Chapter 4

Progress in Haploidentical Hematopoietic Stem Cell Transplantation

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Additional information is available at the end of the chapter

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Abstract

Haploidentical hematopoietic cell transplantation (HaploHCT), with cells from HLA-half-matched first degree related donors (siblings, children and parents), could revolutionize hematopoietic transplantation as it expands this form of treatment to approximately 40% of patients who do not have an HLA-matched donor in USA. This need is particularly acute in developing countries, which usually do not have an unrelated donor registry and/or cost is a major issue in acquiring unrelated donor stem cells. Accordingly, the number of haploSCTs done in USA, Europe, China, and developing countries is on the rise. Advantages to HaploHCT include almost universal (more than 95% of patients will have a half-matched related donor) and immediate availability of donor progenitor cells, the opportunity to select the best donor among family members to minimize treatment-related mortality, decrease relapse rate and improve outcomes [2], and the possibility to collect donor cells for cellular therapy post-transplantation, with the goal to enhance the anti-tumor effects of the graft. Despite its potential advantages, until recently, high donor-recipient HLA-histoincompatibility has proven very difficult to overcome.

Haploidentical transplants initially performed with conventional GVHD prophylaxis in late 70's led to a strong bidirectional alloreactivity, manifested by both high incidence of primary graft failure of approximately 30% as well as the development of a syndrome suggestive of hyperacute GVHD (manifested with seizures, renal failure, respiratory failure in the majority of patients) and very poor outcomes. To prevent GVHD after HaploHCT, *ex vivo* T-cell depletion (TCD) was used successfully in the 80's [5]; however, this approach resulted in a high incidence of graft rejection in up to 50% of cases [6]. This high incidence of graft failure, thought to be primarily related to the remaining T cells in the recipients system and lack of donor T cells in the graft to support engraftment, was improved in the 90's by intensifying the conditioning regimens, combining *ex vivo* and *in vivo* T-cell depletion, and increasing the donor graft inoculum using "mega-doses" of CD34+ cells. Primary engraftment was achieved in >90% patients with a low GVHD rate [8].

In the past decade, significant progress has been made as investigators from around the world have tried to overcome the fore-mentioned barriers in HaploHCT by using T-cell

replete grafts with intensified GVHD prophylaxis, or by the use of methods to selectively deplete T cells from the haploidentical graft [12]. In addition, the development of post-transplant cellular therapy to prevent or treat disease relapse and infectious complications after transplant has found an ideal applicability in related donor transplantation, including haploidentical transplants.

Keywords: Haploidentical Hematopoietic, Stem Cell Transplantation

1. Introduction

A human leukocyte antigen (HLA)-matched sibling is the preferred donor for allogeneic hematopoietic stem cell transplantation (AlloSCT); however, the probability of having such a donor depends on the number of one's siblings and is approximately 30% in the population. The probability of finding a matched unrelated donor (MUD), the second preferred donor, primarily depends on a patient's race and ethnicity. While a Caucasian's chance of having a MUD is 75%, that of an African American is less than 20% [1, 2]. For those without an HLA-matched donor, alternative hematopoietic progenitor cell sources include mismatched unrelated donors, haploidentical related donors, and umbilical cord blood.

While a patient's children and parents share one haplotype with the patient, the chance that one's sibling and cousin would share at least one haplotype is 75% and 37.5%, respectively. Consequently, almost all patients with known parents have at least one haploidentical donor. The use of haploidentical donors as an alternative to HLA-matched sibling donors (MSD) has been gaining momentum recently [3], particularly after the advent of posttransplantation cyclophosphamide [4], which rendered this form of transplantation easier and safer.

