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Optimal Donor Selection for Allogeneic Stem Cell Transplantation in the Era of Post-transplant Cyclophosphamide: A Scoping Review

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Abstract

Allogeneic hematopoietic stem cell transplantation (HSCT) remains a primary curative treatment for numerous hematologic disorders. Historically, the success of HSCT relied on HLA matching to mitigate Graft-versus-Host Disease (GVHD); however, since fewer than 30% of patients have a matched family member, the field has undergone a significant paradigm shift.

The emergence of haploidentical HSCT, facilitated by the post-transplantation cyclophosphamide (PTCy) GVHD prophylaxis platform, has revolutionized donor availability, resulting in clinical outcomes for mismatched transplants that are comparable to those of matched sibling or unrelated donors.

Beyond HLA compatibility, several non-HLA factors are now critical in donor selection. Younger donor age has emerged as a remarkable predictor of survival, reducing both relapse and non-relapse mortality; nevertheless, HLA matching and disease biology remain major drivers.

Furthermore, considerations such as Cytomegalovirus (CMV) serostatus, the presence of donor-specific antibodies (DSA), and the urgency of the procedure—prioritizing time-to-transplant over a perfect HLA match—are essential. Ultimately, while histocompatibility remains a priority, modern HSCT leverages PTCy to balance biological compatibility with clinical speed, significantly expanding the curative potential for patients worldwide.

Keywords: AB0 compatibility, Allogeneic stem cell transplantation, Citomegalovirus, Donor specific antibodies (DSA), Donor selection, Graft versus host disease, Hematological malignancies, Human leucocyte antigen, Post-transplantation cyclophospamide

Literature Search Method

A scoping literature search was performed to identify relevant studies on donor selection in allogeneic stem cell transplantation. The search was conducted in the following electronic databases: PubMed/MEDLINE, Embase, and Scopus. The search covered the period until October 2025.

The search strategy included a combination of MeSH terms and keywords such as: "donor selection", "allogeneic stem cells transplantation", "GVHD prophylaxis", "HLA matching", "AB0 compatibility", "anti DSA", "sex matching", "donor age", "cytomegalovirus". Only articles published in English and Italian and in peer-reviewed journals were included. Manual searching for the reference lists of the retrieved articles was also performed to ensure the inclusion of all relevant studies (secondary searching).

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is considered as a curative treatment for a consistent number of malignant and nonmalignant hematologic disorders. Since the first human bone marrow transplant in the 1950s, allogeneic HSCT is used to treat over 17,000 patients in Europe each year. The selection of the most appropriate donor is of paramount importance to ensure a favorable transplant outcome and the final choice relies on several key factors.

Certainly, HLA matching is an essential component of HSCT in minimizing the risk of graft versus host disease (GVHD). Regrettably, less than 30% of patients who might benefit from HSCT have a fully Human Leukocyte Antigen (HLA) matched family member, depending on patient age, race and ethnicity [1]. In this respect, unrelated stem cell donor registries have a relevant role in providing a suitable donor for those patients in need of an HSCT. The average probability of identifying a matched unrelated donor differs greatly depending on the ethnic origin of the patients and on the matching grade required by the transplant center. Given the actual size of international registries including over 40 million volunteer donors, the likelihood of finding a 9/10 or 10/10 matched unrelated donor (at high resolution at HLA-A, -B, -C, - DRB1 and -DQB1) varies between 50% and 80% [2].

One major change in HSCT practice is the shift towards the preferential utilization of haploidentical family donors. In fact, haploidentical HSCT (Haplos) has the potential to offer the possibility of a transplant to patients who might benefit from this therapeutic procedure but do not have a suitable family or unrelated donor. Based on the 2023 European Bone Marrow Transplant survey report, 20% of allogeneic HSCT were performed in Europe utilizing haploidentical donors [3], and similar results have been reported by the CIBMTR (21%) [4].

The notable increase of Haplos utilization is mainly driven by the shift to post-transplantation cyclophosphamide (PTCy) platform of GVHD prophylaxis. The Baltimore group developed a T-cell repleted protocol, based on the administration of PTCy [5]. Hematopoietic stem cells are resistant to high dose Cyclophosphamide due to the presence of high levels of aldehyde dehydrogenase, the enzyme primarily responsible for detoxification of Cyclophosphamide, while Cyclophosphamide given after the transplant targets donor alloreactive T cells reducing the risk of graft rejection and GVHD [6]. Similarly, T_{REG} cells, considered necessary to prevent GVHD, are resistant to PTCy-induced cytotoxicity due to high levels of aldehyde dehydrogenase [7]. Based on these biological assumptions, several clinical trials have analyzed the outcomes of patients receiving Haplos after PTCy, showing excellent results similar to those obtained in patients receiving grafts from matched sibling donors (MSD) and matched unrelated donors (MUD) [8–10].

Relationship between donor and recipient is another aspect that should be considered when PTCy-HSCT is the procedure of choice. Overall, offspring and siblings are equally preferred over parents, due to higher rate of graft failure (GF) and relapse rate in HSCT with PTCy [11].

Even in the setting of grafts from unrelated donors, the use of PTCy is able to mitigate the detrimental effect of HLA mismatch on transplant outcomes [12].

In the setting of mismatched HSCT, the presence of antibodies that target specifically the donor HLA, defined as donor specific antibodies (DSA), correlates with poor marrow function and graft failure [13]. According to these observations, either desensitization strategies to remove alloantibodies before the transplant or the selection of a different donor if available are options highly recommended [14]. Interestingly enough, a recent study showed that for patients receiving T cell replete grafts including PTCy following myeloablative conditioning, the presence of DSA has a negligible effect on engraftment [15].

