Use of Post-Transplant Cyclophosphamide with Nonmyeloablative Conditioning in HLA-Haploidentical Stem Cell Transplants for Sickle Cell Disease

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Abstract
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Methods: A comprehensive search on the most up to date information was performed with MEDLINE, PubMed, MEDLINE-Ovid, EBSCO-Host including all databases, and Web of Science with the terms cyclophosphamide or cytoxan, bone marrow transplant(ation) or stem cell, and sickle cell. Articles and abstracts generated were screened and analyzed by one independent reviewer via inclusion and exclusion criteria and related publication appraised in PubMed. Studies were assessed for quality using GRADE criteria.

Results: Five studies using HLA-haploidentical patient-donor related matches with nonmyeloablative techniques have shown promise in decreasing toxicity to patients while providing an alternative, curative treatment for individuals who previously did not have that option. Nonmyeloablation via John Hopkins protocol with post-transplant cyclophosphamide (PTCy) show minimal acute/chronic graft-versus-host disease effects similar to what is seen in HLA-matched sibling donors but with decreased stable engraftment.

Conclusion: A combination of peripheral blood stem cell (PBSC) and bone marrow transfusions in haploidentical patients from all trials show stable engraftment with minimal cGVHD. Further studies to increase efficacy are needed to modify this conditioning regimen with a need for a large randomized control trial with increased TBI and Thiotepa needed to support findings presented.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

Keywords
haploidentical, sickle cell, cyclophosphamide, stem cell, bone marrow, nonmyeloablative

Subject Categories
Medicine and Health Sciences

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Use of Post-Transplant Cyclophosphamide with Nonmyeloablative Conditioning in HLA-Haploidentical Stem Cell Transplants for Sickle Cell Disease

Rebecca Hayman

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 10, 2019
Faculty Advisor: Dr. Mark Pedemonte
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted]
Abstract

Background: Hematopoietic stem cell transplantation is the only curative therapy for individuals with sickle cell disease but due to the limited donor pool and complications with adult infusions, new methods are in development for applicability to all populations. The new method utilizes a treatment regimen developed by John Hopkins with only small trials currently being performed.

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Keywords: Cyclophosphamide, bone marrow transplant(ation), stem cell, and/or sickle cell.
Acknowledgments

To Eddie; my driving force through this entire adventure whose love and support has taken me so far. You always have my back and are my partner in all aspects of life. Plus you helped me with formatting my figures on Microsoft; way beyond the call of duty.

To my parents; the ones that always believed in me throughout my life.

To Professor Sommers: for guiding me through the process and providing insight where I lacked.
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List of Abbreviations

SCD- sickle cell disease
GVHD-graft versus host disease
PBSC-peripheral blood stem cell
TRM-transplant related mortality
Flu-fludarabine
Cy-cyclophosphamine
ATG-antithymocyte globulin
TBI-total body irradiation
PTCy-post transplant cyclophosphamine
HU-hydroxyurea
Use of Post-Transplant Cyclophosphamide with Nonmyeloablative Conditioning in HLA-Haploidentical Stem Cell Transplants for Sickle Cell Disease

Background

Sickle cell disease (SCD) is genetically induced hemolytic anemia that causes lifelong morbidity with vaso-occlusive complications and early mortality in homozygous individuals. SCD is prevalent in approximately 1 in every 365 African American births and is predicted to increase globally 30% by 2050 with the largest growth in lower to mid socioeconomic status countries and population migration in higher SES countries.\(^1\) Current estimations of SCD in the United States are 100 000.\(^2\)

Supportive treatment has been well established with the use of hydroxyurea in decreasing mortality in pediatrics but creates a large population of young adults with end stage organ damage and other SCD related health concerns.\(^3,4\) Common complications of SCD include acute chest syndrome, stroke, pulmonary hypertension, and renal failure.\(^5-7\) Presently, the only curative measures available are myeloablative allogenic hematopoietic stem cell transplantation (HSCT) from HLA-matched related donors (MRD) which has proven efficacious with rates approaching 95% and considered the standard of care in developed countries. Alternative disease modifying treatments are needed due to major limitations in therapy being only 14% of SCD patients have an MRD overall which is even lower in minorities\(^8-10\) and the limited therapies available for adults.