The primary challenge in AlloSCT from haploidentical related donors (HaploSCT) is overcoming the high HLA histoincompatibility barrier. In fact, first HaploSCT attempts in the late 1970s led to a strong bidirectional alloreactivity, leading to both high incidence of graft failure and the development of hyperacute graft-versus-host disease (GVHD) [5, 6]. To prevent GVHD after HaploSCT, ex vivo T-cell depletion (TCD) was used in the 1980s [7]; however, this led to a high incidence of graft rejection due to the lack of T cells in the graft that would have eliminated the remaining recipient T cells [8]. Outcomes after HaploSCT were improved in the 1990s by intensifying the conditioning regimen, combining *ex vivo* and *in vivo* T-cell depletion, and increasing the donor graft inoculum using "mega-doses" of CD34+ cells [9]. This led to intensified work on HaploSCT and, in the 2000s, Johns Hopkins group introduced a forgotten method, high-dose cyclophosphamide early after graft infusion, bringing HaploSCT to mainstream use. These strategies have been improved upon and newer ones are being developed to tackle the high-HLA histoincompatibility barrier, while at the same time fastening posttransplant immune reconstitution and preserving graft-versus-leukemia (GVL) effect. These transplant approaches may be grouped into two: those including ex vivo T-cell depletion or manipulation of the graft and those relying on modification/intensification of GVHD prophylaxis without graft engineering. The strategies covered in this chapter and their rationales are summarized in Table 1.

Approach	Mechanism and rationale	Potential shortcomings
Complete/partial ex vivo T-cell depletion	Most efficacious GVHD preventive method	↑ graft rejection ↑ NRM and possible ↑ RI due to delayed immune reconstitution
T_{reg} and T_{con} co-infusion	Addition of T_{cons} to promote immune reconstitution while preventing GVHD with T_{regs}	T_{reg} may decrease GVL effect T_{reg}/T_{con} ratio needs to be optimized
NK-cell co-infusion	Addition of NK cells to enhance GVL effect and decrease TRM	Clinical efficacy not proven
Engineered donor lymphocytes with a safety suicide switch	To prevent/treat disease relapse and improve immune reconstitution post transplant. Safety switch allowing T-cell suicide in case of GVHD precipitation → higher T-cell doses are possible	T cells are not targeted → while immune reconstitutive effect is demonstrated, GVL effect is not yet clear
T cells with chimeric antigen receptors	T cells engineered to recognize specific antigens (CD19) provide GVL effect without GVHD	Clinical efficacy after HaploSCT has not been shown yet
Allodepletion using anti-CD25 antibodies	ex vivo depletion of alloreactive T cells by targeting activation marker CD25 after incubation with APC recipients	T_{reg} also express CD25 Clinical efficacy not proven Possible effect on GVL response
Allodepletion with phototoxic dye	ex vivo depletion of alloreactive T cells with TH9402 that accumulates in activated T cells	Clinical efficacy not proven Possible effect on GVL response
Selective αβ T-cell depletion	Preservation of γδ T cells (unlikely to induce GVHD while effective against infections with an innate-like response) while eliminating αβ T cells most responsive for aGVHD Potential to avoid posttransplant immunosuppression	Clinical efficacy not proven Promising early data available Possible effect on GVL response
Selective $CD45RA^+$ T-cell depletion	Elimination of $CD45RA^+$ naïve T cells (capable of precipitating GVHD) while preserving memory T cells (active against infections) Potential to avoid posttransplant immunosuppression	Clinical efficacy not proven Possible effect on GVL response

Approach	Mechanism and rationale	Potential shortcomings
Alloanergization	Alloreactive T cells are anergized by blocking co-stimulatory CD80/86 signal	T cells are not depleted ↑ GVHD rate
High-dose posttransplantation cyclophosphamide RIC/NMA conditioning	Eliminating the alloactivated T cells early after transplant without affecting stem cells. T-cell preservation allows lower intensity conditioning extending transplantation to elderly patients Low incidence of cGVHD	Low cost GVHD incidence higher than after ex vivo T-cell depletion; however similar to matched transplantation Higher leukemia relapse incidence after NMA conditioning
Myeloablative conditioning	To decrease relapse incidence in leukemia patients	↑ in NRM and possibly in GvHD
Peripheral blood as stem cell source	To decrease relapse incidence and possibly improve immune reconstitution through higher T-cell content in PB	↑ in acute GvHD potential
Intensified immune suppression	To demeliorate immune reaction both ways G-CSF priming of BM and PB graft to induce T-cell hyporesponsiveness	Higher aGVHD and cGVHD incidence