Over the most recent years, younger donor age has been reported as a significant predictor of outcomes in many studies including both MUD and Haplos [16,17], and surprisingly enough, some data even suggest that a younger MUD may be preferable to an older MSD [18]. The potential survival benefit observed with younger donors seems to be primarily driven by a reduction in relapse risk [19] and non-relapse mortality (NRM) [20] as reported either in Haplos with PTCY [21] and in MUD HSCT recipients [22]. A lower rate of acute and chronic GVHD has been observed in patients who underwent HSCT from younger Haplos [21] and unrelated donors [12] with the use of PTCy. In addition, aging is associated with a higher risk of clonal hematopoiesis of indeterminate potential (CHIP) eventually leading to cardiovascular events, unexplained cytopenias and GVHD [23].

Another aspect that has great relevance is the time to the transplant. Several lines of evidence support the notion that keeping the time to transplant as short as possible may be more important than waiting for a better HLA-matched donor, particularly when patients are considered at high risk of disease relapse [24]. When the chance to find a perfect HLA matched unrelated donor is low, it seems wiser to move to a different donor such as Haplos or cord blood, and this has been made possible following the availability of the PTCy platform.

In 30% to 50% of patients, donors and recipients have ABO blood group incompatibility. ABO incompatibility between the donor and the recipient has been associated with an increased risk of delayed red blood cell (RBC) engraftment and pure red cell aplasia (PRCA). However, reliable data on the effect of ABO-mismatching on the outcome of HSCT recipients are lacking or even conflicting [25,26].

Historically, donor/recipient (D/R) Cytomegalovirus (CMV) serostatus has been recognized as one of the major determinants in predicting the risk of post-transplant CMV reactivation and transplant-related morbidity and mortality. Whenever possible, the selection of seronegative donor for seronegative recipient (D-/R-) represents the best choice in order to reduce the possibility of primary CMV infection, while the combination of D-/R+ is clearly associated with a poorer outcome, although the recent use of Letermovir as CMV prophylaxis may potentially redefine the role of D/R serostatus [27].

In conclusion, donor selection for allogeneic HSCT represents a crucial as well as a complex process in maximizing the benefit of transplant procedure. **Figure 1** summarizes the factors involved in the choice of donor. The overriding goal of current donor selection strategies is to prioritize donor-recipient histocompatibility however non-HLA factors need be evaluated extensively, although it should be emphasized that the underlying disease biology continues to supersede donor features for the final outcome of HSCT patients.

HLA Matching

The first HSCT was performed in the late 1960s from an MSD, and for decades it was the only available source for transplantation. Currently, an MSD is available for only a minority of patients eligible for HSCT, due to factors such as population aging and declining family sizes. In recent years, other categories of donors have been tested to extend the procedure to most patients who might benefit from a transplant.

According to HLA matching, the five categories of allogeneic HSCT donors are: fully matched sibling (MSD), matched or mismatched unrelated donors (MUD or MMUD), unrelated umbilical cord blood donors (UCB) and Haplos [28]. UCB is mainly restricted to pediatric patients [29].

The first transplant from an MUD was done in 1973. Currently, according to World Marrow Donor Association (WMDA; www.wmda.org), more than 40 million volunteer donors are registered worldwide, but not all ethnic groups are equally represented, resulting in differences in MUD availability (from 29% for Africans to 79% for Europeans).

The use of MMUD or Haplos has been challenging for decades; now, it is feasible thanks to the discovery of *ex vivo* techniques for a negative selection of alloreactive lymphocytes and selecting CD34 cells, avoiding the need for strict HLA matching to prevent severe GVHD [30]. Moreover, the introduction of PTCy in GVHD prevention has opened the way for Haplos. MMUD or Haplos family donors are very appealing because almost every patient has a potential donor.

MSDs are historically associated with lower incidence of GVHD compared to other donor sources; but its limitation is the availability [1].

