Review Article

Haploidentical stem cell transplant: Established treatment, expanding horizons

ABSTRACT

Haploidentical stem cell transplantation offers an oppurtunity for transplant for almost all patients for whom transplant is indicated. Traditionally, it is associated with higher incidence of graft failure, graft vs host disease and non relapse mortality as compared to matched donor transplant. However, recent advances in the field have tried to mitigate these issues and offer haploidentical transplant as a safe and viable option. In this review, we shall discuss the basics of haploidentical transplantation, how to choose the best donor amongst various haploidentical donors available and understand the various recent advances in the field of haploidentical transplantation and how they addressed the problems associated with it and make it a feasible alternative to matched sibling or unrelated transplant in various diseases.

Key words: Graft versus host disease; haploidentical stem cell transplantation; hematopoietic stem cell transplantation; posttransplant cyclophosphamide

Introduction

Hematopoietic stem cell transplantation (HSCT) or bone marrow transplant (BMT) is a potentially curative therapy for a variety of blood cancers and genetic diseases. Allogeneic SCT (stem cell of related/unrelated donor) is usually recommended for acute myeloid leukemia (AML), high risk acute lymphoblastic leukemia, aplastic anemia, thalassemia and sickle cell anemia, and immunodeficiency syndromes. It relies on giving chemotherapy and immunosuppressive therapy to eradicate abnormal cell clone and suppress host immunity to allow donor's stem cell to engraft over 2–3 weeks. These donor cells subsequently provide lasting graft versus tumor (GVT) effect which helps maintaining long-term disease control.

The best donor for allogeneic HSCT is a human leukocyte antigen (HLA)-matched sibling donor (MSD).[1] With the establishment of worldwide registries of voluntary donors, a fully matched unrelated donor (MUD) can be utilized for many cases. However, the probability of finding an MSD is 30–40% in most cases and unrelated donor can be mobilized in time for as many as 40–50% cases and can be very expensive. Further, finding an MUD donor can be difficult for ethnically under-represented minorities such as African-Americans and South Asians in donor registries. Many patients become too ill or relapse while waiting for an MUD to be mobilized, with usual waiting time of 2–3 months in most cases. Recent advances have allowed to perform transplants using partially matched (haploidentical) related donors with nearly equivalent outcomes.

An HLA-haploidentical donor is a related donor who shares at least one HLA haplotype with the recipient, with variable sharing of HLA genes on the other haplotype. Biological parents and children are potential haplo donors. In addition, each sibling has a 50% chance of sharing at least one

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haplotype. As a result, more than 90% of patients needing a transplant have a usually readily available haploidentical donor. Moreover, the cost of stem cell collection is lower with haplo SCT than cord or MUD transplants. Theoretically, there was the idea that the broad HLA disparity involved in haplo-HSCT would result in a stronger graft-versus-leukemia effect in comparison with HLA-matched transplants. However, these advantages were marred by higher rates of graft versus host disease (GvHD), graft failure, prolonged immunosuppression, and subsequent higher nonrelapse mortality (NRM). The HLA reactive T-cells in haplo transplant may contain memory T-cells, which make GvHD more difficult to manage.

As the role of alloreactive T-cells in the pathogenesis of GvHD was identified, several attempts have been made in the allograft to decrease their number. Furthermore, these alloreactive lymphocytes are commonly associated with high degree of noninfectious fevers, diarrhea, and rash and rarely with hypotension and pulmonary edema. Earlier studies of haplo SCT without T-cell depletion reported severe GvHD incidence as high as 50%.[1,2] However, T-cell depletion is accompanied by higher incidence of primary graft failure and higher incidence of opportunistic infection.[3] There is a need to balance all these potentially fatal complications after haplo SCT. This balance can be achieved either by selective removal of alloreactive lymphocytes from the graft or by enhancing immune reconstitution following T-cell depletion.

Choosing a Haploidentical Donor

Commonly, more than one haploidentical donor is available for a given patient. Final selection among them is guided by multiple factors including degree of HLA mismatch, presence of anti-donor antibodies, NK cell alloreactivity, noninherited maternal or paternal antigens, and age.

