International Journal of Pharmaceutical and Bio-Medical Science

ISSN(print): 2767-827X, ISSN(online): 2767-830X

Volume 03 Issue 02 February 2023

Page No: 57-79

DOI: https://doi.org/10.47191/ijpbms/v3-i2-04, Impact Factor: 5.542

Current Trends in Transplantation of Patients with Hematological Malignancies

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is widely used to treat hematological malignancies and nonmalignant hematological disorders. Many advances have been made in improving the success of bone marrow transplantation. However, lack of available matched related or matched sibling donors has posed a significant challenges to the availability and proper utilization of hematopoietic stem cell transplantation in patients with hematological malignancies. The rising availability of alternative donors, particularly haploidentical donors (HIDs), has propelled the rapid rise of allo-HSCT. The aim of this review is to highlight and evaluate the recent advances in the development of HSCT, focusing mainly on the selection of suitable hematopoietic stem cell donors, HID-HSCT and some current advances in the use of umbilical cord blood cells as an alternative graft source. Haplo-HSCT has shown a promising result and better outcomes due to the number of advantages, including a wide range of stem cell sources, increased GVL effects, improved immunologic reconstitution, and positive clinical outcomes. In the near future, haplo-HSCT is likely to be considered as a better option for patient donor selection particularly in AML patients while HLA matching is unlikely to be the most important factor in AML patient donor selection. In addition, the use of umbilical cord blood cells has shown a promising role as an alternative source of HSCT even with other available sources such as bone marrow and peripheral blood. Other transplantation procedures, such as T-cell depletion allografts, Post-transplant cyclophosphamide (PTCY), G-CSF-mobilized allografts, and antithymocyte globulin, have contributed to significant improvements in haplo-HSCT outcomes in recent decades.

KEYWORDS: HSCT, Hematological Malignancies, Haplo-HSCT, UCB-HSCT

ARTICLE DETAILS

Published On:
08 February 2023

Available on:
https://ijpbms.com/

1. INTRODUCTION

Bone marrow transplantation is a form of cellular therapy that has been considered for many decades as treatment option for many hematological diseases and solid malignancies. It has long been employed as standard therapy for the control and/or cure of a wide array of malignant and non-malignant hematologic diseases, solid tumors, immune system, metabolic diseases, congenital and acquired diseases (Kanate *et al*., 2020). Many patients with hematological malignancies have largely benifited and supported with hematopoietic stem cell transplantation (HSCT) (Wildes *et al.*, 2014). Several reports from various surveys of transplantation activity conducted by the Worldwide Network for Blood and Marrow Transplantation Group, the Center for International Blood and Marrow Transplant Research (CIBMTR), the European Group for Blood and Marrow Transplantation (EBMT), and the Asia-Pacific Blood and Marrow Transplantation Group (APBMT), have shown an increase in the annual global frequency of HSCT (Worel *et al*.,2021; Passweg *et al*., 2021; Muhsen *et al*., 2020; Phelan *et al*., 2020; Aljurf *et al*., 2019; Lida *et al*., 2019). Despite significant progress in the various therapeutic options for haematological malignancies, haematopoeitic stem cell transplantation remains a potential curative alternatives, indicated for patients with

haematological malignancies especially those with high risk of relapse.

The aim of this paper review is to provide information on the current trends and to discuss and evaluate recent advances in haematopoeitic stem cell transplantation in patients with haematological malignancies.

2. Clinical Indications for Hematopoietic Stem Cell Transplantation in Hematological Malignancies

Adult AML patients should always be considered for HSCT, but the decision to proceed should be determined on the balance of disease relapse risk and transplant-related mortality (Cornelissen and Blaise, 2016). The choice should also be based on the comparison between predicted relapse rates following chemotherapy and predicted relapse rates following allogeneic transplantation, together with the predicted treatment-related mortality of each approach (Appelbaum, 2014). In Europe, acute myeloid leukemia (AML) is the most common reason for allogeneic HSCT, followed by acute lymphoblastic leukemia (ALL) (Passweg *et al*., 2018; Passweg *et al*., 2017; Passweg *et al*., 2016; Passweg *et al*., 2015). This is the same in China in which a report showed that, the predominant indications for allogeneic HSCT were AML (37%) and ALL (24%) (Xu *et al*., 2021). Before now, the use of morphology as basis for risk assessment of AML has shown to be of less value but cytogenetics still play a significant role and more recently practice the combination of cytogenetics and mutational analyses of *CEBPA*, *NPM1*, and *FLT3*-ITD, have continued to be of value to in categorizing AML into the four risk categories: favorable, intermediate 1, intermediate 2, and adverse (Appelbaum, 2014).

In the past, ALL patients particularly children who has positive Philadelphia chromosome (Ph+), high white blood cell count among others, are usually considered as indicators for HSCT as standard therapy especially when induction therapy fails to induce remission for the second time (Diorio and Maude, 2020), however these markers are no longer considered as frontiers when deciding for transplantation. (Algeri *et al.*, 2021).

In contrary, some research suggests that allogeneic hematopoietic stem cell transplantation may be more beneficial in individuals with high-risk ALL, especially those with the Philadelphia chromosome (4, 11) (Yanada *et al*., 2006). However, recent development has employed the addition of tyrosine kinase inhibitors (TKIs) to first-line therapy with an improved overall results. In a large retrospective analysis, post-transplant TKI maintenance was linked to a lower risk of relapse and should thus be regarded a viable strategy (Giebel *et al*., 2016). The main criterion for HSCT indication in patients with ALL is the response of the disease to induction therapy and another most important marker is MRD at selected time points and is considered as the most powerful indicator in childhood ALL (Borowitz *et al*., 2008). The use of chimeric antigen receptor (CAR) -T cells that target CD19 have demonstrated promising results in patients with advanced types of ALL, including those who have relapsed or become refractory after allogeneic HSCT. Thus the introduction of CAR-T cells has revolutionalize the treatment of some patients with relapsed/refractory ALL and other severe or poor-prognosis malignancies. The EBMT, along with other societies and professional groups, is working to design a roadmap for implementing CAR-T cell programs that addresses potential limitations, ensures accurate assessment, manages toxicities and long-term monitoring (Duarte *et al*., 2019).

Over time, HSCT has shown significant cure rates for CML patients, but with the discovery of alternative first line drugs such as imatinib, second line drugs like tyrosine kinase inhibitors the treatment approach for CML has taken another shape and HSCT is now reserve for patients with CML who are refractory to first-line medicines (Khaddour *et al.*, 2021; O'Brien *et al*., 2003). With its ability to provide excellent response rates and minimal toxicity, imatinib has been established as the treatment of choice for chronic phase CML, and it was initially believe that HSCT was no longer indicated at least in chronic phase (Hochhaus *et al*., 2009; Druker *et al*., 2006), not until issues of resistance in chronic phase surfaced (O'Dwyer *et al.*, 2004). CML patients can also be considered as candidates for allogeneic HSCT on any EBMT modality if there is no hematological response to second-line treatment. CML patients should be treated with third-line TKI based on ABL mutation analysis and are considered candidates for HSCT in optimal response as soon as possible if their EBMT risk score is 0–1, or if their EBMT risk score is 0–4 and they had previously lost cytogenetic response to second-line TKI (Duarte *et al*., 2019). A patient who has a syngeneic donor is always a good candidate for a standard conditioning Outside of clinical studies, autologous HSCT is generally not indicated (Duarte *et al*., 2019).

Despite multiple and several alternative drugs in use for the treatment of CML, transplantation still remain indicated in patients with hematological malignancies.