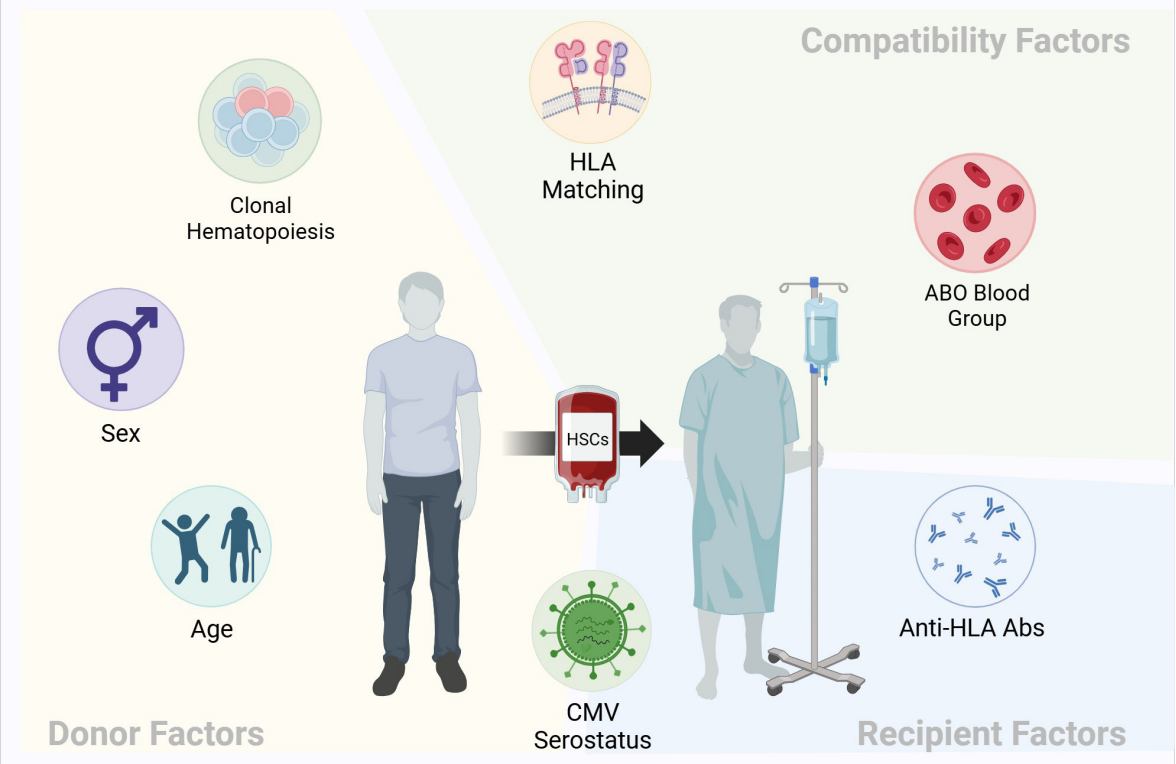

Figure 1. Illustration of all the factors involved in donor selection in allogeneic HSCT, divided into donor factors, recipient factors and compatibility factors.

In the current era, MUDs are the most common donor source for HSCT [31]. Studies since 2010s have shown similar outcomes compared to MSD when calcineurin inhibitor (CNI)-based graft prophylaxis is used [32-34]. MUD is a very good alternative to MSD, but its only limitation is the time to donor procurement.

MUD selection relies on genotype matching at the antigen recognition domains of HLA-A, -B, -C and DRB1. When all the domains are matched, the donor is called 8/8. The possibility of finding an 8/8 for a single patient depends on his ethnic group [35]. Moreover, other mismatches are evaluated for donor selection: HLA-DRB 3/4/5, DQB1 and DPB1.

Among 8/8 matched donors, mismatching at HLA-DRB 3/4/5 is found in 10–15% donors, and it correlates to inferior outcomes [36,37]. By contrast, Furst et al. [38] found that an isolated HLA-DQB1 mismatch in an 8/8 MUD transplant is not associated with decreased overall survival (OS) nor with decreased disease-free survival (DFS), but the presence of more than one locus mismatches, including HLA-DQB1, may have a detrimental effect. HLA-DPB1 mismatching can be permissive or nonpermissive, based on a model on T cell epitope grouping introduced by Fleischhauer et al., which demonstrated that nonpermissive DPB1 mismatches are associated with a significantly increased risk of OS, NRM and risk of grade III-IV acute compared to permissive mismatches [39]. Data from recent analysis of CIBMTR register support that nonpermissive HLA-DPB1 mismatches have detrimental effects in the context of CNI-based GVHD prophylaxis [40] while with the use of a PTCy platform, HLA-DPB1 nonpermissive mismatches, permissive mismatches and no mismatches have all similar outcomes [40,41]; similarly, HLA-DPB1 permissive mismatches in both recipients of CNI-based regimens or PTCy were not associated with a worst outcome. The presence of both a DQB1 and a DPB1 mismatch in an otherwise matched donor transplant is associated with an increase incidence of GVHD but has an uncertain impact on OS and NRM [42].

MMUD represents a viable alternative when an MUD is unavailable or cannot be secured quickly. Including MMUD (4-7/8 match along HLA-A, -B, -C, -DRB1) as an option increases the number of potential unrelated donors. Shaffer et al. [43] in a CIBMTR study shows that in the PTCy context, MMUD HSCT and MUD HSCT have comparable outcomes in terms of OS and GRFS, while MMUD are associated with worse outcomes in a non-PTCY context, although this study only included 7/8 mismatches. Shaw et al did not observe a difference in OS depending on HLA matching grade, but this data is debatable [9]. The ongoing phase II protocol ACCESS, including a greater number of 4–7/8 MMUD, will provide important insights in this setting [44]. In contrast, in a European Society for Blood and Marrow Transplantation (EBMT)-based study PTCy did not abrogate the detrimental effect of HLA mismatching [45], however there are significant differences in the two cohorts' study, including year of treatment, variance in definition of GRFS and usage of antithymocyte globulin (ATG) [46]. Recent studies highlight the need to consider which mismatches are associated with different outcomes in PTCy platform [47,48].

Haplos are available for most patients. They are usually found among first-degree relatives, offering several advantages, such as greater availability and reduced costs. In addition, they are also younger than the recipients, which can be beneficial for transplant outcomes (*see below*). One major concern is the risk of the presence of donor-specific HLA antibodies (DSAs), which can interfere with graft acceptance and increase the likelihood of rejection [49].

