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Short Review

Feasibility and Outcome of Haploidentical Hematopoietic Stem Cell Transplant with Post-Transplantation Cyclophosphamide in High-Risk Malignancies in Children

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Abstract

The use of haploidentical hematopoietic stem cell transplantation with post-transplant cyclophosphamide (Haplo-PTCy) is increasing in adults, but also in children; this procedure is a good alternative for transplanting pediatric patients lacking a matched family donor; indeed, this is very relevant in regions with economic constraints or with a population which is not well represented in the international donor registries which make access to unrelated cord blood units or bone marrow donors difficult. However, it is still not clear which is the best conditioning regimen and the ideal cellular source in cases of children with high-risk hematological malignancies. In this short review, we summarize our experience with the use of Haplo-PTCY using a reduced-intensity conditioning regimen and peripheral blood as the stem cell source in 42 children with high-risk leukemia. We also compare and discuss the results obtained by other groups in children with high-risk malignancies. Although studies in children have been increasing, it is necessary to continue conducting more prospective studies with larger numbers of patients to define the intensity of the preparative regimen and the ideal cellular source in children with high-risk hematologic malignancies who undergo Haplo-PTCy with the aim to achieve tolerable toxicities and good survival rates.

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Introduction

Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) is an important curative therapy for children with high-risk leukemia; but, the lack of matched family donors represents a limiting factor in this group [1,2]. This issue is more relevant in regions with economic constraints or with a population which is not well represented in the international donor registries, both circumstances make access to unrelated cord blood units or bone marrow donors difficult. Haploidentical HSCT with post transplantation cyclophosphamide (Haplo-PTCy) is an alternative option for these patients; it is an effective and low-cost procedure that does not require any special technology for its implementation.

In children, myeloablative conditioning regimens are the recommended option; however, they are associated with several toxicities such as growth retardation, infertility, increased of mortality and secondary malignancies; these complications can be decreased with the use of a Reduced Intensity Conditioning (RIC) regimen [3]. The anti-tumor effect of these regimens plus a low rate of toxic deaths produces an encouraging good overall survival [4-6]. In a survey done by the EBMT Pediatric Diseases and Complications and Quality of Life WP [6], near 40% of 161 centers from 30 different countries reported the use of an RIC regimen for treating malignant diseases with acceptable outcomes. Other study reported by Saglio [7] compared the outcomes of Haplo-PTCy from transplantation with unrelated HLA-Matched Donor (MUD) and HLA Mismatched Unrelated Donor (MMUD) in children; the Haplo HSCT was based on the non-myeloablative conditioning regimen reported by Luznik et al. [8], while the patients undergoing MUD and MMUD HSCT were transplanted using a myeloablative conditioning. There were not any differences in main outcomes among the groups.

On the other hand, the use of Peripheral Blood Stem Cell Transplantation (PBSCT) has increased over the recent years, and now accounts for up to 32% of pediatric allogeneic hematopoietic cell transplantations [9]. A previous systematic review and meta-analysis comparing Bone Marrow Transplant (BMT) and PBSCT for hematologic malignancies in adults concluded that Overall Survival (OS) and incidence of relapse were comparable between BMT and PBSCT [10]. However, in the Haplo-PTCY setting the use of peripheral blood stem cells instead of bone marrow was associated with fewer relapses [11-13].

So, with the goal to decrease the toxicity but keeping a good antileukemic effect and a good engraftment rate, we decided to use in our Haplo-PTCy platform for transplanting children with high risk leukemia, a combination of an intermediate intensity regimen, instead of a truly non-myeloablative protocol as Johns Hopkins platform [14], and PBSC as the cellular source.

Our results were recently published [15]. In short, the conditioning regimen used was a combination of fludarabine 160 mg/m2, split in four days, busulfan 8 to 12 mg/kg split in two days, or melphalan 100-140 mg/m2 in one day, plus total body irradiation 200-400 cGy.

All patients received PT-Cy 50 mg/kg/day on days +3 and +4. Starting on day +5 mycophenolate and cyclosporine were given for 2 and 6 months respectively.

