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Haploidentical bone marrow and stem cell transplantation: experience with post-transplantation cyclophosphamide

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ABSTRACT

Allogeneic blood or bone marrow transplantation (BMT) is a potentially curative therapy for high-risk hematologic malignancies not curable by standard chemotherapy, but the procedure is limited by the availability of human leukocyte antigen-matched donors for many patients, as well as toxicities including graft-versus-host disease (GVHD). Our group has developed the use of high-dose post-transplantation cyclophosphamide (PTCy) to selectively remove alloreactive T cells without compromising engraftment. This protocol has allowed for successful transplantation of human leukocyte antigen (HLA)-haploidentical (haplo) grafts, thus expanding the donor pool for the many patients who would not otherwise be a candidate for this life-saving procedure. In this review we will summarize the data that led to the development of PTCy, then focus on the outcomes of haploBMT trials with PTCy across different transplant platforms for patients with malignant hematologic diseases, and finally we will discuss emerging evidence that suggests equivalency of haploBMT with PTCy compared with more traditional transplants.

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1. Introduction

Pioneering early clinical studies by the Seattle bone marrow transplant team demonstrated that of all potential sources of allogeneic (allo) blood or bone marrow transplants (BMT), those from human leukocyte antigen (HLA)-matched siblings produce the best transplantation outcomes with respect to graft-versus-host disease (GVHD), overall survival (OS), and progression-free survival (PFS). Unfortunately, many patients who are candidates for alloBMT will not have an optimal donor—that is, a donor who is matched at high resolution at the *HLA-A*, *HLA-B*, *HLA-C*, and *HLA-DRB1* loci located on the short arm of chromosome 6. For patients who lack an HLA-matched sibling, there are three alternative sources of stem cells for alloBMT: (1) unrelated donors, (2) umbilical cord blood (UCB), and (3) partially HLA-mismatched, or HLA-haploidentical (haplo) related donors. Since any patient shares exactly one HLA haplotype with each biologic parent or child and half of siblings, an eligible haplo donor can be rapidly identified in nearly all cases. The fundamental clinical obstacle to haploBMT arises from intense, bi-directional responses from T cells responding to allogeneic HLA molecules resulting in unacceptably high incidences of graft rejection or GVHD. Indeed, early studies using T-cell–replete haploBMT and standard GVHD prophylaxis with methotrexate and calcineurin inhibitors (CNI) such as tacrolimus reported high toxicity relative to HLA-matched transplants [1–4], in particular acute grade III/IV GVHD and graft rejection. After it was discovered that T-cell depletion (TCD) of the donor graft prevents GVHD after alloBMT in mice [5] there was substantial interest in preventing GVHD after HLA haploBMT using ex vivo TCD. While this technique was indeed successful in reducing the incidence and severity of GVHD, there was a compensatory increase in the risk of graft failure, disease relapse, and non-relapse mortality (NRM) [6–8]. However, in the last two decades several novel methods for haploBMT have been developed that yield encouraging results with high rates of engraftment, effective GVHD control and favorable outcomes. Approaches using ex vivo TCD with "megadose" $CD34^+$ cells [9,10] or combining granulocyte colony-stimulating factor-primed allografts with intensive pharmacological immunosuppression and in vivo TCD with anti-thymocyte globulin [11–13] will be the focus of other manuscripts in this volume. Herein we will focus on haploBMT with post-transplantation cyclophosphamide (PTCy) and review the outcomes in patients with hematologic malignancies treated with this approach.

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2. Preclinical rationale behind PTCy

Based on studies published by several groups in the 1960s–1990, our group became interested in PTCy to induce immunologic tolerance in the context of alloBMT as a method to suppress GVHD without causing global immunosuppression [14]. In 1963, Berenbaum showed that cyclophosphamide (Cy) administration prolonged the survival of allogeneic skin grafts in mice, especially if the drug was given 1–3 days after placement of the skin graft [15]. At Johns Hopkins, Santos and Owens found that Cy suppressed the incidence and severity of GVHD in rats given allogeneic spleen cells, especially if dosing was commenced on day 2 after the splenocyte infusion [16]. Nomoto and colleagues at Kyushu University developed a method for inducing tolerance to major histocompatibility antigens (MHC) by giving mice an intravenous injection of MHC-matched, allogeneic splenocytes followed in 2–3 days by an intraperitoneal injection of high-dose Cy [17,18]. Colson et al. demonstrated in a mouse model of partially MHC-mismatched BMT that the dose of conditioning total body irradiation (TBI) required for stable engraftment was decreased when mice were given Cy 2 days post BMT, regardless of the degree of MHC-mismatch [19,20].

With these results as background, we sought to develop a strategy to administer PTCy that would permit the sustained engraftment of partially HLA-mismatched (haploidentical) grafts without severe GVHD. This objective was achieved in a mouse model of MHC-mismatched alloBMT using pre-transplant conditioning with fludarabine (a highly immunosuppressive purine analog) and low-dose TBI, and GVHD prophylaxis with high-dose PTCy [21,22]. These results, together with the observation that hematopoietic stem cells express high levels of aldehyde dehydrogenase which confers cellular resistance to Cy [23,24], provided the rationale to proceed with the first clinical trial, and also served as a platform for future laboratory studies to decipher the mechanisms behind this novel approach [25,26].

