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Haploidentical transplantation: selecting optimal conditioning regimen and stem cell source

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ABSTRACT

Recently, haploidentical donor transplant (HIDT) has emerged as a viable option for patients in need of an allogeneic stem cell transplant without an immediately available well-matched human leukocyte antigen (HLA) sibling or unrelated donor. Given the near immediate availability of haploidentical donors, along the high likelihood of a haploidentical match within a patient's first-degree family, HIDT is becoming increasing attractive, particularly for patients with high-risk disease. In the last decade, several strategies of T-cell–replete bone marrow or peripheral blood HIDT has been developed with diverse conditioning regimens and graft-versus-host disease prophylaxis based on diverse in vivo T-cell modulation strategies conducting to a wide development for the treatment of benign and malignant hematological disorders. Several conditioning, different stem cell sources, and graft-versus-host disease (GVHD) prophylaxis regimens have been designed by different groups at the same time. They all demonstrated the feasibility of such transplants with limited non-relapse mortality (NRM) and promising survival rates. However, comparative studies between the different transplant strategies had not been performed. Herein, we discuss the conditioning regimens and stem cell sources that have been used for haploidentical transplant.

1. Introduction

Haploidentical donor transplants (HIDTs), or the so-called "half-matched" transplants have recently been shown to be an effective transplantation strategy for some patients with hematologic malignancies in need of allogeneic stem cell transplantation. In the past, if patients did not have a well-matched donor, these patients often would succumb to their disease while waiting for a donor to be identified. Recent advances in allogeneic stem cell transplantation have showed that haploidentical donors, which typically include parents, siblings, and children, are increasingly viable possible donor options. Thus, almost all patients in need of a donor will have one potentially identified when haploidentical donors are consider, and in general these donors are almost immediately available for transplantation. With the advent of recent research showing improvements in post transplant complications, this type of transplant is emerging as a potentially comparable strategy to matched sibling and unrelated donor transplants.

2. Conditioning intensity

2.1. T-cell depletion and myeloablative regimen

Historically, high incidences of graft rejection and severe graft-versus-host-disease (GVHD) were the major limiting factors to the success of HIDT [1,2]. This led researchers to look at T-cell depletion (TCD) of haploidentical grafts. Initial studies used this strategy to overcome the intense bidirectional alloreactivity that was being seen and was accomplished by negative selection by soybean agglutination and erythrocyte rosetting [3,4]. Conditioning regimens were myeloablative and consisted of 8 Gy of total-body irradiation (TBI) on day −9 in a single fraction; thiotepa (5 mg/kg daily) on days −8 and −7; fludarabine 40 mg/m^2 daily on days −7 to−3, and rabbit anti-thymocyte globulin (ATG) at 5 mg/kg daily from days −5 to −2. No additional immune suppression was

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given as GVHD prophylaxis, and no granulocyte colony-stimulating factor (G-CSF) was administered post-transplantation. Grafts were primarily bone marrow grafts. This strategy unfortunately led to higher rates of graft rejection and high rates of opportunistic infections [5]. The same group would look at $CD34^+$ immunoselection in the setting of peripheral blood (PB) grafts [6] and while their results showed that HIDTs were feasible with low incidences of acute GVHD (aGVHD) and chronic GVHD (cGVHD) with comparable relapse rates, non-relapse mortality (NRM) was high and in the range of 30%–50% and attempts to modify TCD HIDT have not been successful at reducing the excessively high NRM [5,6].

2.2. Peking University experience

Another group of researchers at Peking University developed the GIAC protocol in the setting of HIDT without the use of in vitro TCD. The protocol entailed treating donors with G-CSF to induce donor immune tolerance, use of ATG for prophylaxis of GVHD and graft rejection, and combination of G-CSF–primed bone marrow and PB as stem cell grafts. What they found was that when compared to HLA-matched sibling donor transplants, HIDT outcomes in this setting had similar relapse rates, NRM, disease-free survival (DFS), and overall survival (OS). The conditioning regimen was a was modified BUCY2 in matched sibling transplantations consisting of cytarabine (2 g/m^2 per day) intravenously on days –10 to –9; busulfan (4 mg/kg per day) orally on days –8 to –6; cyclophosphamide (1.8 g/m^2 per day) intravenously on days –5 to –4; and Me-CCNU (250 mg/m^2) orally once on day –3. In HLA-mismatched HCT, patients received the BUCY2 regimen consisting of a higher dose of cytarabine (4 g/m^2 per day) intravenously on days –10 to –9, but otherwise an identical regimen to the HLA-matched patients, along with ATG (thymoglobulin 2.5 mg/kg per day. Stem cell grafts combined bone marrow and PB using standard G-CSF mobilization (5 μg/kg per day; filgrastim) for both. bone marrow was harvested on day 0 while PB was harvested on day 1. Their results showed that all patients achieved full engraftment with comparable rates of grades II–IV aGVHD and cGVHD. NRM and relapse rates (RR) in the HIDT and MDS groups were similar at 14% versus 22% ($P = .10$) and 13% versus 18% ($P = .40$), respectively. Two-year DFS was 71% and 64% ($P = .27$), and OS was 72% and 72% ($P=.72$), respectively, indicating that this strategy is a feasible transplantation option [7].