Legend: GVHD – graft-versus-host disease, NRM – nonrelapse mortality, RI – relapse incidence, T_{reg} – regulatory T cells, T_{con} – conventional T cells, APCs – antigen-presenting cells, GVL – graft-versus-leukemia effect, RIC – reduced-intensity conditioning, NMA – nonmyeloablative conditioning, HaploHCT – haploidentical transplantation, PB – peripheral blood, BM – bone marrow, G-CSF – granulocyte–colony-stimulating factor, NK – natural killer

Table 1. The rationale and potential shortcomings of the current approaches in haploidentical stem cell transplantation.

2. HaploSCT with *ex vivo* T-Cell depletion or manipulation

The first successful HaploSCT strategy was grafting a "mega-dose" of progenitor cells through TCD of the bone marrow (BM) and peripheral blood (PB) products. To further decrease graft rejection, *in vivo* TCD with antithymocyte globulin (ATG) and a myeloablative-conditioning regimen were used [9]. Further technical revisions in the protocol led to primary engraftment in 95% of patients [10]. Although GVHD rates were low, transplant-related mortality (TRM) rate approached 40% primarily due to opportunistic viral infections, likely related to the delayed immune reconstitution. Furthermore, the use of myeloablative conditioning restricted this type of transplant to younger patients with good performance status. Two general approaches were used to enhance GVL and immune reconstitution after TCD HaploSCT: (1)

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selective lymphocyte add-back during or after TCD graft infusion and (2) selective depletion or deactivation of T cells capable of inducing GVHD while preserving the rest.

2.1. Selective lymphocyte add-back during or after TCD graft infusion

2.1.1. Co-infusion of regulatory T cells (T_{reg}) and conventional T cells (T_{con})

T_{regs} modulate the immune system maintaining tolerance to self-antigens. Studies showed that T_{regs} may suppress GVHD [11] and facilitate posttransplant immune reconstitution when coinfused with T_{cons} [12]. Whether T_{regs} affect GVL effect is under investigation [13]. To boost the GVL effect and immune reconstitution with T_{cons} while preventing GVHD with T_{regs}, Di Ianni et al. infused donor T_{regs} before the infusion of TCD PB progenitor cells and donor T_{cons} [14]. Of 28 patients, 26 achieved engraftment and 2 developed acute GVHD (aGVHD). Despite the rapid development of a wide T-cell repertoire, 8 patients still died of opportunistic infections. A recent follow-up study also demonstrated high engraftment, low GVHD, and high TRM rates [15]. These findings suggest that adoptive immunotherapy with T_{regs} may counteract the GVHD potential of conventional T cells in HaploSCT; however, the high incidence of opportunistic infections and TRM remains a concern.

2.2. Natural Killer (NK) cells

It is thought that NK cells, a vital part of the innate immune system [16], recognize their targets through both inhibitory and activating receptors. According to the widely used "missing self" model, an NK cell recognizes a cell as foreign when the particular cell lacks one or more HLA class I alleles specific to the inhibitory receptors (killer immunoglobulin-like receptors, KIRs) on the NK cell [17, 18]. NK cells primarily attack hematopoietic cells sparing the solid organs; therefore, they are almost incapable of causing GVHD [19]. NK-cell infusions after HaploSCT have been utilized to exploit innate immunity against a variety of tumors [20]– [22]. Yoon et al. reported no acute side effects in 14 patients who were infused with donor NK cells 6–7 weeks after T-cell replete HaploHCT using a reduced-intensity conditioning [23]. Two patients who received NK-cell infusions during active leukemia did not have a response and 4 patients developed cGVHD. More recently, the same group reported no acute toxicity after NK-cell infusions up to 1×10^8 cells/kg. When compared with historical controls, NK-cell infusions were associated with lower leukemia relapse rate [24]. Further studies are needed to assess the utility of NK-cell infusions after HaploSCT, and such a study is currently recruiting patients at our institution.

