Haploidentical Donors: Can Faster Transplantation Be Life-Saving for Patients with Advanced Disease?

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Key Words

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Abstract

Haploidentical stem cell transplantation is a therapeutic option for patients without an HLA-matched donor. It is increasingly being used worldwide due to the application of post-transplantation cyclophosphamide and is associated with lower incidence of graft-versus-host disease and treatment-related mortality. Haploidentical donors are generally available for most patients and stem cells can be rapidly obtained. Delays in transplantation while waiting for unrelated donor cells can be potentially problematic for patients with advanced disease at risk for progression; thus, the use of haploidentical donors, especially in this setting, can be life-saving. Here we reviewed the literature on haploidentical stem cell transplantation performed with posttransplantation cyclophosphamide.

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Introduction

Hematopoietic stem cell transplantation is an effective treatment for advanced hematological malignancies. An HLA-identical related donor is preferred; however, such donors are unavailable for the majority of patients (70%) [1, 2]. The traditional alternative donor has been a matched unrelated donor. However, acquisition of unrelated donor cells is limited by significant expenses and delays which are on average approximately 4 months [3, 4]. Such a delay in performing an unrelated donor transplant could mean that a proportion of patients with advanced disease may progress while awaiting transplantation. Haploidentical hematopoietic stem cell transplantation (haploSCT) is increasingly being performed worldwide. Mismatched relatives represent an alternative source of readily available progenitor cells for virtually all patients [5, 6]. Historically, haploidentical stem cell transplantation has been limited by high rates of graft rejection and acute graft-versus-host disease (GVHD) elicited by the presence of donor T cells in the haploidentical graft, while a strong antitumor effect was observed [7]. The use

of a T-cell-depleted graft from mismatched relatives decreased the rate of GVHD at the expense of a higher risk of rejection and reduced graft-versus-leukemia effect with an increased relapse rate and severe infections [8]. Two main alternative approaches to complete T-cell depletion have been developed – the use of a T-cell-replete graft followed by posttransplantation cyclophosphamide (PTCy), tacrolimus and mycophenolate for GVHD prophylaxis, and partial T-cell depletion (e.g. depletion of $\alpha\beta$ T cells from the graft) [9, 10]. PTCy is gaining widespread acceptance due to the low cost of the drugs, lack of sophisticated devices to manipulate the graft and rapid applicability. Transplant outcomes using haploidentical donors with PTCy have improved over the past several years and are comparable with outcomes of matched unrelated donors [11–13]. These encouraging early results will likely extend this form of transplantation worldwide. Here we review the literature on this topic, probably the most important development in transplantation at present, and report the first successful application of this type of transplant in Romania.

PTCy for GVHD Prevention

Over the last few years, haploidentical donors have become a viable source of stem cells in transplant hematology due to a better understanding of the HLA barriers, control of alloreactivity and improvements in immunological reconstitution. These have been primarily accomplished by the use of PTCy as the main method of GVHD prevention in patients treated with a T-cell-replete graft [14]. In a seminal paper published by Berenbaum and Brown [15] in 1963, the first investigation of the effects of cyclophosphamide on the immune system was presented. This group injected 200 mg/kg cyclophosphamide in the peritoneum of mice, which had also received a major histocompatibility mismatched skin graft. The transplanted mice treated with cyclophosphamide 3 or 4 days after the skin graft exhibited a delayed graft rejection. This proved that PTCy exerted a favorable effect on graft survival, correlating with a time-dependent immune suppression. Three years later, Santos and Owens [9] applied this hypothesis in stem cell transplantation at the Johns Hopkins Medical Institutions (JHMI) and showed that rats treated with PTCy 2 days after transplant had a much lower incidence of skin GVHD. The preclinical data on mice and PTCy were also confirmed by Mayumi et al. [16], who proved that tolerogen, antimitotic drugs and their doses, timing, route of administration, combined immunosup-

pressants, and supportive treatment were all crucial for successful induction of a long-lasting skin tolerance. Luznik et al. [17] subsequently showed that major histocompatibility-mismatched bone marrow cells have the ability to engraft donor cells following nonmyeloablative conditioning chemotherapy consisting of fludarabine or cyclophosphamide, plus total body irradiation, and use of PTCy on day +3. These results were strengthened by an improvement in survival of mice that received PTCy.

After the administration of cyclophosphamide, the alloantigen-stimulated T lymphocytes are directly effected first, with both antihost T cells and recipient antidonor T cells undergoing apoptosis after a few days [18]. Alloreactive T lymphocytes have the ability to proliferate extensively in the immediate posttransplant period because of the major HLA mismatch. Still, donor stem cells and memory T lymphocytes are spared, owing to their quiescent nature and lack of susceptibility to cytotoxic chemotherapy which eliminates predominantly differentiated cells. Persistence of stem cells would reconstitute donor hematopoiesis, and memory T cells likely help the defense against posttransplant infections, as seen in figure 1. An improvement in immunological reconstitution and a lower incidence of infectious complications was first assessed by the physicians at The University of Texas MD Anderson Cancer Center (MDACC) [19]. This group treated a similar number of patients with a T-cell-replete haploSCT with complete T-cell depletion with CD34+ selection, and showed significantly improved outcomes of patients treated with PTCy. This has made the change from complete T-cell depletion to partial depletion of alloreactive T cells with PTCy, offering the clinical proof for the improved efficacy with this approach. The issue of immunological reconstitution was also investigated at the San Raffaele Scientific Institute in Milano a few months ago, concluding that at the antigen-specific and clonal level, memory stem T cells can differentiate directly from naïve precursors infused within the graft and that the extent of their generation might correlate with interleukin 7 serum levels [20]. In the same issue of *Blood*, another group from Milan transplant immunology group described their experience and affirmed that donor-naïve T cells specific for exogenous and tumor antigens persist in the host and contribute to peripheral reconstitution by differentiating into effectors. In a similar manner, pathogen-specific memory T cells generate detectable recall responses, but only in the presence of the cognate antigen [21]. Another mechanism by which PTCy is associated with a drug-induced tolerance is the decrease in the number of antihost T cells derived from the hematopoietic