Huang et al would also report a similar protocol of G-CSF primed grafts without in vitro T-cell depletion in 171 patients who underwent HIDT. Conditioning regimens were similar with the exception of addition of simustine (Me-CCNU). One hundred sixty-seven patients were treatment on regimen A, which consisted of cytarabine (4 g/m^2 per day IV) on day –10 and –9; busulfan (12 mg/kg) orally over 12 doses on days – 8 to day –6, cyclophosphamide (Cy) (1.8 g/m^2 per day IV) on days –5 and –4, Me–CCNU (250 mg/kg IV) on day –3, and ATG (20 mg/kg/d IV if porcine or 2.5 mg/kg/d IV if rabbit) on days –5 to –2. Four patients received regimen B, which was similar with the exception of lower doses of Bu (6–9 mg/kg) and Cy (1.0 g/m2/d). Grafts were also G-CSF–primed bone marrow and PB. All patients achieved sustained full donor chimerism. The cumulative incidence of grade III–IV aGVHD was 23% and of extensive cGVHD, 47%. The 2-year probability of relapse was 12% and 39% for standard-risk and high-risk diseases, respectively. The 2-year probability of DFS was 68% for standard-risk patients and 42% for high-risk patients ($P = .0009$). For standard-risk patients, NRM was 9.1% at day 100, 17.4% at 1 year, and 19.5% at 2 years, while NRM was higher in the high-risk group at 12.7%, 29.7%, and 31.1%, respectively. Grade III–IV aGVHD was associated with better DFS ($P = .0017$) [8].

Huang et al would later report outcomes of 250 consecutive patients with acute leukemia treated on their protocol, all of whom would achieve sustained full donor chimerism. Incidences of aGVHD were not associated with the extent of HLA disparity and grades II–IV aGVHD was 45.8% and grades III–IV was 13.4%. Total cumulative incidence of cGVHD was 53.9% and was extensive in 22.6% in 217 evaluable patients. DFS for acute myeloid leukemia (AML) was 70.7% and 55.9% for standard- and high-risk groups, respectively, and for acute lymphoblastic leukemia (ALL) was 59.7 and 24.8%, respectively. Day 100 NRM for the standard- and high-risk AML groups were 6.8% and 5.9%, respectively, and for ALL were 6.9% and 25.9%, respectively. At 3 years, NRM was 19.4% and 29.4% for the AML group and 21.2% and 50.8% ($P = .049$) for the ALL group based on standard- or high-risk status, respectively. Their analysis showed that patients with high-risk ALL had the highest NRM risk with RR of 2.422 (95% confidence interval [CI], 1.005–5.835) [9].

Comparison studies have been done and showed similar DFS after HIDT using these protocols compared with outcomes using MSD transplantation [9–12,27]. Though these protocols used myeloablative conditioning with either G-CSF–primed bone marrow and PB, the need for less intensive conditioning to improve NRM and GVHD rates led to the development of non-myeloablative (NMA) conditioning regimens for HIDT. This along with the use of post-transplant cyclophosphamide (PTCy) was developed by the Johns Hopkins group to reduce the risk of graft rejection and GVHD. Their protocol was initial conceived in preclinical mouse models and showed that Cy, which is a highly immunosuppressive alkylating agent, promoted tolerance to allogeneic major histocompatibility (MHC)-mismatched skin grafts in mice [13]. This would be further studied in the allogeneic hematopoietic transplant setting and Luznik et al showed in the mouse model that Cy administered on day +3 was able to achieve stable engraftment despite the MHC-incompatible cells with less lethal and nonlethal GVHD [14]. What was shown was that the use of PTCy as a means of selective in vivo allodepletion was feasible, one that balanced the need to remove the alloreactive T cells in the graft while leaving behind the donor lymphocytes needed and responsible for immune reconstitution.

2.3. Johns Hopkins non-ablative regimen

Luznik et al published the results of their novel study evaluating the safety and efficacy of high-dose PTCy to prevent graft rejection and GVHD after nonmyeloablative conditioning and T-cell–replete bone marrow transplants from haploidentical donors. The protocol consisted of Cy 12.5 mg/kg/d IV on days –6 and –5, fludarabine 30 mg/m^2/d IV on days –6 to –2, 200 cGy of TBI on day –1, followed by bone marrow infusion on day 0. On day +3 or on days +3 and +4, patients received 5 mg/kg of Cy administered with mesna by IV infusion. Additional GVHD prophylaxis in the form of tacrolimus or mycophenolate mofetil (MMF) was not allowed until the day following completion of PTCy. Patients also received filgrastim support dosed at 5 μg/kg/d by subcutaneous injection starting on day 4 and continuing until recovery of neutrophils to >1,000/μL for 3 days. Their results showed a median time to neutrophil recovery of 15 days and to platelet recovery of 24 days. Graft failure occurred in 13% of patients and was ultimately fatal in one patient. The cumulative incidences of grades II–IV and grades III–IV aGVHD by day 100 were 34 and 6%, respectively. The cumulative incidence of NRM was 15% at 1 year, but the cumulative incidence of relapse at 1 year was high at 51%. Patients who had lymphoid malignancies did better with improved DFS compared with those with myeloid malignancies ($P = .02$). Although their results showed acceptable rates of fatal graft failure and severe aGVHD and cGVHD, the relapse rate reported high, largely felt due to the nonmyeloablative approach [15].