HLA-haploidentical donors conditioning regimen are being established for stem cell transplants in SCD, thalassemia’s, and hematologic malignancies to widen the donor pool and allow universal access to a therapeutic treatment.\(^6,7,11-13\) High dose post-transplant cyclophosphamide has been proven to be an integral part of haploidentical transplantation to reduce rates of acute and chronic graft vs host disease (GVHD) and transplant related mortality (TRM) through immunosuppression via eliminating alloreactive lymphocytes while
simultaneously preserving regulatory T cells.\textsuperscript{6,14,15} To expand treatment to adults, advancements in reduced and nonmyeloablative techniques are being utilized due to myeloablative therapy increasing mortality and morbidity from SCD complications.\textsuperscript{12,16}

The studies in this review show promise in the application of peripheral blood and bone marrow stem cell transplants in HLA-haploidentical matches employing reduced or nonmyeloablative techniques to decrease toxicity to chemotherapy and post-transplant cyclophosphamide to expand a known curative treatment to all populations.

\textbf{Methods}

A comprehensive search of english written or translated articles on MEDLINE, PubMed, MEDLINE-Ovid, EBSCO-Host including all databases, and Web of Science with the terms \textit{cyclophosphamide} or \textit{cytoxan}, \textit{bone marrow transplant(ation)} or \textit{stem cell}, and \textit{sickle cell}. Articles and abstracts generated were screened and analyzed by one independent reviewer.

Eligible studies were nonmyeloablative or reduced intensity/toxicity with post-transplant cyclophosphamide, HLA-haploidentical donors, patients in all age groups with some type of hemoglobinopathy related complication, human trials, and the use of peripheral blood stem cell transplant (PBSCT) or bone marrow transplant. Studies excluded if utilizing myeloablative regimen, umbilical cord stem cell transplant, HLA-matched sibling donor available, and written in the last 6 years due to recent advancements in the field and protocol.

All publications were evaluated via the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group Guidelines (Table 1).\textsuperscript{17}

\textbf{Results}
After elimination of duplicates, search results yielded 26 different publications since 2012. Five of the appraised papers met the criteria (see Table 1). Bolaños et al, 2012, at John Hopkins University was the first to establish and implement a nonmyeloablative procedure (Figure 1) for HLA-haploidentical and MSD patients. The trial incorporated 19 individuals with 14 being haploidentical and having a hemoglobinopathy complication and followed for a mean period of 711 days after bone marrow infusion. The protocol evolution of adding ATG to regimen, moving from tacrolimus to sirolimus to prevent posterior reversible encephalopathy (PRES) and G-CSF primed grafts to increase stable engraftment were based off recent research developments and new publications. No aGVHD or cGVHD was observed in all haploidentical patients but 43% had either primary or secondary graft rejection (Table 2). The other 53% showed full donor chimerism measured with CD3+ and CD34+ levels. The study provides an efficacious regimen for adults and supports the use of PTCy in GVHD prophylaxis.

Dhedin et al, 2016, developed 3 different cohorts and nonmyeloablative conditioning regimen with 35 SCD individuals from ages 3-50, all transfused with haploidentical related bone marrow based off modified John Hopkins protocol (Figure 1). In cohort 1, only 40% of patients had stable engraftment while cohort 2 had the addition of thiotepa on D-7 and showed 87.5% stable engraftment with only one aGVHD which was managed and cured used corticosteroids (CS). Cohort 3 had 22 patients that underwent preconditioning with HU and azathioprine with 18.2% having aGVHD and a mortality of 13.6% (Table 2). G-CSF primed bone marrow was used in this study as well as all following studies. The authors of this multi-institution learning collaboration concluded that the addition of thiotepa increases engraftment while preconditioning therapy of HU and azathioprine have no summative affect compared to thiotepa alone with minimal toxicity.