For individuals with myeloproliferative diseases other than CML, allogeneic HSCT remains the curative treatment of choice unless the disease has advanced to myelofibrosis or secondary leukemia, polycythemia vera and essential thrombocythemia (Duarte *et al*., 2019). Before now the decision to embark on HSCT in patients with myelofibrosis (MF) was largely depend on various diseases risk scores such as IPSS, DIPSS etc, and it has been reported that patients with low-risk disease are generally not considered for transplant because survival rates appear to be higher with pharmacologic and supportive therapy, at least in the pre-JAK inhibotors (ruxolitinib) era (Jain *et al*., 2017). However, the discovery of JAK inhibitors such as ruxolitinib has successfully shape the MF treatment with significant improvement in both symptoms and overall survival, as well as quality of life (Jain *et al*., 2017). Although the exact role of JAK inhibitors in the therapy of myelofibrosis is unknown, they may help to reduce constitutional symptoms and shrink

the spleen before transplantation (Stübig *et al*., 2014). More recently, some studies have reported that sub-clonal mutations (i.e., ASXL1, EZH2, IDH1/2, and SRSF2) have an adverse effect on overall and leukemia-free survival (Vannucchi *et al*., 2013; Tafferi, 2010), and could be used as deciding tool before transplant (Guglielmelli *et al*., 2018). Despite development and use of pharmacological treatment approach in the treatment of myelofibrosis , allogeneic hematopoietic stem-cell transplantation (HSCT) currently remains the only available therapy that may target and modify the natural history of MF (Deeg *et al*., 2003).

MDS patients or AML that has progressed from MDS benefit from allogeneic HSCT. The introduction of reduced-intensity conditioning regimens, the expansion of the indication to older patients and the increasing use of unrelated or mismatched family donors have all been credited for increased activity and use of HSCT in MDS (Kroger, 2012).

Allogenic stem cell transplant is considered being curative in cases of disease progression and is only indicated in intermediate-or high-risk patients with MDS (Khaddour *et al*., 2021).

Other additional prognostic variables such as marrow fibrosis, multilineage dysplasia, refractory cytopenia, transfusion need, and somatic mutations are all need to be consider before commencing allogeneic HSCT. (Bejar *et al.*, 2014**;** Bejar *et al*., 2011; Kroger *et al*., 2011; Malcovati *et al.*, 2005).

Generally the justification to treat CLL patients warrant only when patients become symptomatic (Hallek *et al*., 2008). HSCT indication for CLL have been revolutionized by the current use of signaling pathway inhibitors (PIs), such as Bruton's TKI ibrutinib, phosphatidylinositol-3-kinase inhibitor idelalisib, and BCL2-inhibitor venetoclax (Dreger *et al*., 2012). The European Blood and Marrow Transplantation Society (EBMTS) and ERIC (European Research Initiative in CLL) recently proposed a revised classification of high-risk CLL based on TP53 alterations and responsiveness to PI therapy (Dreger *et al*., 2018). Patients with chemo-immunotherapy resistant CLL who are fully responsive to PI (high-risk I) should be treated with these drugs, and allogeneic HSCT should be utilized only in carefully selected patients who are at low risk from the procedure. Patients with CLL who are resistant to both chemo-immunotherapy and PI (high-risk II) and have used up all of their pharmacological alternatives should be consider for cellular treatments, such as CAR-T cells and allogeneic HSCT, if they are eligible (Duarte *et al.*, 2019). It's worth noting that cellular and molecular therapies aren't mutually exclusive and can be utilized in tandem to maximize their effectiveness (Duarte *et al.*, 2019). In patients with a histological transformation that is clonally unrelated to CLL, autologous HSCT should be evaluated as a therapeutic alternative, although it is generally not indicated in CLL otherwise (Cwynarski *et al*., 2012).

For the time being, HSCT remains the standard of care for patients with relapsed HL who are chemosensitive to salvage therapy, with autologous HSCT for those who have never had an autograft and allogeneic HSCT for those who have had a failed prior auto-graft. In the future, targeted therapy like brentuximab vedotin and checkpoint inhibitors may change the transplant algorithms for HL. (Messer *et al*., 2014; Sureda *et al*., 2012; Sarina *et al*., 2010; Schmitz *et al.*, 2002; Linch *et al*., 1993).

In patients with recurrent disease or who had not reached complete remission with initial therapy, a combination of high-dose chemotherapy and autologous or allogeneic HSCT has resulted in complete remissions (Ayers *et al*., 2020).

For patients with Early-stage primary cutaneous T cell lymphomas HSCT is not indicated because of the disease good prognosis when subjected to standard therapy. Patients with advanced EORTC/ISCL stages IIB to IV, on the other hand, have a poor prognosis with standard therapy (Trautinger *et al*., 2017; Jawed *et al*., 2014; Whittaker *et al*., 2003). Despite the dearth of well-designed comparison trials, allogeneic HSCT offers these patients a clinically relevant and sustained graft-versus-lymphoma impact (Duarte *et al*., 2014; Duarte *et al*., 2010; Duarte *et al.*, 2008).

The above report suggest that HSCT offers good clinical outcome and is a better clinical alternative for these patients than their outcomes with only conventional therapy and hence, HSCT still remain useful and should be indicated when certain criteria are met.

Although HSCT does not cure multiple myeloma, it is advised for these patients because high-dose chemotherapy combined with early autologous HSCT has shown to have a considerable survival advantage over conventional chemotherapy. It's unclear whether double autologous HSCT (tandem transplants) provide a benefit. (Shah *et al*., 2015).

In view of the current trends on HSCT indication, the most notable has been a continuous increase allo-HCT in acute myeloid leukemia. This increase was largely due to extending allogeneic HCT to include older patients that fails to maintain long-term remissions. For the same reason, increases were also seen for patients with acute lymphoblastic leukemia and myelodysplastic syndromes (MDS). In contrast, allogeneic HSCT for chronic myeloid leukemia, chronic lymphocytic leukemia (CLL), and MM have either remained at very low levels or declined. These trends were influenced by the introduction of alternative therapies for these diseases, including tyrosine kinase inhibitors, a BCL-2 antagonist, Bruton tyrosine kinase inhibitors, bi-specific or mono-specific monoclonal antibodies, proteasome inhibitors and chimeric antigen receptor (CAR) T cells, among others.

3. Comparison of Bone Marrow and Peripheral Blood Transplantation: Which One is has better outcome?

In hematopoietic stem cell transplantation, both peripheral blood (PB) and bone marrow (BM) are commonly employed (HSCT). However, it is uncertain whether PB or BM gives a better outcome in haploidentical HSCT, especially in patients receiving the conventional therapy of post-transplant

cyclophosphamide (PTCy) (Yu *et al.,* 2019). Several studies comparing the use of bone marrow stem cells with peripheral blood stem cells in people with hematological malignancies have been reported. The most successful treatment for CML is bone marrow transplantation from suitable donors (Or *et al*., 2003). For patients who are resistant to chemoradiation therapy and have a high risk of relapse, allogenic bone marrow transplantation is an effective alternative treatment option (Slavin *et al.,* 1998). When compared to peripheral blood stem cells, patients receiving bone marrow SC transplantation have less GVHD (PBSCs) (Holtick *et al*., 2015). Various hematologic malignancies, such as AML, ALL, and CML, are treated via bone marrow–SC transplantation. The rates at which stem cells obtained during transplantation begin to proliferate and create new blood cells (known as engraftment) have been reported to be faster following the transplantation of peripheral blood stem cells (PBSCT) than bone marrow stem cells (BMT) platelets in the majority of these investigations (Holtick *et al*., 2014). According to some research, PBSCT is linked to a higher risk of developing GvHD than BMT. GvHD is linked to a decreased chance of relapse, indicating the immune system's ability to attack malignant cells simultaneously (Graft versus tumor effect). GvHD, on the other hand, can have a role in transplant-related mortality and morbidity. PBSCT and BMT have typically been reported to have similar disease-free and overall survival rates (Holtick *et al.,* 2014). From the outcome of a study by Yu et al. it has been concluded that, in patients having PTCy haploidentical HSCT, the efficacy of PB is comparable to that of BM in terms of primary outcomes such as OS, DFS, NRM, and recurrence. However, PB graft is ideal for haploidentical HSCT in terms of convenience and pain alleviation, but with a higher risk of acute GVHD. The use of peripheral SCs as a source of SCs has the potential to cause GVHD (Ruggeri *et al.,* 2018). Even if they have such effects, the immune system has been strengthened as T-cell secretion has increased. T cell elevation, on the other hand, may contribute to the development of GVHD (Holtick *et al*., 2015); nevertheless, PBSC collection in children may result in metabolic problems such as hypocalcemia and hypoglycemia (Orbach *et al*., 2003).

In view of the current available data, it is uncertain to indicate which one is better as both serves as therapeutic alternative to patient with haematological malignancies. However, careful selection between BMSC and PBSC should be made according to patient diseased condition, conditioning regimen and age of patient among others, before considering HSCT in patients with hematological malignancies.