Post-transplant cyclophosphamide

PTCy opened the way to transplants with donors different from MSD or MUD. The first phase I study with the use of PTCy in mismatched transplants was published in 2002 [50]. It demonstrated that single dose 50 mg/kg PTCy in 13onpients of a nonmyeloablative HSCT from partially HLA-mismatched related donors had no significant impact on engraftment failure. Then, the safety and efficacy of PTCy in Haplos were evaluated in 2008 [51], when Cyclophosphamide was administered on day 3 and 4 after transplantation at the dose of 50 mg/kg, showing acceptable rates of acute and chronic GVHD. This led to the awareness that haploidentical transplantation is feasible when PTCy is combined with tacrolimus and mycophenolate mofetil to prevent GVHD.

Lately, the efficacy of PTCy prophylaxis, in association with calcineurin inhibitors or antimetabolites, has also been evaluated in MSD, MUD or MMUD recipients. The phase 3 trial BTM CTN 1703 [52] compared in a 1:1 ratio experimental prophylaxis (PTCy- tacrolimus-methotrexate) versus standard GVHD prophylaxis (tacrolimus-methotrexate) in MSD, MUD or MMUD recipients after a nonmyeloablative conditioning. The results of the trial showed a significant difference in 1-year GVHD free and relapse free survival (GRFS) in the experimental group (52,7% vs 34,9%, hazard ratio (HR)= 0.64). Meanwhile, some retrospective studies suggested that dual GVHD prophylaxis, eliminating the antimetabolite, may perform as well as triple prophylaxis [53].

The superiority of PTCy-based platforms was confirmed by the HOVON 96 trial [54] which showed a lower risk of acute and chronic GVHD with dual prophylaxis (PTCy plus cyclosporin) than standard prophylaxis (cyclosporin plus mycophenolate mofetil) in patients receiving MSD or MUD transplants after a nonmyeloablative regimen. The incidence of acute grade II-IV GVHD is 30% in the experimental group vs 48% in the standard group, while the rate of extensive chronic GVHD was 24% vs 52% in the two groups respectively. In addition, a significant improvement in GRFS, along with a similar incidence of relapse, progression free survival (PFS) and OS, was observed.

Anti-thymocyte globulin (ATG) has been introduced over the last decades for GVHD prophylaxis in MUD transplants on the basis of two randomized trials [55,56]. A phase 2 trial [57] comparing the use of PTCy with ATG-CSA-MTX in 10/10 MUD and MSD transplantation after an intensity-reduced conditioning shows similar results in terms of GRFS and DFS at 1 year.

The use of PTCy in the setting of myeloablative conditionings (excluded from both the BMT CTN 1703 and HOVON-96 trials) remained uncertain. A recent phase 3 prospective randomized trial [58] compared patients undergoing a MSD HSCT after myeloablative or reduced-intensity conditioning to receive either PTCy plus cyclosporin (experimental group) or cyclosporin plus methotrexate (standard group). The 3-year GRFS is 49% in the experimental arm and 14% in the standard arm, with a significant difference in 2-year OS (83% in experimental arm vs 71% in standard group), confirming that the PTCy platform is effective even in the setting of myeloablative regimens and MSD transplants.

Limitations of PTCy include delayed immune reconstitution and increased infectious risk, although the latter remains matter of debate. Indeed, randomized trials comparing PTCy-based GVHD prophylaxis with standard CNI-based strategies have in some cases demonstrated a statistically significant difference in the incidence of infections in the PTCy group [54] due to prolonged neutropenia, while other cases did not show significant differences in severe infections rate [52], although it should be noted that this was not the primary endpoint of those studies. Regarding viral complications, PTCy-treated patients have been shown to carry a higher risk of CMV reactivation, as demonstrated by retrospective data [59]; however, Letermovir prophylaxis appears to effectively offset this additional risk [27].

Outcome of transplants between different donor types

The superiority of MSD compared to other types of donors is supported by several results [60]. This analysis highlighted the importance of considering disease aggressiveness in selecting a donor: in the setting of low and medium risk disease, MSD HSCT were associated with lower risk for mortality versus MUD HSCT, while in patients with high risk disease, MUD and MSD were associated with similar survival, because the increased NRM in MUD recipients was counterbalanced by a lower risk for relapse. Haplo recipients with low and medium risk disease were also associated with lower relapse risk, but as expected, an increased NRM.

Scattered studies have compared MUD transplants to MMUD and Haplos, with different outcomes between groups. Some large studies focusing on acute leukemias found no significant differences in survival between the three groups [61,62].

A metanalysis including 25 studies and 11,359 patients demonstrated similar results with a 1.60 HR of developing chronic GVHD for Haplos compared to MUD or MSD recipients [63]. A meta-analysis of 11 studies [64] compared Haplos with PTCy against MSD without PTCy. Transplants from Haplo donors using PTCy-based GVHD prophylaxis are associated with a lower risk of chronic GVHD (HR 0.55) compared to MSD without PTCy, but higher risk of NRM (HR 1.36), suggesting infections and delayed immune reconstitutions as the factors potentially influencing the increased rate of NRM. Results of OS, DFS, relapse rate and acute GVHD were not significantly different between the two groups.

Another meta-analysis including 30 studies and 22,974 patients [8], compared transplants from different donors: Haplos using PTCy to MSD, MUD and MMUD without PTCy. Haplos are associated with increased all-cause mortality compared to MSD (OR = 1.17) and to MUD (OR =1.06), but lower all-cause mortality compared to MMUD (OR = 0.75). Haplos with PTCy are associated with worse NRM compared to MSD (OR= 1.20) but better compared to MUD (OR =0.75) and MMUD (OR = 0.51). Relapse incidence is similar in Haplos, MSD, MMUD but Haplos showed increased risk of relapse compared to MUD (OR =1.20). This meta-analysis suggests that transplantation from MSD is the best option, but Haplos with PTCy is preferred over MMUD.

