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# Nonmyeloablative Haploidentical Bone Marrow Transplantation with Post-Transplantation Cyclophosphamide for Pediatric and Young Adult Patients with High-Risk Hematologic Malignancies

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A B S T R A C T

Lower-intensity conditioning regimens for haploidentical blood or marrow transplantation (BMT) are safe and efficacious for adult patients with hematologic malignancies. We report data for pediatric/young adult patients with high-risk hematologic malignancies (n = 40) treated with nonmyeloablative haploidentical BMT with post-transplantation cyclophosphamide from 2003 to 2015. Patients received a preparative regimen of fludarabine, cyclophosphamide, and total body irradiation. Post-transplantation immunosuppression consisted of cyclophosphamide, mycophenolate mofetil, and tacrolimus. Donor engraftment occurred in 29 of 32 (91%), with median time to engraftment of neutrophils >500/μL of 16 days (range, 13 to 22) and for platelets >20,000/μL without transfusion of 18 days (range, 12 to 62). Cumulative incidences of acute graft-versus-host disease (GVHD) grades II to IV and grades III and IV at day 100 were 33% and 5%, respectively. The cumulative incidence of chronic GVHD was 23%, with 7% moderate-to-severe chronic GVHD, according to National Institutes of Health consensus criteria. Transplantation-related mortality (TRM) at 1 year was 13%. The cumulative incidence of relapse at 2 years was 52%. With a median follow-up of 20 months (range, 3 to 148), 1-year actuarial overall and event-free survival were 56% and 43%, respectively. Thus, we demonstrate excellent rates of engraftment, GVHD, and TRM in pediatric/young adult patients treated with this regimen. This approach is a widely available, safe, and feasible option for pediatric and young adult patients with high-risk hematologic malignancies, including those with a prior history of myeloablative BMT and/or those with comorbidities or organ dysfunction that preclude eligibility for myeloablative BMT.



## INTRODUCTION

Allogeneic (allo) blood or marrow transplantation (BMT) is the only curative option for many pediatric and young adult patients with relapsed or refractory hematologic malignancies. Typically, high-risk patients have undergone several rounds of intensive chemotherapy or have relapsed after prior BMT, increasing the likelihood that organ toxicity and/or reduced performance status would preclude a myeloablative (MA) conditioning regimen. Additionally, only 50% of those in need of an alloBMT have a suitable HLA-matched unrelated donor, and this number is as low as 20% in some minority populations [1]. On the other hand, haploidentical related donors are almost always identifiable. Combining a lower-intensity conditioning regimen with partially matched, haploidentical, related donor BMT (haploBMT) is therefore crucial for expanding the availability of BMT to this high-risk group of young patients.

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Post-transplantation cyclophosphamide (PT/Cy) has gained worldwide acceptance as a highly effective method of graft-versus-host disease (GVHD) prophylaxis [2-10]. When given on days +3 and +4 after BMT, high-dose PT/Cy selectively depletes alloreactive T cells while preserving hematopoietic stem cells and quiescent memory T cells responsible for protection against common pathogens that are encountered after transplantation [11-14]. In adults, rates of engraftment, GVHD, and transplantation-related mortality (TRM) after nonmyeloablative haploBMT with PT/Cy are similar to those seen with HLA-matched related and HLA-matched unrelated donors [2,3,15-17]. There has been success using reduced-intensity conditioning (RIC) BMT in pediatric patients using HLA-matched related, HLA-matched unrelated, and HLA-mismatched unrelated donors, with bone marrow, cord blood, or peripheral blood stem cells [18-21]. Herein, we report outcomes using nonmyeloablative (NMA) haploBMT with PT/Cy looking exclusively at pediatric and young adult patients with high-risk hematologic malignancies who underwent transplantation at our institution from 2003 to 2015.

## MATERIALS AND METHODS

### *Patients*

This study was approved by the institutional review board of The Johns Hopkins Hospital. We retrospectively reviewed all pediatric and young adult patients (ages 1 month to 25 years) with hematologic malignancies who underwent NMA alloBMT using a haploidentical related donor at Johns Hopkins Hospital from January 1, 2003 through June 30, 2015. All patients ages 18 years or older and all guardians of patients age 17 or younger gave consent for transplantation. Patients were either treated on a prospective institutional review board–approved institutional clinical trial (n = 28, 70%) or after the current open study (n = 12, 30%), if they were unable to be enrolled secondary to insurance coverage limitations, or as standard of care after study closure if they otherwise met eligibility criteria. Sixteen of these patients have been previously reported in other manuscripts describing outcomes in our adult population [2,3].

Eligibility criteria included patients with high-risk leukemias and lymphomas, as previously published [2,3,15], Eastern Cooperative Oncology Group performance status ≤2 or Lansky/Karnofsky score ≥60%, left ventricular ejection fraction ≥35%, forced expiratory volume in the first second, and functional vital capacity ≥40% of predicted (≥60% of predicted after thoracic or mantle radiation), not on dialysis, and absence of uncontrolled infection. Morphologic complete remission (CR) was required for acute leukemias and partial remission or better were required for aggressive lymphomas. Donors were first-degree relatives or half-siblings who were HLA-haploidentical based on high-resolution typing at HLA-A, -B, -Cw, -DRB1, and -DQB1, as previously described [2]. Donor selection criteria, in order of priority, included medical fitness, no antidonor HLA antibody, no major ABO incompatibility, matched cytomegalovirus (CMV) immunoglobulin G serostatus, no minor ABO compatibility, and sex (male donor preferred for male patient).