4. Comparison of UCBT to BM and PB Stem Cell Sources

UCB is a valuable source of HSCs because of its lower GVHD complication rate and less rigorous HLA-matching requirements (Saudemont and Madrigal, 2017).

Studies comparing UCBT to alternative graft sources have s hown the benefits of UCBT such as decreased incidence of chronic GVHD and higher graft-vs-leukemia (GVL) effects for MRD-positive patients. UCB is a valuable source of HSCs because of its lower GVHD complication rate and less rigorous HLA-matching requirements (Saudemont and Madrigal, 2017). In terms of colony-forming unit granulocyte/macrophage progenitors and CD34+-cell content, it is more enriched with HSCs/progenitor cells than peripheral blood (Joshi *et al*., 2000). Because the impact of HLA mismatching is less severe in mismatched UCB transplantation than in unrelated peripheral and bone marrow–blood transplantation more mismatched donors may be able to donate to save lives (Yabe *et al.,* 2018)

In comparison to matched related or unrelated transplantation, 47 UCBT has shown comparable overall survival and a very low incidence of chronic GVHD with good GRFS. (Sharma *et al*., 2020; Zheng *et al.,* 2017; Tong *et al*., 2017). When HLA-matched or mismatched unrelated donor transplants were compared with myeloablative conditioning in patients with acute leukemia or MDS, the relative risks of death and relapse appeared to differ depending on the presence of MRD status before transplantation. The probability of OS after UCBT was at least as good as that after an HLA-matched unrelated donor transplant and much better than that after an HLA-mismatched unrelated donor transplant in patients with MRD (Xhu *et al.,* 2021).

However, the cost of delaying engraftment with CB, the danger of infection and its limited volume remain barriers to its use in hematologic malignancies. (Ballen, 2017; Bhatt, 2016).

Taken together, it is safe to say that UCB has shown a promising role as an alternative source of HSCT even with other available sources such as bone marrow and peripheral blood but more researches need to be done to overcome some notable challenges.

5. Current Practice in the Choice of Stem Cell Donor for HSCT in Hematological Malignancies

Once transplantation is being evaluated as a treatment option, a suitable donor must be found. HLA histocompatibility typing for direct family members is conducted for allogeneic transplants, first utilizing intermediate-resolution typing (Moore *et al*., 2021).

For the treatment of AML, ALL, and MDS, HID-HSCT has a clinical outcome that is equivalent to MSD- or MUD-HSCT. When a well-matched unrelated donor or cord blood is not available, a haploidentical donor may be considered. The advantage of this donor source is availability, as numerous persons, including parents, siblings, and children, are frequently available to serve as potential donors within a given family. In contrast to the availability of matched, unrelated donors, another advantage is the equal availability of donors for all ethnic and racial groups (Moore *et al.,* 2021). Mismatching of mother antigens rather than paternal antigens appears to be tolerated better in haploidentical transplants, possibly due to prenatal and perinatal exposure to maternal

HLA antigens. Although early studies suggested that haploidential HSCT was associated with a significant rate of acute GVHD, methods such as graft T-cell depletion and post-transplant cyclophosphamide have greatly reduced this risk. Haploidentical donors are now being used more frequently in both myeloid and lymphoid malignancies, as well as nonmalignant disorders, thanks to the efficacy of those treatments. (Sirinoglu *et al*., 2012).

The following are some of the benefits of HIDs: almost all patients can be matched with a HID in a timely manner; a HID is better suited for urgent allo-HSCT, especially during the coronavirus disease 2019 (COVID-19) pandemic (Algwaiz *et al*., 2020). Another advantage is that re-donation is possible for additional cellular therapy, especially in high-risk relapsed patients; bone marrow and/or peripheral stem cells can be obtained in high-risk hematological malignancy patients. HID-HSCT is associated with a reduced rate of relapse than MSD-HSCT (Chang *et al*., 2020; Li *et al*., 2020; Yu *et al*., 2020; Zheng *et al*., 2020; Chang *et al*., 2017). It should be highlighted that the rate of GVHD in HID-HSCT patients is still greater than in MSD-HSCT patients. The degree of HLA match between the donor and recipient is likely the most critical element in these transplants; well-matched transplants reduce the likelihood of graft rejection and GVHD, two of the most serious post-transplant complications. Furthermore, allogeneic transplants are associated with lower relapse rates than autologous transplants due to the graft-versus-tumor effect (Zhang *et al*., 2021).

In both hematological malignancy and nonmalignant hemato logical illness patients, clinical outcomes of URD-HSCT have been demonstrated to be equivalent to those of MSD-HSCT and HID HSCT.

Zhang et al. studied 85 patients with SAA and found that tho se who had MSD, URD, and HID,HSCT had identical 3year OS rates (92.1 percent vs. 100 percent vs. 86.7 percent, p = 0.481) (Zhang *et al*., 2020). The China Marrow Program has received almost 10,000 donations, with URD-HSCT accounting for 13% of allo-HSCTs. Several considerations, including the likelihood of finding an eligible donor, urgent transplantation needs, re-donation for innovative cellular therapies, and the COVID-19 pandemic, may limit the use of URD-HSCT (Zhang *et al*., 2021).

Although most centers require a complete match at the HLA-A, HLA-B, and HLA-DRB1 loci for an individual to be used as a transplant donor, some centers consider the use of single antigen–mismatched siblings. As expected, transplants from such donors pose a higher risk of GVHD, although the overall survival rate may not differ significantly from that observed with fully matched siblings (Zhang *et al*., 2021).

However, when a related donor can't be found, a search for an unrelated donor is frequently launched (Figure 1). The procedure begins with the recipient's high-resolution HLA typing, which determines the precise DNA sequence of the HLA molecule's antigen binding region and is a more accurate technique of typing than the serologic method (Nunes *et al*., 2011). Then, within 24 hours, a preliminary search of registration databases is conducted, which may be completed very fast and produce general information such as the number of possible marrow donors and cord blood units. As of May 2021, there were almost 39 million potential donors and over 800,000 cord unit available (Moore *et al*., 2021). Horan *et al* (2012) found that HLA mismatches are associated with graft failure but not with GVHD when nonmalignant illnesses are treated with HSCT using unrelated donors. The researchers looked at 663 HSCTs that used bone marrow or peripheral blood stem cells from unrelated donors and identified a connection between patient mortality and HLA-A, HLA-B, HLA-C, and HLA-DRB1 mismatches, but not HLA-DQB1 or HLA-DPB1 mismatches (Horan *et al*., 2012).

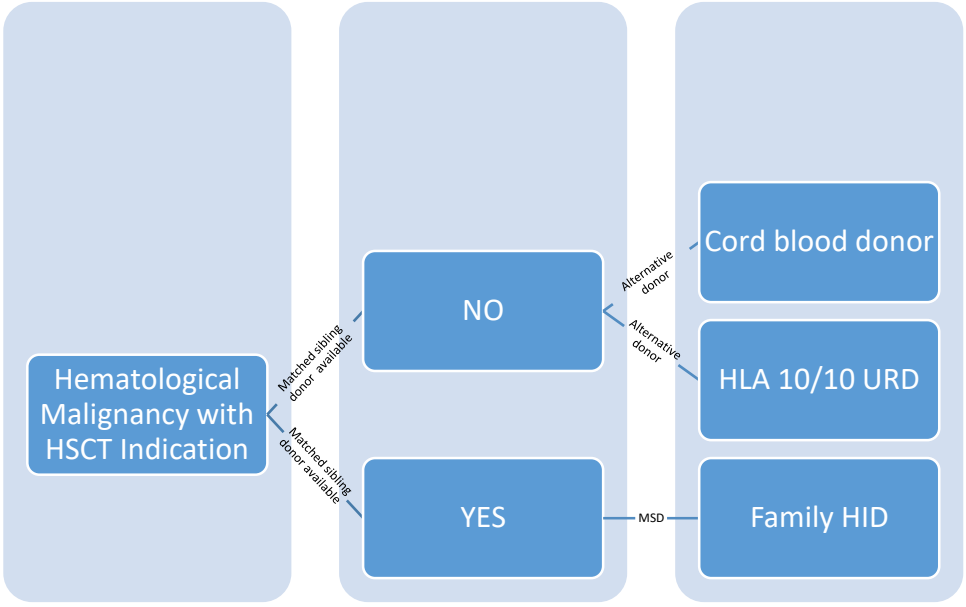

Figure 1. Summary of the criteria for selection of donor for haplo-HSCT in patients with hematological malignancies

6. Haploidentical Matched Donor VS HLA-Matched Sibling Donor Transplantation in Hematological Malignancies

Acute myeloid leukemia patients can benefit from allogeneic hematopoietic stem cell transplantation (allo-HSCT) (AML) (Blume *et al*., 1980). Because of quick hematopoietic and immunologic reconstitution and decreased rates of infections and acute graft-versus-host disease (GVHD), HLA-matched sibling donors (MSDs) remain the preferred donor source. However, only 25–30% of patients can get HLA-matched sibling donor transplantation (MSDT). Alternative donor sources, such as HLA-matched unrelated donors, HLA-haploidentical donors, or umbilical cord blood, may be preferable possibilities for the majority of patients (Kanakry *et al.*, 2015).