Fitzhugh et al, 2017, was a phase 1/2 clinical trial that split haploidentical individuals into 3 cohorts with varying concentrations of PTCy and utilizing PBSC. Cohort 1
had a dose of 0mg/kg and ended after 1 out of 3 individuals rejected engraftment. Cohort 2
dosed 8 individuals 50mg/kg day +3 with 63% engrafting which increased in cohort 3 to
83% 50mg/kg/d on day +3/+4 to 12 patients. The results showed no TRM and increasing
rate of chimerism from 0% to 25% to 50% in cohort 3. With 2 days of PTCy, only 1
individual had both aGVHD and cGVHD (Table 2). In conclusion, the authors report a need
to integrate other studies involving other hematologic pathology research in developing
appropriate dosing schemas for SCD and PTCy an integrative part of PBSC transplantation.6

A recent experimental study by Frangoul et al, 2018,14 used four haploidentical
patient-donor matches that underwent the same conditioning regimen as one Dhedin et al,
2016,18 with thiotepa. Patients were 12-23 in age with all 4 having aGVHD grade 2 that was
resolved with CS. Additionally all 4 had 100% donor chimerism and decreased SCD
symptomology at the 1-year follow up. The research supports the need for further studies
with thiotepa because it has manageable toxicities to patients.14

In a PBSC haploidentical study with 12 participants by Saraf et al, 2018,13 2 patients
underwent a reduced intensity myeloablation and with both failing to engraft. The protocol
was modified to incorporate the John Hopkins protocol but with increased TBI on D-1 for the
following 8 patients ages 30-38 years (Table 2). Approximately 87.5% of patients had
>95% chimerism post-transplant at the 1-year follow up with 2 episodes of aGVHD grade
II/IV with 1 of the same individuals having cGVHD who later died from unknown causes.
Authors discussed that the addition of increased TBI to 3Gy decrease graft rejection in PBSC
transplants while still maintaining acceptable toxicity for adults.13

Discussion

The cumulative data from these five studies6,7,13,14,18 support the necessity of
expanding alternative methods for stem cell transplantation in sickle cell disease and
support that nonmyeloablative is a plausible methodology. Additionally, the benefits of PTCy
with thiotepa improve engraftment and decrease incidents of GVHD.\textsuperscript{6,14,18} Historically mismatched donors have increased mortality >50\% until the establishment of the John Hopkins protocol which lay the basis for nonmyeloablative procedures. Following research typically revolved around this procedure due to the negligible toxicity and no TRM but the high graft rejection rate calls for slight alterations.\textsuperscript{7} No cytopenia in reduced intensity or nonmyeloablative allows it to be a safer method in certain individuals with comorbidities.\textsuperscript{19} While myeloablative procedures are currently the method of choice for pediatrics, both can cause increased risk of malignancy but alkylating agents more so than radiation thus nonmyeloablative may be best in both kids and adults.\textsuperscript{10,20}

Studies involving non-related donors are in development for SCD with limited success of more developing aGVHD grade >2, cGVHD and a TRM of 24\% from GVHD.\textsuperscript{10} Further studies are required to create safer regimes for individuals who necessitate stem cell transplants but have no related donors.

**Conclusion**

In conclusion, nonmyeloablative procedures with PTCy have shown decreased rates of both acute and chronic GVHD and increasing levels of stable engraftment. Furthermore, it is cost effective and requires minimal cell processing thus can be implemented in countries of lower socioeconomic status where SCD rates tend to be the highest.\textsuperscript{1,21} Advantages of alleviating symptoms of a life-threatening disease outweigh the risks of graft failure, however unfavorable, if the risk of TRM is minimal at 5.3\% when considering quality of life and the decreased lifespan of those with SCD. Measures to minimize mortality can be made by utilizing bone marrow when possible over PBSC transplant and providing antibiotic and vaccinations prophylaxis will further diminish mortality rates.\textsuperscript{7,22} With only experimental research in phase 1/2 trials and taking into account the growing population of patients suffering from SCD there is a demand for a large prospective randomized control trial with thiotepa, PTCy, and elevated TBI to allow all individuals access to a curative treatment.
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with Post-Transplant Cytoxan Plus Thiotepa Improves Donor Engraftment in Patients
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Myeloablative Regimens in Allogeneic Hematopoietic Stem Cell Transplantations. Balk

Pediatrics and the Associated Radiation Exposure and Estimated Cancer Risk. JAMA

21. Wiebking V, Hütker S, Schmid I, Immler S, Feuchtinger T, Albert MH. Reduced toxicity,
myeloablative HLA-haploidentical hematopoietic stem cell transplantation with post-

22. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-Haploidentical Bone Marrow
Transplantation for Hematologic Malignancies Using Nonmyeloablative Conditioning and
High-Dose, Posttransplantation Cyclophosphamide. Biol Blood Marrow Transplant.
Table 1: Quality Assessment of Reviewed Articles