Age and sex

Choosing a donor <30 years age for haplo SCT is associated with superior transplant outcomes than a donor more than 30 years old. As compared to a female donor, haplo SCT using a male donor is associated with lower NRM and lower GvHD, together with better overall survival (OS).[4]

Degree of human leukocyte antigen mismatch

It appears obvious that greater the HLA disparity more will be chances of severe GvHD and subsequent NRM. However, with availability of better immunosuppression modalities (both prophylactic and therapeutic), the detrimental impact of HLA disparity appears to be mitigated. Kasamon *et al*.[5] examined the impact of HLA mismatching on the outcomes of 185 hematologic malignancy patients treated with non-myeloablative (MA), HLA-haploidentical BMT, and high-dose posttransplant cyclophosphamide (Pt-Cy). No significant association was found between the number of HLA mismatches in the GvH direction and risk of severe acute GvHD (aGvHD) (hazard ratio [HR] of 0.89; *P* value of 0.68 for 3–4 compared with fewer antigen mismatches). Huo *et al*.[6] examined the impact of HLA mismatching on the outcomes of 481 patients undergoing MA conditioning with GvHD prophylaxis comprised cyclosporine A, short-course methotrexate, and mycophenolate mofetil. They concluded that even though mismatching at HLA-B was associated with increased risk of aGvHD and NRM, it did not result in a significant decrease in OS or leukemia-free survival.

Anti-donor human leukocyte antigen antibodies in the patient

The presence of anti-donor HLA antibodies in the recipient is associated with high risk of graft failure and is considered an absolute contraindication for haplo transplant with this donor.[7] These antibodies can be detected by lymphocytotoxic cross-matching, flow cytometric cross-matching, and solid-phase immunoassay (SPI). Usual cut-off for antibody titer is mean fluorescence intensity >1000 on SPI. Finding a suitable donor in such situation can be really difficult and sometimes desensitization with combination of immunosuppressive medications may be considered.

NK cell alloreactivity

NK cells mediate GVT effect after SCT.[8] However, how this is influenced by donor's killer immunoglobulin receptor (KIR) genes has been a matter of debate. Two models of NK cell alloreactivity have been put forward in this regard – missing self-theory and missing ligand theory. The missing ligand model predicts that only HLA genes of the recipient have an effect on outcome while the missing self or KIR ligand incompatibility model suggests predicts that HLA genes in the donor and the recipient both influence outcome. Different studies have supported both theories, depending on intensity of conditioning regimen and T-cells in graft.[9] Several studies suggest better prognosis with activating KIR genes such as KIR2DS1 or KIR2DS2 or the KIR "B" haplotype containing most activating KIR genes.[10]

Noninherited maternal or paternal antigens

The maternal immune system and hence mother's T-cells are exposed to a host of fetal antigens during pregnancy. This results in better tolerance of maternal immune cells to patient's antigens, leading better survival. However, this benefit could be demonstrated only in T-cell–depleted

haplo SCT[11] but not so clearly in T-cell–replete SCT grafts. Similarly, haplo SCT with sibling donor with mismatched noninherited paternal antigens tend to have worse GvHD and transplant-related mortality (TRM) than haplo sibling with mismatched noninherited maternal antigens.[12]

Selective T-cell Depletion in Haploidentical Stem Cell Transplantation Allograft

Ex vivo techniques

T-cell depletion in an allograft can be achieved by a negative selection of alloreactive T-cells or by positive selection of CD 34 positive cells. CD 34 selection is associated with lower incidences of GvHD, but poor immune reconstitution as several other immune cells including NK cells, monocytes, and dendritic cells are also removed. Selective depletion of CD 3+ and CD 19+ cells serves similar purpose, with better immune reconstitution. Federmann *et al*. treated 61 patients of hematologic malignancies with reduced intensity conditioning (RIC) and CD3 and CD19 depleted haplo grafts.[13] NRM was 23% at 100 days and 42% at 2 years, with relapse rate of 31%. The cumulative incidences of Grades II–IV aGvHD and chronic GvHD (cGvHD) were 46% and 18%, respectively.

Negative selection of T-cells expressing alpha-beta T-cell receptor preserves the gamma delta T-cells population in the allograft. These cells have potent anti-leukemia effects.[14]

Alloreactive T-cells can also be depleted by using a photosensitizing compound, which accumulates in them and subsequent elimination by light. The approach appears promising, but immune recovery may be delayed.[15]

Selective depletion methods of T-cells have not been widely used due to high cost involved and need for specialized equipped laboratories and trained personnel.