Forty-two patients less than 18 years of age with high-risk leukemia were transplanted; Twenty-six had Acute Lymphoblastic Leukemia (ALL), 13 acute myeloid leukemia, 2 juvenile myelomonocytic leukemia, and 1 blast crisis of chronic myeloid leukemia. Thirty three percent were in first remission (CR1), 50% in second (CR2), 14% in third (CR3), and 3% had refractory disease. Twenty one percent had positive Minimal Residual Disease (MRD) previous to transplant. Neutrophil recovery occurred in 100% of 40 patients alive at day+30, transplant-related mortality at 1 year was 14%. The median follow-up for surviving patients was 45 months, the incidence of acute Graft-Versus-Host Disease (aGVHD) grade II-IV was 43%, while grade III-IV was 17%. The percent of patients with moderate-severe chronic Graft-Versus-Host Disease (cGVHD) was 29%. Overall survival (OS) and Event-Free Survival (EFS) at 36 months for the entire cohort were 56% and 46%, respectively, while for patients in first remission it was 71% and 58%, respectively. Regarding the 9 patients who underwent transplant with positive MRD, 44% were alive in remission at the moment of the report.

In children there is a paucity of data regarding the outcomes of Haplo-PTCy; the majority of the studies included patients up to 21 years of age, have shorter follow-up periods, and report heterogeneous diseases [16-19], which makes it difficult to conclude about which is the best conditioning regimen and the ideal cellular source in cases of high-risk acute leukemia.

Ruggeri et al., [20] analyzed the outcomes of unmanipulated haploidentical transplantation using post-transplant cyclophosphamide in 180 pediatric patients with ALL; 69% of them were in CR1 or CR2, median age was 9 years, and the cellular source was PBSC in 36% of the transplants. The engraftment rate was near to 90%, the 100 days incidence of aGVHD II-IV was 28%, cGVHD at 2 years was 21,9% and the non-relapse mortality was 19%. The estimated 2-year EFS was 65%, 44% and 18,8% for patients transplanted in CR1, CR2 and CR3, respectively. In the multivariable analysis of patients in CR1 and CR2, disease status, age and use of PBSC were independent factors associated with decreased overall survival.

Johns Hopkins group has reported its experience with Haplo-PTCY in children and young adults using non-myeloablative [14] and myeloablative [21] conditioning in patients with different malignancies. In both groups the cellular source was mainly BM, 40 patients were given a non-myeloablative protocol and 45% of them had high risk leukemias. The incidence of aGVHD grade II-IV was 33%, whereas the cGVHD was 24%, transplant-related mortality at 1 year was 13% and the 1-year actuarial overall and event-free survival were 56% and 43%, respectively. The group who received a myeloablative preparative regimen consisted of 96 children and adults, from 1 to 60 years, median age 42 years, and 66% of them had acute leukemia. There is not a clear discrimination between children and adults in the results, however the EFS at 1 and 3 years was 57 and 49%, whereas the incidence of Transplant-Related Mortality (TRM) at 1 year was 11%. In table 1 there is a summary of the main series using Haplo-PTCY in children.

Reference	N	Cellular source	Disease	Conditioning	TRM	aGVHD II-IV	cGVHD	EFS	OS
Ruggeri et al. [20]	180	BM (64%)	ALL	RIC (23%)	7.8% (BM)	28.3%	21.9% @2 years	38.5% @2 years	50.8% @2 years
				MAC/chemo (52%)					
		PBSC (36%)		MAC/TBI (25%)	26.5% (PBSC)				
Klein et al. [14]	40	BM (95%)	ALL, AML, MDS, HL, NHL, MPAL, CML	RIC/TBI	13%	33%	24% @2 years	43% @1 year	56% @1 year
		PBSC (5%)							
Jaiswal et al. [16]	20	PBSC	ALL, AML	MAC	20% @1 year	35%	Reported as negligible	59% @2 years	64% @2 years
Gonzalez-Llano et al. [17]	25	PBSC	ALL, AML, CML	MAC	36% @2.2 months	43%	15%	33% @1 year	50% @1 year
Berger et al. [18]	33	BM (91%)	ALL, AML, MDS, CML, HL, NHL, dendritic cell leukemia	RIC (58%)	9% @1 year	22%	4%	61% @1 year	72% @1 year
		PBSC (9%)		MAC (42%)					
Sawada et al. [19]	15	BM (87%)	ALL, AML, MPAL, neuroblastoma	RIC		50%	50%		
		PBSC (13%)							
Trujillo et al. [15]	42	PBSC	ALL, AML, JMML, blast crisis CML	RIC/TBI	14% @1 year	43%	29% @1 year	46% @3 years	56% @3 years

Table 1: Main series using Haplo-PTCY in children.