Due to high rates of graft failure and GVHD, haploidentical hematopoietic stem cell transplantation (haplo-HSCT), which is now accessible for nearly all patients, had poor results at first. Better GVHD prevention and transplantation procedures, such as T-cell depletion allografts (Aversa *et al*., 2005; Aversa *et al.*, 1994). Post-transplant cyclophosphamide (PTCY), G-CSF-mobilized allografts, and anti-thymocyte globulin, have contributed to significant improvements in haplo-HSCT outcomes in recent decades (Wang *et al*., 2015). In patients undergoing haplo-HSCT, NK cells or T cells should have higher graft-versus-leukemia (GVL) effects due to HLA mismatches between haploidentical donors and recipients (Kolb *et al*., 2004). After haplo-HSCT, however, more severe immunosuppression is used to assure higher rates of engraftment and lower the risk of GVHD (Sidlik-Muskatel and Reisner, 2019). It's uncertain whether the immunosuppressive milieu in which haplo-HSCT patients are treated, can lessen GVL consequences (Zheng and Tian, 2021). Guo et al. reported that haplo-HSCT treated mice may significantly extend survival and reduce tumor burden. Moreover, the group's previous study showed higher expression of CD107a on NK cells in haplo-HSCT-treated patients (Hu *et al*., 2020). These results indicated that GVL effects were enhanced in haplo-HSCT-treated AML patients. This provided one possible explanation for why AML patients receive lmorle favorable clinical benefits from haplo-HSCT (Zhang and Tian, 2021).

Taken together, haplo-HSCT has shown a promising result and better outcomes due to the number of advantages, including a wide range of stem cell sources, increased GVL effects, improved immunologic reconstitution, and positive clinical outcomes. In the near future, haplo-HSCT is likely to be considered as a better option for patient donor selection particularly in AML patients while HLA matching is unlikely to be the most important factor in AML patient donor selection.

7. Haploidentical Donor-Bone Marrow (HID-BM) VS Matched Unrelated Donor -Peripheral Blood (MUD-PB)

In the setting of post-transplantation cyclophosphamide (PTCy) for patients with acute leukemia, using a haplo donor with a BM graft resulted in a lower incidence of GvHD than using a UD-PB stem cell graft (Nagler *et al*., 2021). Disparities in GvHD, on the other hand, did not translate into differences in survival outcomes. UD-PB or haplo-BM should be considered equally as appropriate sources for allo-HCT based on these findings (Nagler *et al*., 2021). In a similar comparative prospective study conducted by Cho et al. which uses a novel haplo-HSCT protocol using RTC with T-cell-replete PBSC showed comparable graft-vs-leukemia (GVL) effects with MUD-HSCT without concerns of higher toxicity, translating into equivalent OS. These data suggest that patients with AML in remission who require allo-HSCT do not need to search for matched unrelated donors—in particular, patients who urgently need transplantation (Cho *et al*., 2021). In this current review, we consider both haplo-BM and MUD-PB as an alternative in the absence of available matched related donor. However, Haplo-BM should always be considered as superior alternative to MUD-PB due to its lower incidence of GVHD (Nagler *et al.*, 2021).

8. Current Approach in Opitimization of Conditioning Regimen for HSCT in Patients with Hematological Malignancies.

In recent time the use of modified busulfan (3.2 mg/kg/day, intravenous, i.v., for 3 days) and cyclophosphamide (1.8 g/m2/day, i.v., for 2 days) are the standard myeloablative regimens. In China, the (mBu/Cy)-based regimen is the most common, accounting for up to 59 percent of allo-HSCT cases while TBI-based regimens are used in 12% of allo-HSCT cases, with TBI + Cy accounting for two-thirds of them. (Sun *et al*., 2021).

More older patients (age 55 and above) and patients with a high risk of comorbidity (such as HCT-CI 3) can undergo allo-HSCT with acceptable NRM thanks to a reduced intensity regimen (RIC) that replaces (or partially replaces) cyclophosphamide with fludarabine (Xhang *et al*., 2021). In China, Bu/Flu-based regimens are used in 23% of allo-HSCT cases. Sun et al. reported that the 1-year NRM, DFS, and OS in 50 patients (age 55) who were conditioned with Busulphan (3.2 mg/kg/day, intravenous, i.v. for 3 days), Fludarabine (30 mg/m2/day, i.v. for 5 days), Cy (1.0 g/m2/day, i.v. for 2 days), and ATG (2.5 mg/kg/day, i.v. for 4 days) were comparable to those of matched patients who received a Bu/Cy/ATG regimen (Sun *et al*., 2021).

For individuals with refractory leukemia, an intensive conditioning regimen may help to lower the high malignancy burden and improve prognosis. Studies on patients with refractory acute leukemia who received successive enhanced conditioning and donor lymphocyte infusion after transplantation in the absence of active GVHD to prevent relapse. In the HID and MSD groups, both the 5-year OS (46

percent vs. 42 percent, p = 0.832) and DFS (43 percent vs. 39 percent, p = 0.665) were promising (Yu *et al*., 2020). MRD prognosis is improved by IDA-intensified HID-HSCT (+ vs. -, CIR 18.9% vs. 11.5 percent, OS 63.6 percent vs. 69.6 percent) (Zhang *et al*., 2017). With a 3-year OS rate of 43.8 percent and an EFS rate of 42.3 percent, sequential chemotherapy (FLAG-IDA) followed by fludarabine + busulfan administration seemed encouraging (Wang *et al*., 2019). In high-risk and very-high-risk MDS patients with MDS. Another study found that adding decitabine to the Bu/Cy/Flu conditioning regimen resulted in excellent 2-year OS (74 percent and 86 percent respectively) (Cao *et al*., 2020).

To achieve GVHD prevention, the conditioning regimen includes intensive GVHD prevention with cyclosporine (CsA), methotrexate (MTX), mycophenolate mofetil (MMF), and ATG. The optimum ATG dosage for GVHD prevention in HID-HSCT patients was validated in two randomized controlled studies. ATG-6 administration resulted with higher incidence rates of grade III-IV acute GVHD (16.1 percent vs. 4.5 percent, p = 0.005) and 5-year moderate-to-severe chronic (c) GVHD (56.3 percent vs. 30.4 percent, p 0.0001) than ATG-10 administration (Chang *et al.,* 2017). Wang et al. recently reported that ATG-6 has been linked to a high risk of GVHD. They discovered a lower rate of infection-related mortality and comparable rates of grade II-IV acute GVHD (27.1 percent vs. 25.4 percent, p = 0.548), 2-year cGVHD (34.6 percent vs. 36.2 percent, p = 0.814), 3-year OS (69.5 percent vs. 63.5 percent, p = 0.308), and DFS (62.2 percent vs. 60.3 percent, p = 0.660), implying that ATG-7.5 administration might be preferred in HID-HSCT following the Beijing Protocol (Wang *et al*., 2021; Lin *et al.,* 2019).