In vivo techniques

High-dose posttransplantation cyclophosphamide

Cyclophosphamide in high doses (50 mg/kg on days 3–4, poststem cell infusion) has been used as a strategy to selectively target alloreactive T-cells, thus helping in reducing the incidence of both GvHD and graft failure. The drug specifically kills antigen responsive lymphocytes that were activated and proliferating in response to the immunogenic antigen exposure while sparing lymphocytes specific for other antigens. Quiescent T-cells such as those active against herpes virus, cytomegalovirus, and other pathogens are spared, thus providing better infection control in the posttransplant period.[16] In the preclinical studies, Luznik *et al*. achieved tolerance and durable chimerism with MHC-incompatible cells by conditioning mice with fludarabine and total body irradiation (TBI), transplanting marrow on day 0, and giving Pt-Cy on day 2.[17]

Pt-Cy as a method of T-cell depletion has been pioneered by John Hopkins Group. Johns Hopkins regimen for RIC haplo SCT consists of the following: Cy 14.5 mg/kg/day on days -6 and -5; fludarabine 30 mg/m^2/day on days -6 to -2; TBI 200 cGy on day 1; Cy 50 mg/kg/day on days 3 and 4 followed by G-CSF 5 mg/kg/day till engraftment and mycophenolate mofetil 15 mg/kg/day and tacrolimus as GvHD prophylaxis. They treated 210 patients with hematological malignancies with RIC haplo transplant and Pt-Cy and reported cumulative incidence of Grade III–IV GvHD and cGvHD as 5% and 34%. Two-year cumulative incidences of relapse and NRM were 51% and 15%, respectively.[18] The data were subsequently updated to 374 patients. The OS and progression-free survival (PFS) at 5 years were 40% and 31% respectively. Five years survival for AML, acute lymphocytic leukemia, B-cell, non-Hodgkin lymphoma, and Hodgkin lymphoma was 43%, 32%, 49%, and 52%, respectively.[19]

Ciurea *et al*.[20] compared haplo SCT with T-cell–replete BMT with Pt-Cy versus T-cell-depleted peripheral blood SCT in 65 consecutive patients treated with fludarabine-melphalan-thiotepa based conditioning regimen. Primary engraftment was achieved in 94% of the T-cell–replete group and 81% of the T-cell-depleted group ($P = 0.1$). NRM at 1 year was 16% for the former group versus 42% for the latter ($P = 0.03$). The cumulative incidences of Grade II–IV aGVHD were 27% versus 11% ($P = 0.5$) and cGVHD were 8% versus 18%, in the T-cell-replete and T-cell-depleted groups, respectively ($P = 0.03$). OS and PFS at 1 year after transplantation were 66% versus 30% ($P = 0.02$) and 45% versus 21% ($P = 0.03$), respectively. The NRM may be explained by rapid recovery of T-cells and NK cells which help in earlier immune reconstitution.

The results from various centers across the globe using John Hopkins protocol have been comparable, suggesting uniform applicability and ease of use with this protocol. However, it is still needed to be compared with mega-dose SCT, MUD, and MSD in prospective trials. Results with benign hematological disorders including hemoglobinopathies, bone marrow failure syndromes, and immunodeficiency syndromes require more mature data.

Two-step approach

Pt-Cy exposes the stem cells to an alkylating agent. Furthermore, the use of cyclophosphamide for T-cell tolerization is associated with very low rates of significant GvHD.[21] To combine these two goals, Grosso *et al*. developed a two-step approach to haplo SCT using both MA and RIC

conditionings.[22] During the conditioning, donor T-cells at a dose of 2 × 10^8/kg are infused on day 6 of transplant after TBI is given, followed by high-dose cyclophosphamide on day -3 and -2 and finally CD 34 + stem cells on day 0. No patients died from GVHD and rates of regimen-related and infectious mortality were low, resulting in a cumulative NRM of only 22.2%. Patients without evidence of disease at the time of HSCT fared well based, with an OS rate of 75%, 4–6½ years later. OS rate for patients with active disease at HSCT was only 27%, with the majority of these patients dying of relapse.