This and other studies comparing different donor types have the limitations of considering different GVHD prophylaxis platforms; therefore, comparisons are made with different transplants platforms instead of different donors. To eliminate the potential bias of different GVHD prophylactic regimens, a retrospective registry-based analysis [65] was conducted in patients with AML receiving grafts in first complete remission with MSD, MUD or Haplos and a uniform GVHD prophylaxis including PTCy. PTCy is safe and effective across the different donors, showing low GVHD rates, comparable to ATG. Haplo HSCTs are associated with a significant increased incidence of grade II-IV acute GVHD and NRM, counterbalanced by a reduced relapse risk, resulting in a nonsignificant difference in OS. Interestingly, in the Haplos setting an increased risk for chronic GVHD wasn't observed.

A Japanese retrospective study [66] involving 799 patients receiving myeloablative or nonmyeloablative conditioning compared MUD HSCT with ATG-based GVHD prophylaxis strategy, MUD without ATG and Haplos with PTCy. The study showed that PTCy had a better performance in preventing both acute and chronic GVHD as compared to the ATG-free MUD group. PTCy Haplos group was superior to ATG-free MUD group also in GRFS, while it was associated with an increased risk for infection-related deaths. ATG-administered MUD group and PTCy Haplos HSCT group show similar results in terms of cumulative incidence of GVHD, GRFS and OS. Surprisingly,

an increased relapse risk has been observed in the ATG-administered MUD group compared to PTCy Haplos group (HR 1.88), which might be due to a different rate of patients in CR in this cohort and to a reduced graft-versus-leukemia effect with ATG. Finally, Grunwald et al. [10] published a study in which patients were biologically randomized to receiving an MSD transplantation or, if not available, a Haplos, both with the same conditioning (reduced-intensity conditioning, including Fludarabine, Cyclophosphamide and total body irradiation), graft source (peripheral blood) and GVHD prophylaxis (PTCy 50 mg/kg on days +3 and +4, mycophenolate mofetil and tacrolimus). No significant differences have been observed in terms of OS, GRFS, NRM, relapse rate and incidence of both acute and chronic GVHD between the two groups, proving evidence that MSD and Haplos have similar outcomes when reduced intensity conditioning and PTCy platform are employed.

Comparing MUD to MMUD, two registry-based studies provided conflicting perspectives on the impact of HLA matching in unrelated donors; the CIBMTR analysis of 10.025 patients [43] undergoing MUD or 7/8 MMUD HSCT using CNI-based protocols or PTCy, found comparable OS rates between MUD recipients versus MMUD in a PTCy-based platform. By contrast, a registry-based EBMT study encompassing 17.292 patients showed inferior outcomes in MMUD irrespective of the GVHD prophylaxis platform used: 5-year OS was 52.2% in the 10/10 group, 46,7% in the 9/10 group e 45,3% in the 8/10 group [45].

Sex Mismatch

Donor sex is currently considered a relatively minor factor in donor selection. Handful of studies suggest that male donors may be associated with improved outcomes, whereas female parous donors are associated to a higher risk of GVHD, particularly chronic GVHD. These observations are primarily based on transplants using CNI-based prophylaxis and HLA-matched donors [67,68]. It remains unclear whether these associations hold true in transplants using PTCy.

Donor Specific Antibodies (DSA)

Primary graft failure (GF) has been reported to occur in 5–35% of the patients undergoing HSCT, depending on several risk factors, namely donor/recipient HLA matching, stem cell content, intensity of preparative regimen, the use of ex vivo T-cell depletion, underlying disease and the presence of donor specific antibodies (DSA) [69]. DSAs were initially associated with higher rates of GF in recipients of haploidentical transplants [70], but subsequent studies have confirmed this risk in other HLA-mismatched HSCT. With the increasing use of HSCT from Haplo and MMUD over recent years, the issue of DSAs has become increasingly significant. Recipients can develop antibodies targeting non-self HLA antigens through various sensitizing events, such as transfusions, pregnancy, or previous transplants [71].

DSA positivity has also been correlated with delayed engraftment and reduced OS [72]. The reported incidence of anti-HLA antibody positivity (of any class) varies among studies, ranging from 20–25% to over 50%, with DSAs specifically found in approximately 10–30% of Haplo HSCT and 5-10% of unrelated donor HSCT [69,71,73–75].

HLA antibodies may target HLA Class I or II antigens, and DSAs are notably more prevalent in female recipients (over 80% of DSA-positive cases), particularly in those with prior pregnancies—further increasing the risk beyond 40%, often with DSAs directed against antigens inherited from their children [14,15,71,76].

Testing for anti-HLA antibodies can be performed using various methodologies. Cell-based assays are largely obsolete due to technical limitations and low sensitivity. Flow cytometry crossmatch tests offer higher sensitivity but are difficult to standardize. Solid-phase immunoassays (SPI) allow for precise identification of antibody specificity and provide a semi-quantitative estimate of binding strength—often reported as median fluorescence intensity (MFI)—although they can yield false negatives [77]. SPI can also differentiate between complement-fixing and non-fixing antibodies. The C1q binding assay is particularly relevant, as complement-fixing DSAs have been linked with an increased risk of graft failure [76].