9. Haploidentical Stem Cell Transplantation in Hematological Malignancies: Moving Forward

HLA-haploidentical donors are being commonly used for allogeneic hematopoietic cell transplantation (AHCT) in patients who do not have an HLA-matched donor or who require an allograft quickly. Over the last decade, the field of haploidentical hematopoietic cell transplantation (HHCT) has grown rapidly (Passweg *et al*., 2017; Niederwieser, *et al*., 2016). The usage of haploidentical donors has increased by about 300 percent since 2005, according to the 2015 European Society for Blood and Marrow Transplant (EBMT) activity survey report (Passweg *et al*., 2017). Nearly all patients who require a transplant can find haploidentical donors (Fuchs, 2012). According to Johns Hopkins data, more than 95 percent of patients have at least one HLA-haploidentical first-degree relative, and the average number of haploidentical donors per patient is two or more. Furthermore, second-degree relatives with a complete haplotype match with the recipient have been successfully transplanted (Fuchs, 2012).

With multiple haploidentical donors typically available for transplantation, determining which donor will result in the best transplant outcomes is critical.

10. Enhancing outcomes of haploidentical stem cell transplantation in Haematological malignancies

Several studies have conclusively linked preformed donor-specific anti-HLA antibodies (DSAs) to the occurrence of primary graft failure in patients receiving AHCT, particularly in HLA-mismatched transplantation (Chang *et al*., 2015; Ciurea *et al.,* 2015; Yoshihara *et al.,* 2012; Ciurea *et al*., 2009). Because the recipient may be allosensitized and generate antibodies against the non-shared donor's HLA antigens during pregnancy, this issue can be more challenging in HHCT, especially in the kid donor to mother recipient context (Ciurea *et al.,* 2015). DSAs are seen in 10–21% of HHCT recipients, with female receivers having a greater rate than male recipients (Table 1) (Chang *et al.,* 2015; Ciurea *et al*., 2015; Yoshihara *et al.,* 2012; Ciurea *et al*., 2009). A research from MD Anderson Cancer Center (MDACC) looked at the outcomes of 122 patients who had TCD and TCR HHCT and found that DSAs were common (18%) and had a strong link to primary graft failure (Ciurea *et al*., 2015). Furthermore, patients with DSAs had a considerably longer time to engraftment (Ciurea *et al*., 2015). Similarly, Yoshihara and colleagues discovered that having a high level of DSAs (>5000 MFI) was the sole significant risk factor for graft failure in unmanipulated HHCT recipients (Yoshihara *et al.,* 2012). Aside from primary graft failure and delayed engraftment, the formation of DSAs has been linked to primary poor graft function (Chang *et al*., 2015), and has been shown to have a detrimental impact on post-transplant survival in both HHCT and other alternative donor transplants (Chang *et al*., 2015; Ciurea *et al*., 2015; Yoshihara *et al*., 2012; Ciurea *et al*., 2009). The capacity of DSAs to produce primary graft failure appears to be dependent on both antibody levels and complement system activation. The MDACC group found that DSAs that activate the complement system, as determined by the c1q assay, are linked to high antibody levels and a significant risk of graft rejection, highlighting the necessity of antibody detection prior to HHCT (Ciurea *et al*., 2015).

In view of these evidences, EBMT now recommends routine DSA testing before selecting haploidentical donors for transplantation, based on these findings. For a recipient with HLA antibodies, using hematopoietic stem cells from a donor without the appropriate HLA antigens is an excellent alternative. If no such donors are available, DSA patients should get desensitization treatment prior to transplantation to avoid graft failure. The latest EBMT consensus guidelines for the diagnosis and treatment of patients with DSAs in HHCT outline current techniques (Ciurea *et al.*, 2018).

Although donor age does not appear to be a limiting factor in HLA-matched AHCTs, transplanting stem cells from a younger donor is significantly linked to a reduced incidence of both acute and chronic GVHD, as well as higher survival (Bastida *et al.*, 2015; Kollman *et al.*, 2001; Eisner and August, 1995). In both TCD and TCR HHCT, the benefit of selecting a younger donor has been proven. When younger

donors were used for pediatric patients with high-risk leukemia receiving CD3/CD19 and TCRb+/CD19 TCD HHCT, González-Vicent et al. found greater immunological recovery, less acute GVHD, reduced non-relapse mortality (NRM), and higher disease-free survival (DFS) (Gonzalez-Vicent *et al*., 2017). Donor age has also been demonstrated to influence transplantation results in TCR HHCT. Wang et al. used the Beijing protocol to discover that donors younger than 30 years old had considerably lower NRM and better survival than older donors (Wang *et al*., 2014). The effect of donor age appears to be more important in older HHCT recipients than in younger ones. When patients over the age of 40 were transplanted with stem cells from an older donor, the Acute Leukemia Working Party (ALWP) of the EBMT found an increased NRM, inferior leukemia-free survival (LFS), overall survival (OS), and GVHD-free, relapse-free survival (GRFS), whereas donor age did not predict transplant outcomes in recipients younger than 40 years (Canaani *et al*., 2018). Ciurea et al. also discovered that younger donor age (>/=40 years) was an independent predictor of better OS in older patients (>/=55 years) with AML and MDS who had HHCT with PTCy for GVHD prevention (Ciurea *et al*., 2018).

Although data from two other retrospective studies of HHCT with the PTCy platform found no significant impact of donor age on transplant outcomes (McCurdy *et al*., 2018; Solomon *et al*., 2018) using a younger donor may provide additional benefits, such as better CD34+ cell yield, especially with a BM graft (Zhang *et al*., 2010), and a lower likelihood of clonal hematopoiesis, which can increase the risk of developing hematologic malignancies later in life in recipients of stem cells from older donors (Jaiswal *et al*., 2014). Younger donors are also more likely to be physically healthy, allowing them to better handle the stem cell collecting technique and ensuring that the treatment is completely safe for the donor.

Minor histocompatibility antigens (mHAgs) encoded on the Y chromosome (H-Y) have been theorized to be recognized by female donor T cells and may be responsible for an increased risk of GVHD and NRM in female donor to male recipient transplantation. However, because H-Y antigen can be expressed on tumor cells, this risk can be offset by the advantage of increased graft-versus-tumor effect and a lower chance of relapse. When minor HLAs are the principal target of donor alloreactive T cells in HLA-matched transplantation, this is especially relevant (Kongtim *et al*., 2015; Stern *et al*., 2008; Frassoni *et al*., 1996). However, with HLA-haplotype matched transplants, the negative impact of using a female donor to a male recipient appears to be more severe. Kasamon et al. discovered that TCR HHCT with PTCy for GVHD prevention with a female donor to a male recipient resulted in shorter survival. Although the detrimental impact on survival was not totally explained by a considerably increased risk of GVHD, this study nevertheless implies that, at least in an HHCT with PTCy platform, a male donor should be favored when selecting a haploidentical donor for a male recipient. Outside of the female to male transplant context, the effect of donor gender on HHCT outcomes has also been investigated. Wang et al. used the Beijing protocol of unmanipulated HHCT to show that female donor transplantation was related with a greater rate of severe acute GVHD, NRM, and lower survival. When maternal donors were removed from the analysis, however, the deleterious impact was gone (Nagler *et al.*, 2021).

Several research have looked into the effects of donor relationship on HHCT outcomes Solomon and colleagues looked at TCR HHCT with PTCy and found that a parent donor (either maternal or paternal) had a considerably higher chance of relapse and lower survival than a sibling or child donor, and that the influence of donor relationship on outcomes remained after correcting for donor age (Solomon *et al*., 2018). Furthermore, a recent study by McCurdy and colleagues found that patients who received haploidentical grafts from their parents had a considerably higher chance of graft failure, although graft failure risk was not different between sibling and offspring donors (McCurdy *et al*., 2018). These findings imply that for HHCT, an offspring or sibling donor is preferred to a parent donor (Table 2). When comparing outcomes with different parental donors, however, there were some discrepancies.

Another consideration is the use of one-haplotype match second-degree related donors, particularly younger donors, when no first-degree related donor is available if the donor is too old or young to donate. With their non-myeloablative PTCy-based procedure, the Hopkins group has shown the viability of employing second-degree related donors (Elmariah *et al*., 2018). Using their transplant platform, the Chinese group observed a similar survival rate among recipients of a collateral and immediate haploidentical family donor (Zhang *et al.*, 2014).