2.3. Engineered donor lymphocytes with a safety switch

Donor lymphocyte infusions (DLI) are more practical after HaploSCT than after transplants from unrelated donors due to the availability of the related donors. While DLI may be used to prevent or treat disease relapse and enhance posttransplant immune reconstitution, it may also induce GVHD. T cells engineered to express safety suicide switches in case of GVHD may be used for a safer DLI. Ciceri et al. engineered donor lymphocytes to express *Herpes simplex* virus-thymidine kinase suicide gene (TK cells), which can be triggered by the

use of ganciclovir [25]. TK cells were engrafted in 22 of 28 patients who underwent HaploSCT with TCD–PB grafts and received TK cells once a month for 4 months. Immune responses against cytomegalovirus (CMV) and Epstein–Barr virus improved after TK-cell infusions. Without any GVHD prophylaxis, 10 patients developed acute GVHD and required ganciclovir resulting in abrogation of GVHD in all. There were no GVHD-related deaths or long-term complications [25].

However, ganciclovir, a commonly used drug to treat CMV after transplantation, is not a well-suited drug to induce suicide of T cells. Baylor group used an alternative approach and engineered donor lymphocytes to express an inducible caspase-9 transgene (iC9), activated by a bio-inert molecule, AP1903 [26]. All of 10 pediatric patients (age 3–17) who underwent HaploSCT with TCD grafts and were infused with iC9-T cells between 30 and 90 days after transplantation, achieved engraftment of iC9-T cells [27]. In 5 patients who developed GVHD after iC9-T-cell infusion, iC9-T cells were >90% eliminated within 2 hours of AP1903 administration, and GVHD was rapidly reversed. Viral replication or disease was resolved within 4 weeks of iC9-T-cell infusion in all patients who had evidence of viral replication. Although very promising with a strong rationale, engineering T lymphocytes requires good manufacturing practice (GMP) facilities and patient-specific tailoring and is expensive.

2.4. T cells with Chimeric Antigen Receptors (CAR)

Lymphocytes, irrespective of whether they have been engineered to express suicide genes or not, have a broad target range that may or may not include the underlying malignancy. To give them a specific target, T cells are engineered to express CARs (CAR T cells) – fusion proteins with an extracellular antigen recognition moiety and an intracellular T-cell activation domain. CAR T cells have significantly higher antitumor efficacy for B-cell hematological malignancies without the added risk for the development of GVHD. Kochenderfer et al. reported their findings in 10 patients who received anti-CD19 CAR T cells for B-cell malignancies relapsed after transplantation from matched related or unrelated donors [28]. All patients had received standard DLIs prior to CAR T cells with only 2 responses. Two patients achieved responses lasting >3 and >9 months after CAR T-cell infusions, whereas 6 patients achieved stable disease lasting between 1 and more than 11 months. None of the patients developed GVHD after the infusion.

CAR T cells after HaploHCT may also be generated from the same donor and used to prevent/treat relapses. At our institution, we have so far treated 3 acute lymphoblastic leukemia (ALL) patients – one with active disease – with HaploSCT followed by CAR T cells. All patients tolerated the infusions well with no significant GVHD. The two patients who received CAR T cells as preemptive therapy are alive in remission more than 6 months post transplant, whereas the other patient died of disease relapse. To our knowledge, these are the first HaploSCT patients treated with CAR T cells. Although the experience is limited, the prevention of disease relapse post transplant for high-risk ALL patients appears to be the most important therapeutic benefit of CAR T cells presently.

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2.5. Selective T-Cell depletion/deactivation of the graft

2.5.1. Allodepletion

Allodepletion methods include, first, generating an alloresponse by co-culture of donor T cells and recipient cells and, then, depleting the activated donor T cells through surface activation markers or photoactive dyes, which are preferentially retained in activated T cells [29].

