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Brief Articles

Long-Term Outcome of Fludarabine-Based Reduced-Intensity Allogeneic Hematopoietic Cell Transplantation for Debilitating Paroxysmal Nocturnal Hemoglobinuria

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A B S T R A C T

Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by intravascular hemolysis, venous thrombosis, and bone marrow failure. Seventeen patients with debilitating PNH, including 8 who were HLA-alloimmunized, underwent a reduced-intensity allogeneic hematopoietic cell transplantation (HCT). All received cyclophosphamide/fludarabine +/− antithymocyte globulin followed by a granulocyte colony-stimulating factor–mobilized HCT from an HLA-matched relative. Glycosylphosphatidylinositol-negative neutrophils were detectable after engraftment but disappeared completely at a median 100 days after transplantation. With a median follow-up of nearly 6 years, 15 patients (87.8%) survived, all without any evidence of PNH, transfusion independent, and off anticoagulation. Allogeneic reduced-intensity HCT remains a curative therapeutic option for PNH patients who are not candidates for eculizumab treatment.

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INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a nonmalignant clonal disorder of hematopoietic stem cells, characterized by a somatic mutation in the *PIG-A* gene [1]. Due to a defect in the glycosylphosphatidylinositol (GPI) anchor, PNH stem cells and their progeny lack GPI-anchored surface proteins, some of which (eg, CD55 and CD59) protect erythrocytes from complement-mediated lysis [2]. Patients with PNH may manifest a variety of symptoms, including recurrent intravascular hemolysis, venous thrombosis [3], and hematopoietic failure [4], all of which shorten survival compared with healthy age-matched controls [5,6].

Eculizumab, a monoclonal antibody to C5a, is highly effective in preventing both hemolysis and thrombosis associated with this disorder [7]. However, this agent requires lifelong therapy and may be unaffordable for many patients. After treatment, low levels of persistent extravascular hemolysis as a consequence of complement C3 opsonization can occur, leading to the persistent need for erythrocyte transfusions in a minority of eculizumab-treated patients [8]. Furthermore, although eculizumab can be effective in controlling intravascular hemolysis in PNH patients with bone marrow failure, it does not improve hematopoiesis in these patients, requiring additional therapy, such as immunosuppression with antithymocyte globulin or allogeneic hematopoietic cell transplantation (HCT). Although allogeneic bone marrow transplantation can be curative for PNH, the procedure has historically been associated with high rates of rejection and regimen-related mortality [9,10]. This is likely the consequence of these patients being heavily transfused and having a high incidence

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of HLA alloimmunization. Further, historical preparative regimens were often more myeloablative than they were immunosuppressive, and patients typically underwent transplantation with bone marrow grafts, which contained lower numbers of $CD34^+$ cells and T cells, all factors that may have increased the odds of graft rejection. Previously, we reported that fludarabine-based reduced-intensity (RI)-HCT could be used to reduce the risk of graft-rejection in heavily transfused and HLA-alloimmunized patients. Further, we described that T cells engrafting after RI-HCT can immunologically eradicate PNH through a graft-versus-marrow effect. Here, we the report long-term outcome on the use of this approach in 17 patients with severe, debilitating PNH who underwent an RI-HCT from an HLA-matched relative.

METHODS

Eligibility for transplantation included a diagnosis of PNH with 1 or more of the following: (1) transfusion dependence, (2) a history of thrombotic events, or (3) recurrent debilitating hemolytic crises. Patients were eligible for treatment on this research trial and were included in this analysis if, by definition [11], they had classic PNH, or clinical or subclinical PNH (PNH clone of at least 5%) in the setting of other bone marrow failure conditions.

Seventeen consecutive patients with PNH underwent a peripheral blood allogeneic RI-HCT at the National Heart, Lung, and Blood Institute on institutional review board–approved protocol 99-H-0050. Bone marrow failure, patient preference, or drug unavailability precluded the use of eculizumab in all patients. Patients received a T cell–replete granulocyte colony-stimulating factor (G-CSF)–mobilized peripheral blood HCT from a 6/6 HLA-matched relative after conditioning with intravenous cyclophosphamide 60 mg/kg/day (days −7 and −6) and fludarabine 25 mg/m^2/day (days −5 to −1). To prevent graft rejection, patients with a significant transfusion history had equine antithymocyte globulin (40 mg/kg/day days −5 to −2) added to the conditioning regimen (n = 14). Graft-versus-host disease (GVHD) prophylaxis consisted of initially of cyclosporine (CSA), administered alone (n = 1) or with mycophenolate mofetil 1 g by mouth twice daily (n = 4). Because an analysis of a similar transplantation regimen for hematological malignancies demonstrated superiority of combined CSA/methotrexate over CSA/mycophenolate mofetil for reducing acute GVHD [12], the last 12 PNH patients who underwent transplantation on this study received CSA combined with methotrexate 5 mg/m^2/day given on days +1, +3, and +6. On day 0, an unmanipulated G-CSF–mobilized peripheral blood allograft (target 5×10^6 $CD34^+$ cells/kg recipient weight) from an HLA-identical (6/6) relative was infused. All recipients received their grafts from an HLA-matched sibling, with the exception of 1 patient who received an allograft from her HLA-matched mother (patient no. 4).