BM: Bone Marrow, PBSC: Peripheral Blood Stem Cell, ALL: Acute Lymphoblastic Leukemia, AML: Acute Myeloid Leukemia, MDS: Myelodysplastic Syndrome, HL: Hodgkin Lymphoma, NHL: Non-Hodgkin Lymphoma, MPAL: Mixed-Pediatric Acute Leukemia, CML: Chronic Myeloid Leukemia, RIC: Reduced-Intensity Conditioning, MAC: Myeloablative Conditioning, TBI: Total Body Irradiation, TRM: Transplant-Related Mortality, aGVHD: acute Graft-Versus-Host Disease, cGVHD: chronic Graft-Versus-Host Disease, EFS: Event-Free Survival, OS: Overall Survival.

One of the problems with the use of Haplo-PTCY platform in children, is the incidence of acute and chronic GVHD; in our group it was of 43% and 29% [15], in the Ruggeri series [20] was 28% and 21.9%, and in the John Hopkins non myeloablative study [14] was 33% and 24%, respectively; this occurred despite most of the patients in the Ruggeri and Hopkins series were transplanted with bone marrow cells. Having this in mind, we make an amendment to our protocol: addition of anti-thymocyte globulin on days - 8 and -7, early introduction of cyclosporine before day +3, and harvesting of stem cells from the bone marrow [22]; we expect with these modifications, a reduction of acute and chronic GVHD.

In conclusion, the use of Haplo- PTCy in children with high-risk leukemia offers a very good alternative to patients without a well-matched donor. This is especially relevant in areas with economic constraints where the access to unrelated donors or cord blood units is difficult. However, prospective trials with larger numbers of patients studying the intensity of the preparative regimen and the cellular source in pediatric patients with high-risk hematologic malignancies who undergo Haplo-PTCy are welcome.

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References

1. Gragert L, Eapen M, Williams E, Freeman J, Spellman S, et al. (2014) HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. N Engl J Med 371: 339-348.

2. Jones RJ (2012) Haploidentical Transplantation: Repurposing Cyclophosphamide. Biol Blood Marrow Transplant 18: 1771-1772.

3. Satwani P, Morris E, Bradley MB, Bhatia M, van de Ven C, et al. (2008) Reduced intensity and non-myeloablative allogeneic stem cell transplantation in children and adolescents with malignant and non-malignant diseases. Pediatr Blood Cancer 50: 1-8.

4. Duerst RE, Jacobsohn DA, Tse W, Kletzel M (2006) Reduced Intensity Conditioning (RIC) with FLU-BU-ATG and Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Pediatric Malignancies. Blood 108: 5377.

5. Verneris MR, Eapen M, Duerst R, Carpenter PA, Burke MJ, et al. (2010) Reduced-intensity conditioning regimens for allogeneic transplantation in children with acute lymphoblastic leukemia. Biol Blood Marrow Transplant 16:1237-1244.

6. Lawitschka A, Faraci M, Yaniv I, Veys P, Bader P, et al. (2015) Paediatric reduced intensity conditioning: Analysis of centre strategies on regimens and definitions by the EBMT Paediatric Diseases and Complications and Quality of Life WP. Bone Marrow Transplant 50: 592-597.

7. Saglio F, Berger M, Spadea M, Pessolano R, Carraro F, et al. (2020) Haploidentical HSCT with post transplantation cyclophosphamide versus unrelated donor HSCT in pediatric patients affected by acute leukemia. Bone Marrow Transplant 56: 586-595.

8. Luznik L, O'Donnell PV, Symons HJ, Chen AR, Leffell MS, et al. (2008) HLA-Haploidentical Bone Marrow Transplantation for Hematologic Malignancies Using Nonmyeloablative Conditioning and High-Dose, Post-transplantation Cyclophosphamide. Biol Blood Marrow Transplant 14: 641-650.