The impact of donor–recipient ABO compatibility on transplant outcomes has been studied in a variety of situations, with mixed results (Kanda *et al*., 2009; Goldman *et al*., 2003; Stussi *et al.*, 2002; Benjamin *et al*., 1999). A meta-analysis found that ABO mismatched transplantation had no effect on overall survival in HLA matched related donor transplants. Minor and bi-directional ABO mismatch grafts, on the other hand, were linked to poor overall survival in patients who had unrelated AHCT (Kanda *et al*., 2009).

The effect of ABO mismatch on transplant results appears to be varied, depending on whether the stem cells are obtained from peripheral blood or bone marrow. Logan et al. found that ABO minor mismatch transplantation was associated with higher NRM and negatively affected survival in patients receiving bone marrow but not peripheral blood stem cell grafts. (Logan *et al.*, 2015).

In the HHCT setting, patients who received a major ABO mismatch graft had a lower engraftment rate than those who received ABO matched HHCT. Bi-directional ABO mismatching was associated with an increased risk of grade

II–IV acute GVHD. Patients with large ABO mismatched grafts had a lower overall survival rate only when bone marrow-derived stem cell transplants were employed, but ABO compatibility had no effect in patients who received peripheral blood grafts (Canaani *et al*., 2017). These findings suggest that patients with significant ABO mismatched grafts should get PB stem cells, at least in TCR HHCT with PTCy.

A significant ABO mismatch can cause hemolytic anemia, delayed red cell engraftment, and pure red cell aplasia, in addition to having a negative impact on survival. As a result, graft management is required to reduce the proportion of incompatible RBCs and prevent hemolytic consequences in a significant ABO mismatched graft.

In conclusion, for TCR haploidentical donor transplants with PTCy, the existing evidence supports the choice of an ABO compatible graft over a minor and/or major ABO mismatched graft. When additional donors are unavailable and a major ABO incompatible donor is needed, a peripheral blood graft is preferable.

Natural killer cells are an important aspect of human innate immunity; they recover quickly after transplantation as well as provide antitumor and antiviral activities during the lymphopenia period. Lower recurrence rates and greater survival in patients with larger NK cell numbers early after transplantation suggest that NK cell alloreactivity may give a superior anticancer effect (Russo *et al.,* 2018; Savani *et al*., 2007). The cytotoxic activity of NK cells is primarily mediated by a balance of inhibitory and activating receptors expressed on the cell surface. The Perugia group proposed the KIR ligand incompatibility (ligand–ligand) model. Another study found that using this model in a clinical study of TCD HHCT helped promote engraftment and graft-versus-tumor effect (Ruggeri *et al*., 2002). Missing-self model predicts lower risk of leukemia relapse than the ligand–ligand model in a study of pediatric patients with high-risk leukemia given CD34+ chosen haploidentical graft cells. NK cells react differently if one KIR gene expressed in the donor's NK cell repertoire recognizes none of the HLA molecules in the recipient's ligand repertoire. (Leung *et al*., 2004).

Mancusi and colleagues similarly found that patients who received a KIR B haplotype donor HHCT had lower NRM than those who received a KIR A haplotype donor HHCT (Leung *et al.,* 2004). The benefit of donor–recipient NK alloreactivity in TCR HHCT remains unclear, as conflicting results have been reported. Solomon and colleagues found that KIR mismatch in a receptor-ligand model and group B KIR haplotype with KIR2DS2 were linked to lower recurrence rates and improved post-transplant survival (Solomon *et al*., 2018). Wanquet et al. found that the existence of donor-recipient KIR-ligand mismatch was related with a decreased incidence of relapse, leading to a considerably improved progression-free survival (PFS) and a trend for improved OS, but the risk of acute and chronic GVHD did not rise significantly. However, this advantage was only shown in a subset of patients with active disease, not in those who were in remission at the time of the transplant (Ciurea *et al*., 2020). The reasons for the disparities in results could be due to discrepancies in transplant techniques and inclusion criteria, as well as the model utilized to define NK cell alloreactivity. In TCD HHCT, however, a donor with alloreactive NK cells appears to be the favored option, whereas additional research is needed to resolve this issue in TCR HHCT, particularly when PTCy-based GVHD prophylaxis is used. Recent research by Russo et al. reveals that with PTCy treatment, the bulk of mature NK cells infused with unmanipulated grafts are lost, possibly blunting NK cell alloreactivity in this situation (Russo *et al*., 2018).

Although preemptive medication has reduced the frequency of symptomatic CMV infections (Marty *et al*., 2017; Chemaly *et al.,* 2014; Di Stasi *et al*., 2014), this infectious complication still occurs in a large proportion of all AHCT recipients, and it is affected in part by the CMV sero-status mismatch between donor and recipient (Matthes-Martin *et al.,* 2003). This issue may be particularly concerning in HHCT, as more patients reactivate CMV after receiving an HLA-dissimilar donor transplant, necessitating more powerful immunosuppressive to overcome the HLA barrier. When provided to a CMV positive recipient, using a CMV positive donor in AHCT has been found to avoid CMV reactivation and improve outcome (Ljungman *et al.,* 2014; Zhou *et al*., 2009). This donor–recipient combination may be especially essential when employed in the context of transplant techniques to remove T cells, such as TCD HHCT. Indeed, having anti-CMV T cells available right after transplantation could help overcome CMV viral load when T cells are sparse. To date, however, inconsistent results have been reported on the impact of donor–recipient CMV sero-status match on TCR HHCT outcomes. Solomon et al. discovered that donor CMV-negative sero-status was linked to worse survival, while a protective effect of a CMV-seropositive donor was only seen in CMV-seropositive receivers (Solomon *et al*., 2018). On the contrary, two retrospective studies by McCurdy *et al*., (2018) and Crocchiolo *et al*., (2016) found no evidence of a substantial clinical impact of donor CMV serostatus following TCR HHCT. Furthermore, a study of 983 CMV seropositive TCR HHCT with PTCy recipients from the EBMT group found that donor CMV serostatus had no effect on NRM or OS (Cesaro *et al*., 2018). It's difficult to draw conclusions and provide suggestions about TCR haploidentical donor selection based on donor–recipient CMV serostatus because of these contradictory results.

RM and survival after AHCT from both related and unrelated donors utilizing traditional GVHD prophylaxis have been linked to a higher degree of HLA mismatch between donor and recipient (Kawase *et al*., 2007; Morishima *et al*., 2002; Anasetti *et al*., 1990). However, with the novel techniques utilized for GVHD prevention in HHCT, the negative effect of donor–recipient HLA discrepancy appears to be decreased. The existence of a greater number of HLA mismatches at either the antigen or allele level did not impact overall results

in TCR HHCT employing non-myeloablative conditioning with PTCy for GVHD prevention, according to Kasamon and colleagues. Furthermore, having three or more HLA mismatches in the host-versus-graft (HVG) direction has been linked to improved EFS (Kasamon *et al*., 2010). These findings imply that a higher HLA mismatch between the donor and the recipient is not linked to poorer HHCT outcomes. Other investigations with TCR HHCT that used both PTCy and the Beijing protocol revealed similar results. The overall amount of HLA mismatches, whether bidirectional or in the GVH/HVG direction, had no effect on transplant outcomes in these studies (Huo *et al*., 2018; Raiola *et al*., 2018; Solomon *et al*., 2018; Lorentino *et al*., 2017; Wang *et al*., 2014). In other investigations, a HLA-DRB1 mismatch in the graft-versus-host direction and a HLA-DPB1 non-permissive mismatch were linked to a higher chance of survival (Solomon *et al*., 2018).

Added collectively, these findings suggest that haploidentical donors should not be chosen based on the degree of HLA mismatch. Because inconsistent results have been reported to date, further data is needed to define the impact of individual HLA antigens/alleles on HHCT outcomes.

Table 1: Summary of characteristics considered in selecting donors for haploidentical hematopoietic cell transplantation using T cell depleted cells.