<table>
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<th>Outcome</th>
<th>Number of studies</th>
<th>Study Designs</th>
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<td>Limitations</td>
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<td>GVHD</td>
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<td>Stable engraftment</td>
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<td>3 Experimental research, 2 cohort</td>
<td>Not serious\textsuperscript{a,f}</td>
<td>Not serious</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Bolanos et al and Saraf et al had evolutions in protocol.
\textsuperscript{b} GVHD was graded via NIH guidelines in all studies.
\textsuperscript{c} Variation in all studies in TBI concentrations and the use of thiotepa in Dhedin et al, 2016, Frangoul et al, 2018 and Saraf et al, 2018 affect engraftment and occurrence of GVHD.
\textsuperscript{d} No confidence intervals were provided due to absolute values and small cohorts.
\textsuperscript{e} Fitzhugh et al, 2016 conducted a dose response gradient of PTCy in different cohorts.
\textsuperscript{f} Stable engraftment was measured objectively via CD3+ and CD34+ to determine amount of chimerism.
<table>
<thead>
<tr>
<th>Study</th>
<th>No. Haploidentical Transplanted</th>
<th>Age range (years)</th>
<th>Conditioning Regiment</th>
<th>GVHD prophylaxis</th>
<th>Stem cell Source</th>
<th>Acute GVHD</th>
<th>Chronic GVHD</th>
<th>Stable Engraftment</th>
<th>Overall Survival</th>
<th>TRM Deaths</th>
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<td>Flu 30mg/m2/d, Cy 14.5mg/kg/d, ATG, TBI 2Gy</td>
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<td>PTCy 50mg/kg/d, mycophenolate, and sirolimus</td>
<td>Bone marrow</td>
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<td>20(^b)</td>
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<td>Alemtuzumab 1mg/kg, TBI 4Gy</td>
<td>PTCy 50mg/kg/d</td>
<td>PBSC</td>
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<td>1(^d)</td>
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<td>PTCy 50mg/kg/d, mycophenolate, and sirolimus</td>
<td>3 Bone marrow, 1 PBSC</td>
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<td>13</td>
<td>2</td>
<td>55</td>
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a. One patient with graft failure using the non-thiotepa approach, was re-transplanted >1 yr after initial haplo-BMT with the thiotepa alone containing regimen with successful engraftment.

b. 2 patients had secondary graft failure

c. Deaths mainly from infectious complications and macrophage activation syndrome.

d. aGVHD Grade 1 and ocular cGVHD both responded to CS treatment; 1 death after secondary graft rejection from SCD complications

e. Not all patients had 3 month conditioning of HU prior to treatment; all four had GVHD grade 2 which resolved with CS treatment

f. One patient with aGVHD developed cGVHD and died unexpectantly when improving with CS treatment
<table>
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<td>Alemtuzumab 1mg/kg, TBI 3Gy, PTCy 50mg/kg/d</td>
<td>PTCy 50mg/kg/d, mycophenolate, and sirolimus</td>
<td>PBSC</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>20-38</td>
<td>Flu 30mg/m2/d, Cy 14.5mg/kg/d, ATG, TBI 3Gy</td>
<td>PTCy 50mg/kg/d, mycophenolate, and sirolimus</td>
<td>PBSC</td>
<td>2f</td>
<td>1f</td>
<td>7</td>
<td>87.5%</td>
<td>1f</td>
</tr>
<tr>
<td>Summary</td>
<td>75</td>
<td>3-56</td>
<td></td>
<td></td>
<td>55</td>
<td>Bone Marrow; 23 PBSC</td>
<td>13</td>
<td>2</td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>

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a. One patient with graft failure using the non-thiotepa approach, was re-transplanted >1 yr after initial haplo-BMT with the thiotepa alone containing regimen with successful engraftment.

b. 2 patients had secondary graft failure

c. Deaths mainly from infectious complications and macrophage activation syndrome.

d. aGVHD Grade 1 and ocular GVHD both responded to Cs treatment; 1 death after secondary graft rejection from SCD complications

e. Not all patients had 3 month conditioning of HU prior to treatment; all four had GVHD grade 2 which resolved with Cs treatment

f. One patient with aGVHD developed cGVHD and died unexpectedly when improving with Cs treatment
**Figure 1.** Nonmyeloablative conditioning regimen for stem cell transplantation in SCD haploidentical matched patients developed by John Hopkins University.