The exact mechanism by which DSAs mediate graft rejection remains unclear, though current evidence suggests that complement-mediated cytotoxicity may play a more significant role than antibody-dependent cell-mediated cytotoxicity. The relationship between DSA level, binding strength, and rejection potential remains a matter of discussion. While a general threshold for DSA positivity is an MFI >1000, some studies use a lower threshold of >500. Stronger correlations with GF have been observed at MFI levels >5000 (e.g., 54% vs 9% GF rate), and higher MFI values are often associated with complement-binding activity [76,78].

Consensus recommendations from the American Society of Transplantation and Cellular Therapy (ASTCT) emphasize that patients with low level of DSA (MFI <2000) may not require treatment, while patients with very high level of DSA (MFI>20000) have a high rate of GF and the availability of an alternative donor should be investigated or should be treated with investigational strategies [14]. The EBMT guidelines indicate a threshold of 5000 MFI as the value with a significant likelihood of a detrimental effect on engraftment [72].

Current EBMT guidelines recommend desensitization for DSA-positive patients (particularly with levels >1000–2000 and especially >5000) undergoing allogeneic HCT, with the goal of reducing antibody titers to improve engraftment potential [72]. The effectiveness of desensitization remains uncertain due to heterogeneity in treatment protocols and limited data, often confined to case reports and small series. Desensitization strategies fall into four categories: antibody removal (plasmapheresis or immunoabsorption), inhibition of antibody production (e.g., anti-CD20 monoclonal antibodies or proteasome inhibitors), antibody neutralization (e.g., IVIg or exposure to donor HLA antigens) and complement inhibition. Most regimens combine several strategies, typically involving sequential treatment with plasmapheresis, rituximab, and IVIg [79]. Some protocols include bortezomib pre-plasmapheresis or immunosuppressive agents such as tacrolimus and mycophenolate mofetil [80]. Desensitization efficacy is usually evaluated by measuring reductions in DSA levels. Although the precise degree of reduction required for successful transplantation is not fully defined, decreasing DSA levels is associated with successful engraftment, whereas persistently high DSA levels post-desensitization predict a higher risk of GF. Guidelines also recommend post-transplant monitoring to ensure DSA clearance in the weeks following stem cell infusion [14,72,76].

Lima et al. [81] analyzed 303 patients undergoing first unrelated donor HSCT and reported a 4% rate of GF (primary or secondary) and one case of poor graft function (PGF), namely the presence of multilineage cytopenias while the donor chimerism is 100%. In this cohort, DSAs were associated with delayed neutrophil and platelet recovery, and with a higher risk of primary GF (HR 2.78), particularly in patients with higher MFI values. Notably, all patients with C1q-positive DSAs failed to engraft, although OS was not negatively impacted. A multicenter, retrospective study by GITMO/AIBT [79] evaluated 355 patients for the presence of anti-HLA antibodies, identifying 25.6% positivity, with 25.3% of these being DSA-positive. Approximately half underwent desensitization. This study found that anti-HLA and DSA positivity were associated with delayed engraftment and reduced OS, but not with early or late graft failure. Conversely, some studies have not demonstrated the detrimental effect of DSAs.

Data on the association between DSAs and the risk of GF in the context of Haplos with PTCy-based GVHD prophylaxis are conflicting. Altareb et al. [15] evaluated 107 patients undergoing myeloablative Haplo HSCT with PTCy and ATG: DSA-positive patients received desensitization with plasma exchange. There were no significant differences in OS, cumulative incidence of relapse (CIR), engraftment rate, or GVHD between DSA-positive and -negative patients. All three GF cases were negative for DSAs or anti-HLA antibodies. Collectively, the results of this study suggest that in Haplo-HSCT with PTCy and myeloablative regimens, DSAs may reduce the detrimental effect on engraftment as observed with other transplant programs. On the other hand, two systematic reviews and meta-analyses support the negative impact of DSAs on engraftment. Huang et al. [82] and Xie et al. [83] found that DSAs were associated with a 6/7-fold increased risk of primary GF and were linked to decreased PFS (HR 4.25–4.83) and OS (HR 1.68–3.19). The impact of DSAs on poor graft function remains uncertain, largely due to inconsistencies in the definition of PGF across studies [14].

Donor Age

In recent years, donor age has become an increasingly important factor in donor selection, due to the growing evidence that younger donor age is associated with better transplant outcomes. Scattered studies have explored the reasons underpinning these findings; the leading hypotheses include the increase in clonal hematopoiesis and loss of clonal diversity with age, as well as cellular aging of hematopoietic stem cells [84,85].

In the unrelated-donor transplantation setting, better survival outcomes have been observed when donors are younger (e.g. ages 18–32). Each 10-year increment in donor age is associated with a 5.5% increase in HR for overall mortality [16]. Spellman et al. [86] employed a machine-learning model to refine unrelated donor choice and found that donors under 32 years correlated with better event free survival (EFS).

In haploidentical transplantation, increasing donor age by each decade is associated with worse OS (HR 1.13) and PFS (HR 1.09), mostly driven by higher NRM (HR 1.19), as well as an elevated risk of acute GVHD (HR 1.3) [17]. These observations align with results from an Italian group, which reported poorer OS and PFS but did not find a significant age-dependent effect on relapse incidence [11]. Mehta et al. [87] assessed donor age in haploidentical reduced-intensity conditioning HCT, confirming that younger donors may be preferable, although HLA matching remains a pivotal consideration. In haploidentical allo-HSCT, accumulating data supports the selection of a younger donor to optimize GRFS and to reduce NRM. Although thresholds vary, donors aged under 30–35 years generally appear to provide a favorable balance without necessarily requiring even younger donors [88]. In this respect, Sanz et al. [20] reported HR of 1.36 and 1.32 for NRM and GRFS, respectively, for donors older than 37 years in AML haplo-HSCT.