Peripheral blood samples were collected on post-transplantation days 15, 30, 45, 60, and 100, and monthly thereafter, if necessary to enumerate the percentage of PNH granulocytes and erythrocytes and to quantitate the percentage donor chimerism in myeloid and T cell lineages [13]. Complete donor chimerism was defined as the first time to ≥95% donor-derived cells in peripheral blood. Patients receiving systemic anticoagulation before transplantation continued to be anticoagulated after transplantation for 3 to 6 months after GPI-negative neutrophils became undetectable in the blood, as a protocol-specified safety requirement to avoid thrombotic events in this high-risk cohort. Eculizumab was not used in any patients to reduce the risk of peri-transplantation hemolysis. Acute GVHD was graded and staged prospectively, using criteria from the 1994 Consensus Conference on Acute GVHD Grading. The diagnosis of clinical features of chronic GVHD was determined prospectively and classified into limited or extensive based on the Revised Seattle Classification. Overall survival was estimated by the Kaplan-Meier method, censoring at the last follow-up. The probabilities of development of acute and chronic GVHD and transplantation-related mortality were estimated using the cumulative incidence methods and compared using Gray's test, where death without the specified event was considered a competing risk. Analysis was performed using the R statistical programming software and its cmprsk package (www.r-project.org).

RESULTS

Seventeen patients with PNH, with a median age of 31 (range, 20 to 42 years) underwent transplantation (Table 1). The median percentage of GPI-negative neutrophils before transplantation was 81.6% (range, 5.5% to 99%). Indications for transplantation included PNH-associated bone marrow failure in 10 patients, including 2 with cytogenetic evidence for evolution to myelodysplastic syndrome; thrombotic events in 3 patients; and recurrent debilitating hemolysis in 4 patients, including 2 with erythrocyte-transfusion dependence. Eight patients (47%) were HLA-alloimmunized before transplantation with a median 76.5% (range, 45% to 100%) panel reactive antibody. Allografts contained a median 6.7×10^6 cells/kg (range, 3.1 to 21.1×10^6) $CD34^+$ cells and 2.5×10^8 cells/kg $CD3^+$ cells (range, 1.4 to 4.3×10^8). All patients engrafted with no graft rejection or late graft failure. Neutrophil and platelet recovery occurred at a median 14 days (range, 9 to 18) and 12 days (range, 5 to 15), respectively. Chimerism analysis revealed sustained donor engraftment occurred in both myeloid ($CD14^+$/$CD15^+$) and T cell ($CD3^+$) lineages in all 17 patients; the median time to achievement of full donor myeloid and T cell chimerism was 15 and 30 days, respectively. Sequential peripheral blood flow cytometry analysis revealed evidence for donor immune–mediated eradication of PNH (Figure 1A); although GPI-negative neutrophils were detectable early in all patients after transplantation, these populations declined and disappeared in all patients at a median 100 days (range, 30 to 150) after transplantation. The cumulative incidence of grade 2 to 4 acute GVHD was 47.1% (n = 8) and the cumulative incidence of chronic GVHD was 70.6% (n = 11). The sample of patients is too small to draw conclusions on the effect of GVHD prophylaxis regimens on incidence. No thrombotic events occurred after transplantation. Two patients died, 1 from complications related to acute GVHD (day 169) and 1 from complications of a perforated peptic ulcer 2.8 years later. With a median follow-up of nearly 6 years (range, 2.6 to 11 years), 15 patients (87.8%) survive without any evidence of PNH, transfusion independent, and off anticoagulation (Figure 1B).

DISCUSSION

Although allogeneic HCT can be curative for PNH, there is a substantial risk of mortality [9,14,15] and graft rejection with conventional myeloablative bone marrow transplantation (BMT). Data from a pilot trial evaluating RI-HCT for PNH provided the first evidence that engrafting donor T cells could eradicate abnormal recipient stem cells through a graft-versus-marrow effect, obviating the need for potentially toxic myeloablative conditioning [16]. The current report published here reflects the largest single-institution experience to date of RI peripheral-blood HCT for PNH. Although the optimal transplantation paradigm for this population has not been defined, the excellent outcome and long-term survival observed in our cohort suggest this approach can be used to overcome the high risk of graft rejection that has historically contributed to the poor outcome associated with conventional BMT for PNH. Despite nearly one half of the patients in this series being HLA alloimmunized, all achieved sustained donor engraftment with none experiencing graft rejection, graft failure, or relapse of their PNH. The profound recipient lymphodepletion achieved with fludarabine/cyclophosphamide and ATG conditioning, combined with the transplantation of an allograft containing high numbers of donor $CD34^+$ cells and T cells, likely led to rapid donor T cell engraftment that eradicated both PNH-type recipient stem cells and host T cells that mediate graft rejection.

Although the incidence of both acute and chronic GVHD was high in this series, only 1 patient died from early transplantation-related complications, with long-term survival being excellent at 88% with almost 6 years median

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