell and B-cell depleted grafts, outcomes that are comparable to those reported by Keating. When this cohort was compared to a cohort of similar patients transplanted from MRD or MUD, no difference was found for 5-year LFS and GRFS of 71%.[7] Despite these promising findings, αβ T-cell and B-cell depletion has limited application, lacking FDA approval and the need for institutional expertise to implement.

For children with high-risk malignancy and the immediate need of a donor, haploidentical transplant with PTCy may be the best alternative. To date, there are no randomized trials comparing haploidentical transplant with PTCy to standard of care, but results from nonrandomized trials are supportive. For example, two studies of pediatric and young adult patients with hematologic malignancies receiving nonmyeloablative conditioning followed by haplo-transplant and PTCy demonstrated low rates of nonrelapse mortality and acute and chronic GVHD, with OS and event-free survival (EFS) up to 56% and 46%, respectively.[8,9]

In a single-center study, children with hematologic malignancies received MAC followed by haploidentical HSCT with PTCy, calcineurin inhibitor, and MMF. OS was 70.5% and disease-free survival was 64.7%, with low incidence of acute GVHD and chronic GVHD.[10] A multicenter, prospective study evaluating outcomes for haploidentical transplant and PTCy with MAC enrolled children with high-risk hematologic malignancies and reported that no patient developed grade III-IV acute GVHD and the cumulative incidence of moderate to severe cGVHD at 1 year was 4%.[11] Additionally, 1-year OS and EFS were 77% and 68%, respectively, with a 0% treatment-related mortality (TRM). These promising outcomes and the practicality of using PTCy make it an option for centers that are unable to perform the aforementioned αβ T-cell depletion.

Further experience with PTCy for children in need of HSCT

The European Society for Bone Marrow Transplantation reported on 180 children with acute lymphoblastic leukemia receiving haploidentical transplant and PTCy. Patients received either MAC or RIC regimens and marrow or PBSC products. The reported incidence of grade III-IV aGVHD was 12.4%, and 2-year extensive cGVHD incidence was 9.5%,[12] but TRM was high at 19.6%. It is possible that PBSC, in contrast to marrow grafts, contributed to TRM. The use of bone marrow grafts may reduce TRM and improve EFS. Patients without active disease at the time of transplant also fared better.[12] In other reports, the incidence of grade III-IV GVHD for children receiving haplo-transplants with PTCy following MAC

Table 1. Comparison of haploidentical stem cell transplant outcomes using PTCy for pediatric hematologic malignancies

Reference	N	Donor type	Disease	Grade I-II aGVHD	Grade III-IV aGVHD	Mod-severe cGVHD	Graft failure	TRM	Relapse	EFS
Fierro et al (2023)[11]	32	Haplo (BM)	AL/MDS	13%	0%	4%	9%	0%	32%	68%
Symons et al (2020)[14]	29	Haplo	AL/MDS	17%	4%	14%	N/A	7%	28%	69%
Sharma et al (2021)[10]	17	Haplo (PBSC)	AL	12%	12%	18%	5.8%	5.8%	29%	64.7%
Srinivasan et al (2022)[15]	26	Haplo (PBSC)	Heme malignancy	N/A	11.5%	9.2%	3.8%	0%	19.3%	73.8%
Hong et al (2022)[16]	35	Haplo (PBSC)	AL	34.3%	2.9%	11.4%	0%	0%	25.6%	74.4%

AL, acute leukemia; BM, bone marrow; haplo, haploidentical; TRM, treatment related mortality.

regimens ranges from 0%-12% and the incidence of cGVHD from 4%-18%. The EFS, at 65%-74%, is reassuring and TRM is acceptable at 0%-7%[10,11,14-16] (Table 1). The overall experience for children undergoing PTCy haploidentical transplant compares favorably to outcomes for transplantation employing other donor options and other GVHD prophylaxis.

Just as for adults, this experience has extended the use of PTCy to alternative donor transplants in children and young adults. A recently published phase 2 study evaluated young adults and adults with 7/8 or 8/8 HLA-matched allogeneic transplants receiving MAC and PTCy, tacrolimus, and MMF for treatment of hematologic malignancy/myelodysplastic syndrome (MDS). There were no significant differences in survival outcomes between the 7/8 and 8/8 groups and overall low rates of severe cGVHD (5.5%) and grade III-IV aGVHD (5.5%).[13]

Although rates of relapse and acute and chronic GVHD have been the major focus, the use of PTCy has raised concern for delayed immune reconstitution and increased risk of infections, including cytomegalovirus and BK cystitis. These areas remain under active investigation, but no difference in infectious complications has been established.[14] Nor has it been shown that the incidence of cytomegalovirus reactivation is increased.[16]

Conclusions

HSCT with PTCy for adult patients receiving RIC regimens and PBSC products is safe and effective, and recent studies suggest that GVHD prophylaxis with PTCy is as effective as standard of care (CNI+MTX). While data are limited for children following transplantation from haploidentical donors with PTCy, results thus far show similar OS, EFS, and TRM compared to historical controls. Additionally, the occurrence of acute and chronic GVHD with PTCy compares favorably to that following MRD and MUD HSCT with CNI+MTX prophylaxis. Obviously, future efforts and time will define the true potential for using PTCy with close attention to the incidence of infectious complications, immune reconstitution, and late effects. Prospective studies comparing haploidentical PTCy outcomes to MUDs are an important area of investigation and will be addressed by the Children's Oncology Group ASCT2031 trial. Further studies are needed using PTCy with MUDs and MRDs and for transplantation of nonmalignant conditions. It must be acknowledged that should the FDA approve αβ T-cell depletion, this option warrants comparison to PTCy regimens. Finally, it is important to recognize that haplo-donors may not be interchangeable. Is there an advantage to selecting a haplo-sibling vs a haplo-parent? Is a younger haploidentical cousin a better donor than an aging parent? The results following haplo HSCT from second- and third-degree relatives suggest comparability to first-degree relatives.[17] For adults transplanted from haplo-donors after NMA conditioning, OS, PFS, and aGVHD statistically worsened with donor age.[18] Age has been recognized as a variable contributing to outcome. How age is integrated into donor selection for children and young adults undergoing HSCT will need further examination.

Recommendations for incorporation of PTCy in pediatric HSCT

1. Haploidentical transplant with PTCy should be considered for pediatric patients with high-risk malignancy when an MRD is not available to avoid unacceptable delays to treatment initiation and costs associated with procurement of unrelated donors (strong recommendation, moderate quality evidence).[11,14–17]
2. Post-transplant cyclophosphamide should replace the standard of care (CNI+MTX) for GVHD prophylaxis in pediatric patients with HLA-matched donors (weak recommendation, moderate quality evidence).[13]

Conflict-of-interest disclosure

Erin E. Doherty: no competing financial interests to declare.
Robert A. Krance: no competing financial interests to declare.

Off-label drug use

Erin E. Doherty: nothing to disclose.
Robert A. Krance: nothing to disclose.

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DOI 10.1182/hematology.2023000522