Based on data from over 1,500 patients, Mehta et al. [89] suggest that among older patients (≥50 years), a younger Haplo donor (<35 years) with either B-leader match (improved OS) and/or DRB1-mismatch (reduced relapse) might be preferable to an older MMUD (≥50 years).

In a large study by Nagler et al. [90] involving 2,798 allo-HSCT recipients, patients were stratified by donor type (Haplo vs MMUD) and donor age (< 35 vs ≥ 35). They found a lower incidence of grade 2–4 acute GVHD and reduced NRM in the younger MMUD group compared to older Haplo donors, while other transplant outcomes did not significantly differ. Piemontese et al. [91] studied 345 patients older than 50 years with AML in remission and compared older MSD to younger MUD. In patients receiving intermediate-to-high intensity conditioning, younger donors conferred better outcomes; interestingly, in those receiving reduced-intensity regimens, outcomes did not significantly differ by donor type.

Overall, the influence of donor age on engraftment and graft failure is inconsistent and often not statistically significant across these studies.

Time to Transplant

When an MSD is not available, the search for a suitable donor begins with evaluation of HLA matching of the potential donors. So far, the identification of the best MUD represents the ultimate goal, however the availability of the new PTCy platform has broadened the range of possible choices including MMUD and Haplos, with a remarkable impact for clinicians facing the donor selection.

In a recent study, Lee et al. [24] evaluated a donor search prognosis score to prioritize the use of alternative donors for those patients who are very unlikely to find a MUD. According to this algorithm, 1,751 patients were defined as very likely (54.7%), and very unlikely (15.8%) to identify a MUD. Transplant outcomes did not differ between the two groups, although 94% of patients in the very likely group received a MUD graft, while only 9% in the very unlikely group. The rest of the very unlikely group received Haplo (60%), MMUD (23%), or UCB (8%) transplants. Of note, the time from evaluability to transplant was significantly short with a median time from similar in the two groups (same 3.3 months for both the groups very likely and very unlikely).

These results strongly support the consideration that the time to transplant should be considered at least as important as HLA matching. When the probability to find an 8/8 MUD is very low, a timely identification of alternative donors (MMUD, Haplo, or UCB) may result in OS not different to that achieved when the transplant is performed using a MUD, likely due to the great progress in GVHD prophylaxis with the use of PTCy.

CMV Status

Despite the use of pre-emptive therapy, CMV infection can be harmful to hematopoietic stem cell transplant (HSCT) recipients resulting in increased morbidity and mortality [92]. The risk of infection largely depends on the donor and recipient serostatus, with the highest risk observed in cases where a seronegative donor is paired with a seropositive recipient [93]. In this respect, when possible, the choice of a seronegative donor for a seronegative recipient represented for a long period of time the driving strategy in the selection of the optimal donor for HSCT, and several guidelines supported this indication [94–96]. The advent of primary anti-CMV prophylaxis (PAP) with Letermovir had a remarkable impact on CMV infection in HSCT recipients, owing to a low rate of CMV reactivation (around 3-7%) [27,97] along with the administration of prophylaxis (100 days post-HSCT) and a reduced incidence of end organ disease. Defining the CMV serostatus of the donors is of great importance because the risk of late CMV infections after Letermovir discontinuation is significant, particularly in transplants with donors CMV negative. Whether the extension of prophylaxis up to day 200 will further mitigate the role of donor serostatus needs to be addressed in the next studies. At the present, in case of seronegative recipient a seronegative donor is recommended, while in case of seropositive recipient a seropositive donor is recommended [94].

Clonal Hematopoiesis (CHIP and CH)

CHIP is characterized by the presence of somatic mutations in hematopoietic cells in otherwise healthy individuals. Its prevalence increases with age, affecting over 10% of individuals older than 65 years [23]. Clonal hematopoiesis (CH) has been detected in more than 20% of stem cell donors, with DNMT3A and TET2 mutations being the most common [84]. CHIP and CH are associated with increased risks of hematological malignancies, cardiovascular disease, and overall poorer survival. HSCT itself—through proliferative stress and immunosuppressive therapy—may accelerate the expansion or progression of donor-derived CHIP.

A systematic review and meta-analysis by Xie et al. [98] analyzed five studies on allogeneic HSCT and found that donor CH was associated with a reduced risk of relapse (HR 0.79) but did not significantly affect OS, PFS, NRM, or the incidence of acute or chronic GVHD. Scattered studies identified a higher incidence of chronic GVHD in recipients of donors with CH, particularly those with DNMT3A mutations (5-year cumulative incidence 52.9% vs 35.7%) [99, 100]. While some studies did not report an increased incidence of secondary malignancies, others have described donor-derived leukemias (donor cell leukemia, DCL) arising from CH clones [84, 101]**.** The small number of DCL events limits statistical power, but data suggest that donor-derived CH clones often expand more rapidly in recipients than in donors. Importantly, single DNMT3A or TET2 mutations appear to carry lower risk compared to clones with multiple mutations or those involving TP53 [102,103].