3. Early PTCy experience at Johns Hopkins Hospital

The first phase I/II clinical trial of haploBMT with PTCy to treat high-risk hematologic malignancies was initiated in 1999, and outcomes of the first 13 patients were published in 2002. Conditioning was based on a nonmyeloablative (NMA) regimen comprised of fludarabine and low-dose TBI as developed by Storb and colleagues in Seattle [27] and used in our preclinical rodent studies [21,22]. The protocol allowed for the addition of Cy to the conditioning regimen with flexibility for dose adjustment if failure to engraft was an issue. GVHD prophylaxis consisted of Cy administered as a single-dose on day +3 post-transplant, tacrolimus, and mycophenolic acid mofetil (MMF). Two of the first three patients transplanted after conditioning without Cy rejected their grafts. Thus, Cy was added to the conditioning regimen according to a Bayesian continual reassessment model at a total dose of 29 mg/kg given on days -5 and -6. Engraftment was achieved in 8 of the next 10 patients, so the pretransplant Cy dose in the conditioning regimen was fixed for future trials [28]. Autologous hematopoietic recovery occurred in three of four patients who rejected their grafts. Acute GVHD occurred in six of eight engrafted patients on the phase II portion of the trial, and five patients responded to therapy [28].

With ongoing collaborations between the groups at Hopkins and Seattle, a phase II trial of haploBMT using PTCy continued and a modification was made to the regimen by increasing the dose of PTCy to a total of 100 mg/kg given on days +3 and +4 with the intention of decreasing the incidence of GVHD. With two doses of PTCy the cumulative incidences of grades II–IV and grades III–IV acute GVHD by day 200 were 34% and 6%, respectively. There was no difference in the incidence of severe acute GVHD between one or two doses of PTCy. Furthermore, there was a trend toward a lower incidence of extensive chronic GVHD among recipients of two versus one dose of PTCy. Primary graft failure occurred in 13% of the patients. The cumulative incidences of NRM and relapse at 1 year were 15% and 51%, respectively. Actuarial OS and event-free survival (EFS) at 2 years after transplantation were 36% and 26%, respectively [29]. Subsequent analysis by Kasamon et al [30] of 185 patients who underwent NMA haploBMT at Johns Hopkins demonstrated no association between the degree of mismatching at five HLA loci and the risk of acute GVHD or NRM. Updated results from the growing Hopkins experience using two doses of PTCy for GVHD prophylaxis after haploBMT were published in 2011 by Munchel et al [31], showing similar outcomes in a larger number of patients. Collectively, these early clinical outcome data suggest that PTCy has been successfully translated from basic science research and preclinical models into clinical practice.

4. Expanding the use of PTCy, single-center experiences

Several other centers rapidly adopted PTCy and made various modifications to the original protocol such as increasing the intensity of conditioning or substituting peripheral blood stem cells (PBSCs) for bone marrow as the graft source. These developments were driven in part by concerns that the original NMA conditioning was insufficient to control aggressive hematologic malignancies, and that use of PBSCs may provide ease of protocol acceptance in centers where this graft source is preferred, as well as to decrease the rejection rate due to higher donor T-cell dose in comparison to BM. These modifications will be discussed in turn (see also Table 1). The San Martino Hospital group reported outcomes [32] for a cohort of 148 patient with variety of hematologic malignancies who underwent haploBMT with myeloablative conditioning followed by PTCy. They recently published updated results that confirmed early encouraging outcomes, with the incidence of severe GVHD at 4%, OS at 4 years of 53%, and only 1% graft failure. The relapse rate was 27% in this trial with myeloablative conditioning [33]. The BMT group at Northside Hospital in Georgia also tested myeloablative conditioning using fludarabine, busulfan, and Cy, and engrafted patients with PBSC followed by PTCy. The rate of grade II–IV acute GVHD was 30%, while the incidence of chronic GVHD was 35%. NRM was 10%, and the relapse rate was 40% in this cohort of high-risk hematologic malignancy patients. OS at 1 year was 69% [34]. In a subsequent report by Solomon et al, the same group of investigators reported outcomes using a conditioning method with myeloablative doses of TBI (1,200 cGy) and fludarabine, and continued using PBSC for engraftment. In this study of 30 patients there was no graft failure, and the rates of acute GVHD grade II–IV, grade III–IV, and chronic GVHD were 43%, 23%, and 56%, respectively. At a median follow-up of 2 years 78% of patients were alive [35]. Investigators at Thomas Jefferson University developed an innovative protocol that separated the infusion of T cells and $CD34^+$ stem cells after TBI-based myeloablative conditioning. PBSCs were collected from donors over several days, and T cells and $CD34^+$ cells were sorted ex vivo. After completing conditioning with TBI, patients received a fixed dose of 2 x 10^8 $CD3^+$ donor T cells per kg, then after a rest period of 2 days alloreactivity was ablated with two doses of PTCy, followed by infusion with $CD34^+$ PBSCs. The investigators' goal for this two-step approach was to deliver a fixed dose of T cells and to avoid exposing the stem cells to Cy [36]. Results of patients who were in remission at the time of haploBMT have been encouraging with NRM of 4%, a low relapse rate of 22%, and excellent overall survival of 77% at 2 years [37]. Together,

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