Amrolia et al. used an anti-CD25 immunotoxin to deplete alloreactive lymphocytes ex vivo. Allodepleted lymphocytes of 10^4–10^5 cells/kg were infused on days 30, 60, and 90 of TCD HaploSCT in 16 patients (median age 9 years) [30]. Only two patients developed grade II–IV acute GVHD, and a wider T-cell receptor (TCR) repertoire was observed 4 months after the transplant compared with the retrospective controls. Nevertheless, 9 patients (56%) died due to relapsed disease (5), infection (3), and interstitial pneumonitis (1).

Depletion based on CD25 expression may not be the optimal approach as T_{regs} also express CD25 on their surface. An alternate method to deplete activated T cells using TH9402, a phototoxic dye that accumulates in activated T cells due to their inability to efflux rhodamide-like drugs, was also developed [29, 31, 32]. Bastien et al. showed that photodepletion in transplanted patients with resistant chronic GVHD eradicated proliferating T cells while sparing T_{regs} [33]. HaploSCT with photodepleted T cells may be possible and requires further clinical studies.

Although allodepletion has a strong rationale, clinical studies to date are limited, and its broad use is severely hampered by the requirement of cell cultures in a GMP facility.

2.5.2. Alloanergization

For activation of T cells, two signals from antigen-presenting cells (APCs) are required: presentation of the immunogenic peptide on major histocompatibility complex activating the TCR and a costimulatory or an inhibitory signal through CD80/86 and CTLA-4 on APCs, respectively, to the CD28 on T cells. Although a costimulatory signal would lead to differentiation to T_{cons}, an inhibitory signal from CTLA-4 would induce anergy and the development of T_{regs} [34] allowing transplantation of histoincompatible allografts [35].

Guinan et al. showed the feasibility of HaploSCT using a BM graft in which donor T cells were anergized through incubation with recipient's mononuclear cells and CTLA-4-Ig [36]. Of 12 patients transplanted, 1 died early post transplant, 11 achieved sustained engraftment, and 3 developed acute GVHD. No deaths due to GVHD occurred in this group. In a follow-up study, 5 of 24 transplanted patients were reported to develop severe aGVHD and 12 patients died within 200 days of transplantation (5 due to infection) [37]. Similar to allodepletion methods, use of alloanergization is restricted to those centers with GMP facilities.

2.5.3. CD45RA depletion

Various classification schemes of T cells exist according to their cell surface phenotype and functional activity [38]– [40]. Majority of T cells that can respond to minor H antigens and cause

GVHD are thought to be never exposed to their cognate antigen, in other words, naïve (T_N), with a $CD45RA^+CD62L^+$ surface phenotype [41]. Several in vitro and mouse studies support this hypothesis [42]– [46]. However, depletion of $CD45RA^+$ naïve T cells is not straightforward, as a subset of CD34+ hematopoietic progenitor cells also express CD45RA [47]. To preserve the progenitor cells, Bleakley et al. devised a two-step procedure in which donor-apheresed PB is first selected for CD34+ cells, and then CD34-negative fraction was depleted for CD45RA to preserve all CD34+ cell subsets [48]. Conversely, investigators at St. Jude chose to deplete CD3+ cells from the first day – preserving all CD34+ cells – and CD45RA+ cells from the second-day apheresis products [49]. A 4.5-log depletion in T_N cells was detected in the final product to be infused. In 8 pediatric patients who underwent HaploSCT after myeloablative conditioning, the use of CD3/CD45RA depleted grafts led to engraftment in all and development of GVHD in none of the patients [49]. On posttransplant day 30, almost all T cells were negative for CD45RA. After a median follow-up of 171 days, none of the patients died of infectious complications. Although very promising, these results need to be verified in larger cohorts and in adults.

2.5.4. Alpha-beta T-cell depletion

γδ T cells, with TCRs made up of one γ (gamma) and one δ (delta) chain, possess properties of both innate and adaptive immune system with rapid, innate-like responses and rearranged TCRs yielding adaptability [50]. Remarkably, γδ T cells are thought not to require antigen processing and HLA presentation of antigens, rendering them unlikely to induce GVHD, whereas αβ T cells are thought to be the primary cause of GVHD [51]. Accordingly, a faster recovery of γδ T cells after SCT has been associated with longer disease-free survival [52]. Recently, methods to deplete αβ T cells preserving γδ T cells have been developed [53].