Although CHIP and CH may not significantly impact OS or NRM, they appear to increase the risk of chronic GVHD

and may reduce relapse risk—possibly due to enhanced immunological activity and graft-versus-tumor (GVT) effects. Despite concerns about passing on pre-leukemic clones, systematic CHIP screening of asymptomatic donors with normal blood counts is not currently recommended, though some experts suggest considering it for older donors (>50–55 years) [23,104,105]. To date, no consistent data link donor CHIP/CH to cardiovascular disease in HSCT recipients [106].

ABO Blood Group

ABO mismatch between donor and recipient does not preclude HSCT but is a factor to consider during donor selection. In cases of major or minor ABO incompatibility, red cell or plasma depletion of the graft product is typically required. While ABO incompatibility most often leads to mild hemolytic reactions, it can cause more serious complications such as delayed red blood cell recovery, pure red cell aplasia, and impaired engraftment [107].

A registry study by the Center for International Blood and Marrow Transplant Research (CIBMTR) involving over 6,000 patients found no significant impact of ABO compatibility on overall mortality or GVHD—with either bone marrow or peripheral blood stem cell grafts [16]. Similarly, Ciftciler et al. [108] found no association between ABO mismatch and neutrophil/platelet engraftment or survival in a cohort of 264 patients.

However, other studies report worse outcomes with ABO incompatibility. Remberger et al. [109] identified an increased GF rate of up to 7.5% in cases of major ABO mismatch. A Stanford University study on 1,737 patients found that minor ABO mismatch, but not major or bidirectional, was associated with inferior OS and increased NRM [110]. A subsequent CIBMTR analysis in AML/MDS patients showed a negative impact of major ABO mismatch, but not minor [111]. Based on these results ABO incompatibility between donor and recipient might influence OS predominantly increasing NRM. This negative impact seems to differ based on the population analyzed and the underlying hematological disease.

A large retrospective EBMT study of over 30,000 patients found no significant differences in OS, NRM, or PFS based on ABO compatibility; however, major and bidirectional mismatches were associated with a slightly higher incidence of graft failure [112]. Overall, ABO incompatibility does not appear to substantially impact transplant outcomes and therefore should not be considered a primary factor in donor selection.

Recommendations

The EBMT recommends a 10/10 HLA MUD as the first choice for patients lacking an MSD. If not possible, MMUD, HAPLO, or UCB are all equally acceptable options depending on the transplant team's experience, donor availability and urgency [113]. NMDP/CIBMTR Guidelines suggest a suitable MSD as the first choice, MUD as the second choice, HAPLO and MMUD as third choice and factors to be considered among the different sources are donor age, presence of DSAs, logistic concerns and clinical trials available. Regarding HLA-matching, they recommend avoiding HLA-DPB1 nonpermissive mismatches in MUD transplantations in the CNI setting, while in Haplo HLA-DPB1 nonpermissive mismatches may be associated with increased survival. MUD and MMUD have similar outcomes and there is insufficient evidence to prioritize a specific HLA mismatch when selecting a MMUD [114].

For patients with nonmalignant diseases, a higher risk of graft failure is present and there is a broader need to avoid GVHD. Consequently, the upfront transplant is considered in severe aplastic anemia (SAA) only when an MSD is available; otherwise, an MMUD or an MUD transplant is considered after the failure of other therapies. More recently, the remarkable improvement achieved with the use of PTCy and Haplo provided evidence in favor of HSCT from alternative donors (MUD and Haplo) as a therapeutic option for upfront HSCT in patients with SAA who lack an MSD [115].

Final Remarks and Future Perspectives

Donor selection strategy is a demanding process requiring specific skills: indeed, the identification of the best available donor may be considered as one of the most relevant factors affecting the outcomes of patients receiving allogeneic HSCT. The extensive use of the PTCy platform has reshaped the scenario of GVHD prophylaxis leading to the inclusion of donors other than matched siblings such as alternative donors, for instance MUD, MMUD and Haplos. In this respect, the possibility to broaden the donor search may have the advantage of increasing transplant access for patients from ethic minority groups. In addition to the well recognized factor of HLA matching, non-HLA characteristics have assumed consistent relevance, for instance donor age and time to transplant (**Table 1**). Finally, open questions remain still related to the impact of HLA mismatch permissiveness (i.e. DPB1, B-leader) under new GVHD prophylaxis strategies such as PTCy.

Disclosure Statement

M.C. received honoraria from Incyte, Novartis, Servier, Otsuka, Janssen, Abbvie, Astellas, Jazz, Amgen, Italfarmaco, Pfizer, Gilead.

E.A. received honoraria from Abbvie, Astellas, Jazz.

A.B. received honoraria from Gilead.

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Table 1. Synthesizes the key factors in donor selection for transplantation.

HLA matching	Crucial for preventing GVHD. Historically, MSD and MUD are preferred but the introduction of PTCy is opening the way for Haplo and MMUD.
Sex Mismatch	A minor factor in donor selection for HSCT.
Donor Specific Antibodies (DSA)	If present at high level, they seem to correlate with higher risk of graft failure and delayed engraftment. Desensitization strategies or selection of a different donor should be taken into account.
Donor age	Of increasing importance: the younger the donor, the better the transplant outcomes.
Time to transplant	The search for a donor must be as brief as possible, particularly in high-risk disease.
CMV serostatus	It is preferable to have a CMV seronegative donor/ CMV seronegative recipient transplantation, but the introduction of Letermovir can redefine the role of CMV serostatus.
CHIP	Investigational interest.
ABO incompatibility	Data about its association to graft outcomes is conflicting.

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