Parameter	Status	GVHD	NRM	Selection Status
DSA	No DSAs (MF <1000)	NR	NR	Preferred
DSA	No DSAs (MF>5000)	NR	NR	Desensitize before transplant
Age	Younger	↓ GVHD	↓ NRM	Preferred
〃	Older	↑ GVHD	↑ NRM	Not preferred
Gender	Male	↓ GVHD	↓ NRM	Preferred
〃	Female	↑ GVHD	↑ NRM	Not preferred
HLA Typing	1º relative HLA	NR	NR	Preferred
〃	2º relative HLA	NR	NR	Not preferred
Relationship	Mother	NR	NR	Preferred
〃	Father	NR	NR	Not preferred
ABO	ABO Matched	↓ GVHD	↓ NRM	Preferred
〃	ABO Mismatched	↑ GVHD	↑ NRM	Not preferred
NK Cells	NK Alloreactivity	NR	NR	Preferred
CMV	CMV seropositive	NE	NE	Preferred

*Adopted and modified from the European Society for Blood and Marrow Transplantation (EBMT) consensus recommendations for donor selection in haploidentical hematopoietic cell transplantation (*Ciurea *et al.*, 2021).

GVHD*-Graft versus host disease,* ***NRM****- Non Relapse Mortality,* ***DSAs****- Donor specific antigen,* ***NK cells****- Natural killer cells,* ***NE****- No Effect. NR- Not reported, CMV- Cytomegalovirus.*

Table 2: Summary of characteristics considered in selecting donors for haploidentical hematopoietic cell transplantation using T cell Replete cells.

Parameter	Status	GVHD	NRM	Selection Status
DSA	No DSAs (MF <1000)	NR	NR	Preferred
〃	No DSAs (MF>5000)	NR	NR	Desensitize before transplant
Age	Younger	↓ GVHD	↓ NRM	Preferred
〃	Older	↑ GVHD	↑ NRM	Not preferred
Gender	Male	↓ GVHD	↓ NRM	Preferred
〃	Female	↑ GVHD	↑ NRM	Not preferred
HLA	1º relative HLA	NR	NR	Preferred
〃	2º relative HLA	NR	NR	Not preferred
Relatives	Sibling/offspring	NR	NR	Preferred
〃	Parents	NR	NR	Not preferred
ABO	ABO Matched	↓ GVHD	↓ NRM	Preferred
〃	ABO Mismatched	↑ GVHD	↑ NRM	Not preferred
NK Cells	NK Alloreactivity	NR	NR	Preferred
Parents	Father	NR	NR	Preferred

„	Mother	NR	NR	Not preferred

*Adopted and modified from the European Society for Blood and Marrow Transplantation (EBMT) consensus recommendations for donor selection in haploidentical hematopoietic cell transplantation (*Ciurea *et al.,* 2021).

GVHD-Graft versus host disease, NRM- Non Relapse Mortality, DSAs- Donor specific antigen, NK cells- Natural killer cells, NE- No Effect, NR- Not reported, CMV- Cytomegalovirus.

11. Current Trends in the Use of Umbilical Cord Blood Cells as Alternative Stem Cells Source for Transplantation in Hematological Malignancies

Since the first report in 1989, umbilical cord blood (UCB) stem cells have been effectively employed for hematopoietic cell transplant (HCT) (Gluckman *et al.,* 1989). Since then, over 40,000 UCB transplants have been conducted around the world for a variety of malignant and non-malignant conditions (Dessels *et al*., 2018; Ballen *et al*., 2015). Umbilical cord blood (UCB) is an established alternative source of haematopoietic stem cells (HSC) for allogeneic transplantation when suitable human leucocyte antigen (HLA)-matched sibling or well matched unrelated donors are unavailable. In hematologic malignancies, the treatment outcomes of UCB transplant are comparable to those of related or unrelated bone marrow (BM) or peripheral blood (PB) employed as graft sources (Peffault de Latour *et al*., 2013; Tomblyn *et al.,* 2009). Non-carrier-matched sibling BM and fully matched UCB have similar results in children with hereditary metabolic diseases (Mallhi *et al*., 2017; Boelens et al., 2013), and have been used in the majority of transplants in this patient population (Aldenhoven and Kurtzberg, 2015). UCB transplant results are improving in additional illnesses like primary immunodeficiency disorders, bone marrow failure syndromes, and hemoglobinopathies like sickle cell disease and thalassemia (Vander Lugt *et al*., 2020; Pagliuca *et al*., 2019; Spees *et al*., 2019; Ebens *et al*., 2018; Smith and Wagner, 2009). The creation of cord blood banks has allowed for the secure preservation and quick availability of UCB stem cells for timely transplantation for various diseases.

Cord blood banking began in 1993, and around 5 million cord blood units have been deposited worldwide since then. Over 800,000 UCB units are held in state banks, whereas over 4 million are held in private or family banks (Dessels *et al*., 2018). Under the right conditions, UCB units' biologic qualities can be securely cryopreserved for more than 20 years, with efficient recovery of functional hematopoietic stem cells (HSCs) and hematopoietic progenitor cells (HPCs) (Broxmeyer *et al.,* 2011). The existence of these UCB banks has resulted in a dramatic reduction in the median search time for unrelated donor cord blood stem cells, from 3 to 4 months for bone marrow and peripheral blood stem cells to as little as 2 weeks for UCB stem cells (National Marrow Donor Program, 2009). This is an essential characteristic to consider when selecting a donor HSC source for illnesses where timing and flexibility are critical, such as high-risk cancers and rapidly progressing hereditary metabolic disorders. Various organizations, such as the National Marrow Donor Program, NetCord, and the Foundation for the Accreditation of Cellular Therapy, have set regulatory requirements for the collecting, processing, and storage of these cord blood units in order to preserve the highest possible quality (Navarrete and Contreras, 2009).

12. Umbilical Cord Blood Donor Selection

With the increased availability of high-quality and high-cell-content UCB units, UCBT engraftment and survival outcomes have improved. However, because numerous features must be examined at the same time, unit selection is typically seen as a major hurdle to its adoption. Several prior papers (Dehn *et al*., 2019 ; Ruggeri *et al*., 2019 ; Yanada *et al*., 2019; Barker *et al*., 2017; Hough *et al*., 2016; Ruggeri *et al*., 2016), have provided country-specific selection guidelines. Acceptable quality, appropriate cell dosage, and optimal high-resolution HLA matching are the key principles for CBU selection. While not every UCB-experienced transplant center will use the same criteria, the principles are the same, with all centers emphasizing the importance of finding a unit with a high CD34 cell dose and HLA match at four of the eight HLA antigens when possible, as well as allele level typing at HLA-A, HLA-B, HLA-C, and DRB1.

13. Current Challenges Affecting Development of Umbilical Cord Blood Transplantation

Despite the fact that UCBT is immediately available and associated with a lower incidence of chronic GVHD, the main deficiency in UCB units is still a lack of total nucleated cells and CD34+ cell doses, which results in delayed hematopoietic recovery and increased rates of graft failure, increasing the risk of infection and TRM. Furthermore, notably in Europe, antithymocyte globulin (ATG) is widely given in UCB transplant recipients. T-cell depletion in vivo may lower the risk of GVHD, but it also raises the risk of graft failure and primary disease relapse (Kindwall-Keller and Ballen, 2020). Relapse is still the leading cause of death following a transplant (Zhang and Tien, 2021). Many researchers have looked at numerous approaches to improve the efficacy of UCBT in order to overcome these obstacles.

14 Current Approach for Enhancement of UCBT

14.1 In-vivo Expansion of Umbilical Cord Blood Cells

Using double UCB resulted in in vivo stem cell growth and improved engraftment (Barker *et al.,* 2005). Other methods for in vivo UCB expansion have been employed since then, including haplo-cord transplants, which use a small dosage of haploidentical stem cells for early engraftment and UCB

expansion in the appropriate cytokine environment (van Besien) *et al.,* 2020). Haplo-cord transplant combines the infusion of a lower dose of UCB unit with mobilized PB CD34+ cells from a haploidentical donor in a well-matched combination. The haploidentical donor usually achieves early engraftment and hematopoietic recovery in this situation, resulting in sustained and persistent engraftment to the UCB unit. The results of this technique, which used both myeloablative and reduced-intensity conditioning regimens, showed that infectious and immunologic problems were decreased, and that the patients had good outcomes (Hsu *et al*., 2018; Liu *et al.,* 2011). When a haploidentical donor is available, this technique can be advantageous for adults with limited matched unrelated donor and UCB availability, permitting the use of a single UCB. However, there is concern that these in vivo multiplication approaches increase the danger of graft-versus-host disease (GvHD) and protracted mixed chimerism, despite findings to the contrary (Kwon *et al*.,2014; Liu *et al*., 2011).