Of the few clinical studies available, Bertaina et al. reported primary engraftment in 44 of 45 children (median age of 10 years) with acute leukemia who underwent HaploSCT with TCR-αβ and CD19-depleted PB grafts [54]. With the only pharmacologic GVHD prophylaxis of pre-transplant ATG, none of the patients developed grade III–IV acute GVHD, whereas 13 children developed grade I–II skin-only GVHD. Two patients died of infectious complications. After a median follow-up of 11 months, the 2-year leukemia-free survival was 75%. On a follow-up study of 23 children with nonmalignant disorders, the same strategy led to a TRM of 9.3% and grade III–IV acute GVHD was not found. As with CD45RA depletion, these results are promising but need to be verified in larger cohorts and in adults.

3. HaploSCT without graft engineering

A highly effective GVHD prevention is necessary to overcome the intense bidirectional alloreactivity (in both graft-versus-host and host-versus-graft directions) associated with HaploSCT. Ex vivo TCD is the most efficacious method to prevent GVHD; however, (1) it requires myeloablative conditioning to ensure engraftment compensating for the lack of donor T cells eradicating residual recipient immune cells, (2) it requires a relatively sophisticated cell

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processing laboratory, and (3) it is associated with slower recovery of cell-mediated immune system. To overcome these hurdles, either T-cell depletion methods were modified or augmented as outlined above or a robust GVHD prophylaxis regime was used in place of ex vivo TCD. The latter is typically achieved by either posttransplantation cyclophosphamide or intensification of the traditional GVHD prophylaxis.

3.1. Posttransplantation high-dose cyclophosphamide (Post-Cy)

In 1960s, Barenbaum et al. demonstrated that Post-Cy could prevent skin graft rejection when administered 2–3 days after allografting in a mouse model [55]. This forgotten method was revived by the Johns Hopkins group in the late 1990s when they showed that Post-Cy attenuated lethal and nonlethal GVHD in mice and prolonged their survival [4]. Cyclophosphamide is thought to prevent GVHD by eliminating rapidly dividing donor T cells induced by the major HLA mismatch early after the haploidentical graft infusion. Furthermore, quiescent progenitor cells and memory T cells in the graft are less susceptible to cyclophosphamide due to their high levels of aldehyde dehydrogenase [4, 56].

Post-Cy has been adapted to HaploSCT using nonmyeloablative conditioning and BM grafts that have a lower T-cell content than PB grafts [4, 57]. After various single-center reports, the multicenter BMT CTN 0603 trial demonstrated the feasibility of Post-Cy in HaploSCT with an acceptable incidence of GVHD (32% acute grade II–IV and 13% chronic GVHD) and very low TRM [58]. The disappointingly high relapse incidence (45%) was primarily attributed to the use of nonmyeloablative conditioning for patients with acute leukemias. Conversely, Post-Cy has yielded particularly impressive results in patients with lymphoma. A retrospective analysis of 151 consecutive patients with poor risk or advanced lymphoma who underwent HaploSCT with Post-Cy revealed a progression-free survival of 40% at 3 years [59], similar to what has been observed in patients with Hodgkin's disease after HLA-matched transplants [60].