9. Passweg JR, Baldomero H, Bader P, Bonini C, Cesaro S, et al. (2015) Hematopoietic SCT in Europe 2013: Recent trends in the use of alternative donors showing more haploidentical donors but fewer cord blood transplants. Bone Marrow Transplant 50: 476-482.

10. Holtick U, Albrecht M, Chemnitz JM, Theurich S, Skoetz N, et al. (2014) Bone marrow versus peripheral blood allogeneic haematopoietic stem cell transplantation for haematological malignancies in adults. Cochrane Database Syst Rev 4: CD010189.

11. Yu X, Liu L, Xie Z, Dong C, Zhao L, et al. (2019) Bone marrow versus peripheral blood as a graft source for haploidentical donor transplantation in adults using post-transplant cyclophosphamide-A systematic review and meta-analysis. Crit Rev Oncol Hematol 133: 120-128.

12. Ruggeri A, Labopin M, Bacigalupo A, Gülbas Z, Koc Y, et al. (2018) Bone marrow versus mobilized peripheral blood stem cells in haploidentical transplants using posttransplantation cyclophosphamide. Cancer 124: 1428-1437.

13. Bashey A, Zhang MJ, McCurdy SR, Martin AS, Argall T, et al. (2017) Mobilized peripheral blood stem cells versus unstimulated bone marrow as a graft source for T-cell–replete haploidentical donor transplantation using post-transplant cyclophosphamide. J Clin Oncol 35: 3002-3009.

14. Klein OR, Buddenbaum J, Tucker N, Chen AR, Gamper CJ, et al. (2017) Nonmyeloablative Haploidentical Bone Marrow Transplantation with Post-Transplantation Cyclophosphamide for Pediatric and Young Adult Patients with High-Risk Hematologic Malignancies. Biol Blood Marrow Transplant 23: 325-332.

15. Trujillo ÁM, Karduss AJ, Suarez G, Perez R, Ruiz G, et al. (2021) Haploidentical Hematopoietic Stem Cell Transplantation with Post-Transplantation Cyclophosphamide in Children with High-Risk Leukemia Using a Reduced-Intensity Conditioning Regimen and Peripheral Blood as the Stem Cell Source. Transplant Cell Ther 2021.

16. Jaiswal SR, Chakrabarti A, Chatterjee S, Bhargava S, Ray K, et al. (2016) Haploidentical Peripheral Blood Stem Cell Transplantation with Post-Transplantation Cyclophosphamide in Children with Advanced Acute Leukemia with Fludarabine-, Busulfan-, and Melphalan-Based Conditioning. Biol Blood Marrow Transplant 22: 499-504.

17. González-Llano O, González-López EE, Ramírez-Cázares AC, Marcos-Ramírez ER, Ruiz-Argüelles GJ, et al. (2016) Haploidentical peripheral blood stem cell transplantation with posttransplant cyclophosphamide in children and adolescents with hematological malignancies. Pediatr Blood Cancer 63: 2033-2037.

18. Berger M, Lanino E, Cesaro S, Zecca M, Vassallo E, et al. (2016) 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 22: 902-909.

19. Sawada A, Shimizu M, Isaka K, Higuchi K, Mayumi A, et al. (2014) Feasibility of HLA-haploidentical hematopoietic stem cell transplantation with post-transplantation cyclophosphamide for advanced pediatric malignancies. Pediatr Hematol Oncol 31: 754-764.

20. Ruggeri A, Galimard J-E, Paina O, Fagioli F, Tbakhi A, et al. (2021) Outcomes of Unmanipulated Haploidentical Transplantation Using Post-Transplant Cyclophosphamide (PT-Cy) in Pediatric Patients With Acute Lymphoblastic Leukemia. Transplant Cell Ther 2021.

21. Symons HJ, Zahurak M, Cao Y, Chen A, Cooke K, et al. (2020) Myeloablative haploidentical BMT with posttransplant cyclophosphamide for hematologic malignancies in children and adults. Blood Adv 4: 3913-3925.

22. Trujillo AM, Urueta AJK, Suarez G, Cardona A, Ramirez M, et al. (2020) Early initiation of cyclosporine-mycophenolate plus antithymocyte globulin in haplo transplant with post-transplant cyclophosphamide in children: low incidence of severe acute GvHD with encouraging survival. Poster presented at: EBMT 46th annual meeting, Virtual Congress.

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