Tackling Graft Failure

Primary graft failure, i.e., no neutrophil engraftment occurring after SCT is an ominous sign and is associated with high TRM. Conventionally, high percentage of patients receiving haplo SCT did not engraft. This issue has been dealt by different approaches. Using John Hopkins strategy of Pt-Cy in a T-cell-replete graft, the incidence of graft failure is 10% in MA and 13% in RIC transplants.[23] With the infusion of mega-dose CD 34+ cell dose (median 13.8 × 10^6), Perugia group showed primary graft failure rate of only 9%.[24] The GIAC protocol pioneered in China comprising granulocyte-colony-stimulating factor stimulation of the donor; intensified immunosuppression through posttransplantation cyclosporine, mycophenolate mofetil, and short-course methotrexate; antithymocyte globulin added to conditioning to help prevent GVHD and aid engraftment; and combination of PBSC and bone marrow allografts.[25] Huang *et al*. used a combination of T-cell-replete BM and granulocyte colony-stimulating factor-mobilized PBSCs with MA conditioning regimen and showed almost no primary engraftment failures.[26]

Relapse Rates

Relapse rate after any SCT depends on disease status at time of SCT, risk stratification of disease, GvHD prophylaxis used and type of conditioning. With Pt-Cy and RIC transplant, relapse rate at 1 year was 45% while it was 22% with MA conditioning.[27] With Perugia regimen and mega CD 34 cell dose, relapse rate was 25% at 6 months, varying with 16% in those transplanted in remission versus more than 50% in those transplanted without remission.

Current Status of Haplo SCT

Over the years, with the availability of better supportive care, antifungals, and increasing experience with different types of SCT, the outcome of SCT has improved for most patients. This improvement is most marked in the outcomes of haplo SCT, becoming comparable to MUD and MSD at many centers. The 5-year survival for children receiving transplantations from haploidentical donors has improved from 19% to 88%, from MUDs has increased from 37% to 61%, and from MSDs has increased from 24% to 70%.[28]

Blood and Marrow Transplant Clinical Trials Network compared RIC haplo SCT with double-cord SCT.[27] Conditioning regimen comprised of fludarabine, cyclophosphamide, 200 cGy of TBI with Pt-Cy in haplo arm. Both types had equivalent neutrophil recovery and 100-day cumulative incidence of Grade II–IV aGVHD was 40% after dUCB and 32% after haplo-BMT. NRM and relapse at 1 year were 7% and 45%, respectively after haplo-BMT and 24% and 31% after cord SCT.

McCurdy *et al*. compared risk stratified outcomes of non-MA haplo SCT with Pt-Cy in 374 patients versus 614 patients with MSD/MUD. Their results indicate that survival outcomes for RIC haplo-BMT with Pt-Cy were similar to matched-BMT [Table 1].[29] Similarly, Bashey *et al*. showed that HLA haplo SCT with Pt-Cy resulted in similar rates of aGvHD and cGvHD and OS, when compared to MSD and MUD-SCT.[30]

Anurathapan *et al*. reported outcomes of 31 thalassemia patients with median age of 10 years treated with haplo SCT, with a median follow-up of 12 months (7–33 months).[31] Patients were treated with two courses of pretransplant immunosuppressive therapy with fludarabine and dexamethasone. Conditioning regimen consisting of rabbit antithymocyte globulin, fludarabine, and IV busulfan was given followed by T-cell-replete peripheral blood progenitor cells. GvHD prophylaxis consisted of Pt-Cy and on day SCT +5 tacrolimus or sirolimus was started together with a short course of mycophenolate mofetil. Twenty-nine patients engrafted with 100% donor chimerism. Two patients suffered primary graft failure. Median time to neutrophil engraftment was 14 days (range 11–18 days). Five patients developed mild to moderate, reversible veno-occlusive disease while nine patients developed aGvHD Grade II. Only five patients developed limited-cGvHD. Projected overall

Table 1: Comparison of reduced-intensity conditioning haplo-bone marrow transplant with posttransplantation cyclophosphamide and reduced intensity conditioning-matched bone marrow transplant. Survival outcomes at 3 years postbone marrow transplant

Disease risk index	Overall survival (%)		Progression-free survival (%)	
	Matched (*n*=614)	Haplo (*n*=374)	Matched (*n*=614)	Haplo (*n*=374)
Low	70	73	66	65
Intermediate	47	49	31	39
High	25	37	15	25

and event-free survival rates at 2 years are 95% and 94%, respectively.

Conclusions

Due to paucity of randomized controlled trials comparing various alternative donor transplants and MSD, it is difficult to predict the best donor for any given patient in the absence of MSD. Haploidentical SCT scores a point in being readily available donor in most cases, with cheaper collection and improving but acceptable rates of graft failure, GvHD, and NRM. The spectrum of diseases where haplo SCT is utilized continues to expand with response rates and OS improving in almost all conditions.

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Conflicts of interest

There are no conflicts of interest.

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