3.1.1. Post-Cy after myeloablative conditioning

Relatively high relapse rates with Post-Cy approach in patients with acute leukemia prompted researchers to intensify the conditioning regimen. Early results from the Johns Hopkins group with Post-Cy after myeloablative conditioning demonstrated acceptable GVHD and engraftment rates, albeit in a pediatric and young adult cohort [61]. More recently, Raiola et al. reported grade II–III acute GVHD incidence of 12% and disease-free-survival of 68% after a median follow-up of 333 days in a cohort of 50 patients with high-risk hematological malignancies who underwent HaploSCT with Post-Cy and busulfan or total-body irradiation (TBI)-based myeloablative conditioning [62]. Our experience with Post-Cy approach using a myeloablative yet reduced-intensity conditioning with fludarabine, melphalan +/− thiotepa (subsequently changed to 2 Gy TBI) has been very good, with TRM and progression-free survival of 21% and 53% after a median follow-up of 14 months in 57 patients with advanced hematological malignancies [63]. Updated results for our first 100 patients treated showed a 3-year PFS of 56% for patients with acute myeloid leukemia (AML) in CR1/CR2 or chronic-phase CML (chronic myeloid leukemia), 62% for patients with lymphoid malignancies, and

44% for patients with advanced acute lymphoblastic leukemia [63], results comparable with matched transplants.

3.1.2. Post-Cy with peripheral blood grafts

With a higher T-cell content, the use of PB grafts may lead to faster posttransplant immune recovery and improve graft-versus-leukemia effect with the expense of higher GVHD incidence. Raj et al. reported that while the incidence of grade II–IV aGVHD appeared to be twice as much as with a BM graft, the incidence of severe grade III–IV aGVHD was not much higher than with a BM graft [64]. Nevertheless, it remains to be seen if outcomes with a PB graft are as good as with a BM graft in this setting. If the higher incidence of aGVHD has a negative impact on outcomes, an optimized PB graft will likely be needed.

3.2. Intensification of traditional GVHD prophylaxis

The Chinese investigators developed a different approach to control GVHD after HaploSCT. They used a myeloablative conditioning regimen, an intensified GVHD prophylaxis with ATG, cyclosporine, methotrexate, mycophenolate mofetil, and a donor graft composed of granulocyte–colony-stimulating factor (G-CSF)-primed BM and PB progenitor cells (GIAC protocol after **G**-CSF, intensified immunologic suppression, anti-thymocyte globulin, and combination of PB and BM grafts) [65]. Incidences of GVHD in 250 acute leukemia patients were higher than those seen with Post-Cy (46% grade II–IV aGVHD and 54% cGVHD), whereas almost all patients had successful engraftment. Di Bartolomeo et al. obtained similar results in Europe but reported a lower GVHD incidence using different myeloablative regimens and only a BM graft [66].

4. Haploidentical donor selection

Most patients requiring SCT have more than one haploidentical donor. The presence of recipient antibodies against donor-specific HLA, KIR mismatch predicting NK-cell alloreactivity, degree of HLA mismatch between donor and recipient, mismatch for noninherited maternal versus paternal alleles, donor age, and ABO-match may be important determinants of donor selection for HaploSCT.

Previous pregnancy or blood product transfusions may induce recipient anti-HLA antibodies against donor HLA antigens (DSA). The presence of DSAs is associated with increased risk of graft rejection [67]– [70]. Plasma exchange or rituximab may be used for recipients with DSA.

NK cells primarily attack hematopoietic cells sparing solid organs [19] and express inhibitory receptors, KIRs, that recognize epitopes shared by HLA class I alleles [16, 71]. In recipients lacking HLA class I alleles specific to the donor KIRs, donor NK cells may prevent GVHD and disease relapse by eliminating residual recipient antigen-presenting cells and leukemia cells [17, 72]. Accordingly, KIR mismatch between recipient and donor has been associated with

improved HaploSCT outcomes with both TCD and T-cell replete grafts [17, 72]– [74]; however, this finding has been disputed by other researchers [75, 76].

Although a progressive increase in TRM with increasing genetic disparity has been historically reported, contemporary transplant strategies may negate this correlation by overcoming larger histoincompatibility barriers. In fact, Kasamon et al. and Wang et al. reported a similar incidence of acute GVHD and TRM after HaploSCT from full-haplotype mismatched donors compared with those from better-matched donors [77, 78].