Another approach is the use of double unit umbilical cord blood transplantation. In Europe, the first double-unit UCBT (dUCBT) was performed in 1999. Both recipients showed symptoms of donor engraftment but died 3 months after dUCBT due to recurrence and bleeding. (Rocha *et al.,* 2010). Barker *et al*. transplanted the first two units of UCB from male baby donors into a 53-year-old, 84-kg woman with accelerated-phase chronic myelogenous leukemia (CML) in 2001, and each unit contributed to hematopoiesis for at least 60 days. UCBT from two partially HLA-matched donors as a way of increasing cell dosage, especially for adult recipients, was investigated further after this patient died of disseminated Aspergillus infection 68 days after transplantation (Barker *et al*., 2001). dUCBT has since become a treatment option for patients with insufficient units. According to Eurocord, the number of adult patients getting dUCBT has surpassed the number of adults receiving single-unit UCBT since 2005. (sUCBT) (Sideri *et al*., 2011). Only one unit can usually remain for a long period following dUCBT, implying that the two units may react negatively to one other, reducing transplant efficacy. Wagner et al. conducted an open-label, phase 3, multicenter, randomized experiment to see if the graft composition (double-unit versus single-unit) had an influence on 1-year survival among patients who underwent the same conditioning and GVHD prevention regimen. When compared to individuals who received a suitable amount of sUCBT, the results demonstrated that recipients of dUCBT had no advantage in terms of engraftment or survival. Furthermore, after dUCBT, there was a lower rate of platelet recovery and a higher prevalence of grade III to IV acute and substantial chronic GVHD (Wagner *et al*., 2014). In another study, it was discovered that dUCBT had a greater rate of substantial chronic GVHD than sUCBT. The relapse rate was lower in the dUCBT group than in the sUCBT group in MRD-positive patients who had not received ATG throughout their conditioning regimen, resulting in a higher 3-year OS (Michel *et al*., 2016).

In a retrospective study, 79 patients with hematological malignancies who got UCBT in a single transplant institution between November 2005 and December 2013 were investigated. Patients who received dUCBT had a lower rate of myeloid and platelet engraftment, a greater TRM, and a shorter OS, DFS, and GRFS than those who received sUCBT with an appropriate cell dosage. (Zheng *et al*., 2018).

14.2 Ex-vivo expansion of umbilical cord blood cells

Several researchers have looked into using recombinant hematopoietic cytokines, growth factors, stromal cells, and several small compounds to expand functional UCB cells (HSCs and HPCs) in vitro. Irrespective of the technique, there is a robust increase in CD34+ stem cells and their progenitors, leading to much faster neutrophil recovery and myeloid engraftment after infusion as compared to historical controls (Horwitz *et al*., 2019; Stiff *et al*., 2018; Wagner *et al*., 2016; Horwitz *et al*., 2014; Delaney *et al*., 2010; de Lima *et al*., 2008). UCB primitive hematopoietic cells were originally expanded with recombinant hematopoietic cytokines, which proved favorable for self-renewal. (Cicuttini *et al*., 1994; Mayani *et al*., 1993). Various growth factors, including FLT3 ligand, stem cell factor, erythropoietin, and thrombopoietin, were thoroughly evaluated based on the positive effect of cytokines on the ex vivo expansion of UCB. When UCB cells grown with these growth factors were injected into patients, the quantity of HPCs increased dramatically, but there were no favorable effects in myeloid, erythroid, or platelet engraftment. (Jaroscak *et al*., 2003; Shpall *et al*., 2002). As an ex vivo expansion technique, co-culture with mesenchymal stem cells (MSCs) to give the required components for HSC expansion was investigated (de Lima *et al.,* 2012). It started with a 7-day co-culture with MSCs, followed by cytokine culture. This study included 31 adults who had dUCBT, one with an extended cord and the other without. In the expanded unit, there was a 30-fold increase in CD34+ cell dose.

More studies on different small molecules such as diethylaminobenzaldehyde (DEAB), copper chelator (StemEx), Notch ligand, StemRegenin 1 (SR1), nicotinamide, and UM171, have been reported as agonists for experimental ex vivo expansion of human HSCs and HPCs (Fares *et al*., 2014; Peled *et al.,* 2012; Figueroa *et al.,* 2011; Boitano *et al*., 2010; Chute *et al.,* 2006; Peled *et al*., 2004).

In a clinical context for stem cell transplantation, Delaney et al. administered ex vivo expansion CB in the presence of Notch ligand Delta 1, and the time to neutrophil recovery was reduced to 16 days (Delaney *et al*., 2010). The Nicord product, which was first employed in the dUCBT scenario with the expansion of a single CB unit before infusion, demonstrated 13-day neutrophil engraftment and 1-year OS and PFS rates of 82% and 73%, respectively (Horwitz *et al.,* 2014). Then, in a phase I/II clinical trial using sUCBT expanded ex vivo in the presence of nicotinamide, the median neutrophil recovery time was reduced to 11.5 days and the median platelet recovery time

was reduced to 34 days (Horwitz *et al.*, 2019). A recent phase I/II clinical trial of single UM171-expanded cord blood transplantation found that it was practical, safe, and allowed for the use of small single cords without impairing engraftment (Cohen *et al*., 2020). Although these ex vivo expansion results are promising, there is still much work to be done in this field given to the small sample size, and other mechanisms of HSC amplification need to be researched.

CONCLUSION

Despite alternative therapies, hematopoietic stem cell transplantation has remain indicated as treatment option in many hematological malignancies. Many advances have been made in improving the success of HSCT particularly in the selection of suitable hematopoietic stem cell donors, choice of graft sources, optimizing conditioning. The use of umbilical cord blood cells has shown a promising role as an alternative source of HSCT even with other available sources such as bone marrow and peripheral blood. In addition, haplo-HSCT has shown a promising result and better outcomes due to the number of advantages, including a wide range of stem cell sources, increased GVL effects, improved immunologic reconstitution, and positive clinical outcomes. In the near future, haplo-HSCT is likely to be considered as a better option for patient donor selection particularly in AML patients while HLA matching is unlikely to be the most important factor in AML patient donor selection. Other transplantation procedures, such as T-cell depletion allografts, Post-transplant cyclophosphamide (PTCY), G-CSF-mobilized allografts, and antithymocyte globulin, have contributed to significant improvements in haplo-HSCT outcomes in recent decades.

FUTURE DIRECTION

Many challenges remain, particularly in minimizing disease relapse and the severity of GVHD. More advances must be made in harnessing problems related to post-HSCT relapse, conditioning regimen related toxicities, chronic GVHD prevention and improving graft versus tumor effects. Further research is needed to gain additional knowledge on how to enhance the ability of donor immune cells to eradicate malignant cells without significantly increasing GVHD. This will be possible with the development of novel adoptive immune cell and targeted therapies. This will make allogeneic HCT even more relevant treatment option. For some patients with relapsed/refractory ALL and other severe or poor-prognosis malignancies, the introduction of CAR-T cells could be a true revolution and hence should be well researched. The EBMT, along with other societies and professional groups, is working to develop a roadmap for implementing CAR-T programs that addresses potential limitations, ensures accurate assessment and prediction of efficacy, manages toxicities for safe early delivery and long-term monitoring, and engages key stakeholders in the process.

ABBREVIATIONS

ATG- Anti Thymocyte Globulin
HSCT- Hematopoitic Stem Cell Transplantation
UCB- Umbilical Cord Blood
HID- Haploidentical Donor
DEAB- diethylaminobenzaldehyde
MDACC-MD Anderson Cancer Center
EBMTS- European Blood and Marrow Transplantation Society
ERIC -European Research Initiative in CLL
EBMTR- European Bone Marrow Transplant Registry
PI- Pathway inhibitor
NMDP-The National Marrow Donor Program
WMDA-The World Marrow Donor Association
KIRs- killer-cell immunoglobulin-like receptors
PTCy- Post transplantation cyclophosphamide
TBI- Total Body Irradiation
TKIs- Tyrosine kinase inhibitors
JAK- Janus kinase
CIBMTR- Center for International Bone Marrow Transplant Research.
CAR-T- Chimeric Antigen Receptor- T cells
OS- Overall Survival

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