### *Treatment*

The majority of the patients (n = 36, 90%) received a preparative regimen of fludarabine (30 mg/m$^2$ i.v., days –6 to –2), cyclophosphamide (Cy, 14.5 mg/kg i.v., days –6 and –5), and total body irradiation (200 cGy, day –1) (Figure 1). Two patients received i.v. busulfan (.8 mg/kg i.v. every 12 hours) on days –6 to –3 instead of low-dose Cy because they were enrolled on a clinical trial investigating this alternative NMA preparative regimen. One patient received fludarabine and Cy at the dosing described above along with alemtuzumab (test dose of 3 mg i.v. on day –14 followed by a dose escalation schedule of 10 mg/15 mg/20 mg i.v. on days –14, –13, –12) and melphalan (100 mg/m$^2$ i.v. on day –2) after failing to engraft after 2 prior cord blood transplantations. One patient received alemtuzumab (20 mg i.v. on days –6 through –2) and fludarabine at the dosing described above, as per the previously published regimen for patients failing to engraft after MA alloBMT [22]. All patients received either T cell–replete bone marrow (n = 38, 95%) or peripheral blood stem cells (n = 2, 5%) from haploidentical related donors on day 0. All patients received Cy 50 mg/kg/dose i.v. on days +3 and +4, followed by mycophenolate mofetil 15 mg/kg/dose per oral 3 times daily (maximum daily dose 3 gm/day) from days +5 through +35, and tacrolimus .015 mg/kg/dose i.v. every 12 hours from day +5 through either day +60 or +90 (n = 13, 32%) or day +180 (n = 27, 68%), according to the clinical trial on which the patient was enrolled or following. The tacrolimus was transitioned to oral as tolerated, and the dose was adjusted to maintain a trough level between 5 ng/mL and 15 ng/mL. Filgrastim 5 μg/kg/day was administered starting on day +5 until neutrophil recovery to ≥ $1.0 \times 10^9$/L.

Routine supportive care measures were followed according to institutional standards, as previously described [2,4]. Antimicrobial prophylaxis for *pneumocystic jirovecii* and fungus were given to all patients, as per institutional guidelines. Patients whom were *at risk of CMV reactivation*, defined as either the donor or recipient having positive CMV IgG, received ganciclovir (500 mg/m$^2$) from day 0 through engraftment and CMV PCR levels were measured weekly until day +100. Pre-emptive therapy with either i.v. gancyclovir or oral valganciclovir was initiated when CMV reactivation was detected at more than 500 copies CMV/mL. Patients with a history of varicella zoster virus infection received acyclovir prophylaxis for 1 year after transplantation.

### *Definitions of Disease Status and Clinical Outcomes*

Neutrophil recovery time, or *engraftment*, was defined as the number of days from BMT to the first of 3 consecutive days with an absolute neutrophil count at or above $.5 \times 10^9$/L. *Platelet recovery time* was defined as platelet count greater than $20 \times 10^9$/L without platelet transfusion in the preceding 7 days. Donor chimerism analysis was performed on days +30, +60, +90, +180, and +365 after BMT on peripheral blood and on bone marrow as clinically indicated or per protocol. *Mixed donor chimerism* was defined as >5% and <95% donor chimerism, and *full chimerism* as ≥95% donor chimerism, in whole blood or bone marrow. *Primary graft failure* was defined as <5% donor chimerism in bone marrow by day +60. *Secondary graft failure* was defined as loss of donor engraftment (<5% donor chimerism) after achieving neutrophil recovery. Acute GVHD (aGVHD) was graded per standard criteria [23], and chronic GVHD (cGVHD) was graded per the 2005 National Institutes of Health Consensus Criteria [24]. *Overall survival* (OS) was defined as the time from BMT to death from any cause. *Event-free survival* (EFS) was defined as the time from BMT to death or relapse. *TRM* was defined as death without disease relapse. *Minimal residual disease* (MRD) before transplantation and *relapse after transplantation* were defined as any disease detectable by flow cytometry, molecular, fluorescent in situ hybridization, or cytogenetic analysis. For patients with acute lymphoblastic leukemia (ALL), the MRD cutoff used was .01%, and for patients with acute myeloid leukemia (AML), the cutoff used was .1%. The level of sensitivity of MRD detection for acute leukemia was variable based on the year of BMT and the type of leukemia, ranging in earlier years from 1/500 for AML and T ALL and 1/1000 for pre-B ALL, to 1/10,000 for AML, T ALL, and pre-B ALL in later years.

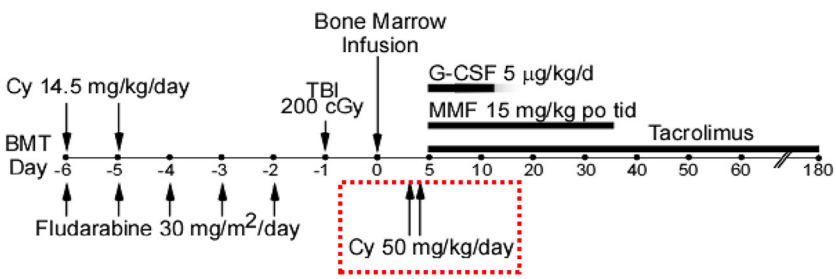


**Figure 1.** Preparative regimen and graft-versus-host disease prophylaxis. Fludarabine 30 mg/m$^2$ i.v. days –6 through –2, cyclophosphamide (Cy) 14.5 mg/kg i.v. days –6 and –5, total body irradiation 200 cGy day –1, graft infusion day 0, Cy 50 mg/kg/dose i.v. days +3 and +4, mycophenolate mofetil (MMF) 15 mg/kg/dose per oral 3 times daily (maximum daily dose 3 gm/day) days +5 through +35, tacrolimus .015 mg/kg/dose i.v. every 12 hours day +5 through either day +60, +90, or day +180, and filgrastim 5 μg/kg/day day +5 through neutrophil recovery.