The immune system is subject to senescence with advancing age. Accordingly, in the largest HaploSCT cohort published to date, Wang et al. reported a lower incidence of GVHD with younger donors compared with older ones [78]. Moreover, having a maternal donor was associated with a higher GVHD incidence and TRM than having a paternal donor. The latter is in contrast to the findings from a small registry study in which HaploSCT from maternal donors was found to be associated with lower TRM and longer OS compared with those from paternal donors [79]. Consequently, van Rood et al. demonstrated no significant differences in TRM, survival, or acute GVHD rates between HaploSCT from maternal and paternal donors [80]. The discrepancies between these studies are difficult to explain. However, both Wang et al. and van Rood et al. also found that HaploSCT from a sibling with a noninherited maternal antigen (NIMA) mismatch was associated with a lower GVHD incidence than that from a sibling with a noninherited paternal antigen (NIPA) mismatch supporting the hypothesis that the immunologic tolerance developed between the mother and the fetus during pregnancy [81, 82] may affect the transplant outcomes if the mismatched haplotype is of maternal origin. It is possible that although an immunologic tolerance is developed primarily in fetus against NIMA, immunity to minor histocompatibility antigen-encoded genes on the Y chromosome remains in the mother [83, 84]. Finally, older multiparous women may be the least preferred donors for male recipients [85].

Transplants involving a major ABO incompatibility require mononuclear cell separation to prevent a hemolytic reaction, which reduces the graft cell dose. If maximizing the infused stem cell dose is indeed important in HaploSCT, then younger, larger donors without a major ABO incompatibility with the recipient should be preferred.

With conflicting data, it is difficult to identify the optimal haploidentical donor. Until further evidence is available, we recommend the donor decision be based on age, NIMA mismatch, KIR mismatch, relation to the patient (mother the last choice), presence and level of anti-HLA antibodies, and ABO mismatch.

5. Outcome comparison with other transplant types

It was just over a decade ago when results from HaploSCT were significantly worse than those from matched and one-antigen mismatched unrelated donors [86]. Currently, the outcomes of HaploSCT are reported to be in par with those of transplants from HLA-matched donors. Among adults with intermediate- or high-risk acute myeloid leukemia in first complete

remission, Wang et al. did not find any significant difference in survival, relapse rate, and TRM between transplants from HLA-identical siblings and haploidentical donors [87]. All transplants were performed with GIAC protocol except that ATG was not used in those from HLA-identical siblings. In another retrospective analysis, Raiola et al. reported a lower TRM with HaploSCT compared with cord blood and unrelated transplants and a longer survival compared with cord blood transplants [88]. In this cohort, Post-Cy and mostly ablative conditioning were used for HaploSCT. Kanda et al. reported worse survival and higher incidence of grade III–IV acute GVHD after HaploSCT compared with transplants from HLA-identical siblings [89]. However, in this study, HaploSCTs were performed with unmanipulated PB grafts and a GVHD prophylaxis including only alemtuzumab and mycophenolate mofetil without Post-Cy. Using the Post-Cy approach, Bashey et al. demonstrated similar outcomes between HaploSCT, transplants from matched related donors, and matched unrelated donors, with probabilities of disease-free survival of 60%, 53%, and 52%, respectively [90]. We have recently compared the outcomes of a uniform cohort of 227 patients with myeloid malignancies treated with the same conditioning regimen (fludarabine and melphalan) and found similar results. The 3-year disease-free survival for patients in complete remission after transplants from matched sibling, matched unrelated, and haploidentical donors were 51%, 45%, and 41%, respectively (p = 0.4) with similar immune reconstitution between the three groups [91].

6. Conclusion

Outcomes of HaploSCT have improved dramatically over the past several years, and its use has extended transplantation to virtually all patients in need. Although the optimal strategy to overcome the HLA–histoincompatibility barrier is debated, Post-Cy for GVHD prevention requires less resources and is associated with low TRM establishing itself as the new standard in HaploSCT. Novel methods for performing haploidentical transplants will have to be eventually compared with this approach. HaploSCT with Post-Cy has the potential to be the preferred transplant option for patients without HLA-matched donors worldwide, especially in developing countries where the cost of developing and maintaining unrelated donor registries or acquiring progenitor cells from the international registries might be prohibitive.

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