Fig. 1. Mechanism of action of PTCy.

stem cells of the thymus [16]. A possible explanation for this differential effect of cyclophosphamide on various cells present in an unmanipulated graft may reside in the fact that hematopoietic stem cells are nondividing cells that express a high level of aldehyde dehydrogenase, an enzyme that allows the cell to be resistant to various drugs, including cyclophosphamide [22–25]. Other cells, such as NK cells and naïve T and B lymphocytes, are more sensitive to cyclophosphamide due to the low levels of the enzyme and are rapidly eliminated [26].

An important technical aspect for treatment of haploSCT patients is the conditioning regimen used in preparation for transplantation which was recently reviewed [11]. Initially, a nonmyeloablative conditioning regimen was used [27] consisting of the administration of 30 mg/m² fludarabine on days –6 to –2, total body irradiation of 2 Gy on day –1, and 50 mg/kg PTCy on day +3. Subsequently, cyclophosphamide was added with fludarabine and another dose of PTCy was also added on day +4 as it was appreciated that patients who received 2 doses had better control of GVHD [28–32]. Comparative outcomes with umbilical cord blood transplantation (UCBT) have been reported with this regimen [33]. While no significant differences were noted in overall survival, remarkably low nonrelapse mortality (NRM) (7%) and no grade III–IV acute GVHD were observed in patients treated with a haploidentical donor. While the NRM was much better in the haploSCT group (7% for haploSCT vs. 24% for UCBT), the relapse rate appeared higher for haploidentical transplants (45% for haploSCT vs. 31% for UCBT).

For this reason, the MDACC group has used a more intense, melphalan-based conditioning regimen for haploidentical stem cell transplantation with PTCy. Melphalan is an alkylating agent with broad antitumor effects including for myeloid and lymphoid diseases [34]. A modified fludarabine-melphalan-based conditioning regimen has been used successfully for these patients, which was initially reported for patients treated with T-cell depletion [29]. This conditioning chemotherapy regimen allowed a high engraftment rate with low NRM and better disease control in patients with acute leukemia and lymphoma [35, 36]. This remarkable American experience was not without consequences in transplant hematology worldwide: the number of haploidentical transplants reported to the CIBMTR database have doubled since 2010 and increased by 96% in Europe in the last 4 years, as reported by the European Group for Blood and Marrow Transplantation (EBMT) [37].

A major concern in using PTCy has been increased posttransplant immune suppression and delayed immunological reconstitution [38, 39]. However, in a recent report from the MDACC group, the kinetics of lymphocyte reconstitution both in HLA-matched transplants performed with conventional GVHD prevention and haploidentical transplants performed with PTCy showed a remarkably similar pattern of immunological reconstitution [37]. CD4+ and CD8+ lymphocytes, naïve and memory T cells, NK cells, and B lymphocytes were evaluated at 1, 2, 3, 6, and 12 months after the transplant and showed almost identical patterns, except that matched siblings tended to have higher numbers of CD4+ and

CD8+ T cells on day +30 posttransplant, which may explain, at least in part, a lower NRM associated with HLA-matched sibling donors. These results suggest that PTCy does not significantly affect the immune reconstitution after haploidentical transplantation, which was also confirmed by Wang et al. [38]. Employing both syngeneic and allogeneic minor antigen-mismatched T-cell-replete models of transplantation, Ross et al. [40] showed that PTCy abrogates GVHD and preserves most cells that are dividing because of the accompanying lymphopenia after exposure. These results are in accordance with the data of Ganguly et al. [41], which state that PTCy-mediated protection against GVHD is not singularly dependent on depletion of donor alloreactive T cells but also requires rapidly recovering donor Tregs to initiate and maintain alloimmune regulation.

Conclusion

Finding a suitable donor is the main challenge for allogeneic stem cell transplantation. For up to 50% of all potential transplant patients, an HLA-matched sibling donor or an HLA-matched unrelated donor cannot be identified or cannot be identified in time, and the patient often relapses and dies from disease progression. Partially HLA-matched related donors, also known as an HLA-haploidentical first-degree relative, which are available for most patients, fill an important need for transplantation.

However, until recently this procedure has been fraught by severe toxicity and treatment-related mortality – initially by a high incidence of hyperacute GVHD [42], and more recently by high NRM associated with extensive T-cell depletion [43]. A major breakthrough was the development of PTCy, which has allowed the use of a

non-T-cell-depleted graft with effective control of GVHD and a lower incidence of infectious complications. PTCy has now been shown to be effective with a variety of preparative regimens with very good results confirmed by several groups and rapid expansion worldwide. The use of haploidentical donors as compared to unrelated donors, including cord blood, is even more important in Eastern European countries such as Romania as well as in other developing countries that do not have public cord blood banks due to the high costs associated with maintaining these banks. Such countries have difficulty obtaining unrelated donor cells due to the high costs associated with acquisition of these products. In addition, a longer time for unrelated donor search, donor ineligibility and longer time to transplantation in general associated with unrelated donor transplantation are important limitations, as seen in this case.

In conclusion, haploidentical stem cell transplantation is emerging as a fast type of transplant irrespective of the race of the recipient, offering a therapeutic alternative for a wide variety of hematological malignancies and thus extending transplantation to patients who, until now, have not had access to this life-saving procedure.

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Disclosure Statement

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