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Abbreviations

AML	Acute myeloid leukemia
ATG	Anti-thymocyte globulin
BM	Bone marrow
CNI	Calcineurin inhibitors
CSA	Cyclosporine A
DFS	Disease-free survival
EBMT	European Group for Blood and Marrow Transplantation
FK	Tacrolimus
G-PB	G-CSF mobilized PB
GvHD	Graft versus host disease
HL	Hodgkin lymphoma
HLA	Human leukocyte antigen

HCT	Hemopoietic cell transplantation
MMF	Mycophenolate
MTX	Methotrexate
PB	Peripheral blood
PTCy	Post-transplant cyclophosphamide
TCD	T-cell depletion
Treg	Regulatory T cells
TRM	Transplant-related mortality

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65.1 Ex Vivo TCD Platforms

The physical removal of donor T cells from the graft has been pioneered on adult patients by the group of Perugia in the late 1990s (Aversa et al. 1998). The original concept was to prevent GvHD by infusing a high-dose CD34-enriched graft with a T cell content $<1 \times 10^4/\text{kg}$ of recipient body weight.

65.1.1 Positive CD34 Selection

The first generation of ex vivo graft manipulation by antibody-based immunomagnetic methodology has been the positive selection of CD34+ cells using the CliniMACS® System. Using G-CSF $\pm$ Plerixafor mobilized PBSC, CD34+ selected grafts provide a megadose of stem cells ($>10^{10}/\text{Kg}$) along with a negligible dose of T cells. (Aversa et al. 1998; Ciceri et al. 2008; Reisner et al. 2011). To ensure engraftment, the

infusion of such a graft required the combination of fully myeloablative and immunoablative conditioning regimens including ATG, TBI, fludarabine, and thiotepa.

Despite the application of such intensive immunoablative regimens, 10–15% of transplanted patients required a second HCT due to primary graft failure or rejection. While this approach was very effective to prevent GvHD, patients given these low dose T cell grafts, and especially when receiving serotherapy as part of conditioning, were typically characterized by substantially delayed immune reconstitution resulting in high incidence of life-threatening opportunistic infections and leukemia relapse (Reisner et al. 2011; Perruccio et al. 2005; Ciceri et al. 2008). Therefore, adoptive cellular therapies were developed to enhance T cell immune reconstitution without concomitant risk for GvHD (Perruccio et al. 2005; Di Ianni et al. 2011; Ciceri et al. 2009). Donor T cells genetically modified to express HSV-thymidine kinase suicide gene (Zalmoxis®) have been registered by the European Medicines Agency as adjunctive therapeutic tool post haploidentical HCT. In the pediatric population, virus-specific T cells have shown promise (Leen et al. 2009; Feucht et al. 2015).

65.1.2 CD3/CD19 Negative Selection

To overcome some of the shortcomings of the CD34+ selection method, a second generation of ex vivo graft manipulation was developed using CD3/CD19 depletion by the same CliniMACS system. This approach keeps stem and progenitor cells untouched while retaining immune effector cells, in the cellular product (Bethge et al. 2006; Federmann et al. 2011, 2012). Compared to CD34+ positive selection, the CD3/CD19 depletion approach seems associated with more favorable CD4 T cell reconstitution, while the difference for other immune and clinical outcome parameters is less evident (Salzmann-Manrique et al. 2018).

65.1.3 TCR α/β and CD19 Depletion

To more selectively remove the GvHD causing T cells from the graft, CD3 depletion was replaced by depletion of TCR α/β expressing T cells with the aim to reduce the risk for GvHD while maintaining the potentially beneficial anti-leukemic and anti-pathogen gamma-delta T cells and NK cells in the graft (Li Pira et al. 2016). In the last decade, this method has been proven to be associated with positive outcomes in pediatric and adult patients with malignant as well as non-malignant diseases, including low rates of TRM, low rates of relapse, fast neutrophil and platelet recovery, and improved chronic GvHD-free/relapse-free survival, compared to unmanipulated mismatched unrelated HCT. These results indicate that the TCR α/β depletion approach can be considered an effective and safe option for patients who require a stem cell transplant but lack a fully matched donor (Bertaina et al. 2014; Locatelli et al. 2013; Lum et al. 2022; Merli et al. 2022; Tsilifis et al. 2022). Despite these advances, delayed reconstitution of TCR α/β T cells remains an issue and is associated with a high rate of viral reactivations (~50%) in the first 2–3 months. To overcome this window of immune deficiency, several adoptive GvHD-sparing cellular therapy approaches have been and are being explored in clinical trials including virus-specific T cells, suicide gene-modified DLI, T cell progenitors, and memory T cell infusions (Sect. 65.1.5).

65.1.4 Co-Infusion of Regulatory T Cells

The Perugia group as well as others recently implemented a new variation of ex vivo TCD, which includes the co-infusion of regulatory T cells, followed by mature T cells (Pierini et al. 2021): preferential migration of regulatory T cells to the lymph nodes, but not the bone marrow, prevents GvHD (in the lymph nodes) and allows, at the same time, a strong graft versus

leukemia (in the bone marrow). The result is an extremely low incidence of leukemia relapse (Pierini et al. 2021).

65.1.5 CD45RA+ Depletion

Mouse models have demonstrated the capacity of naïve T cells (CD45RA+) to cause severe GvHD, whereas memory T cells (CD45RA-RO+) induced mild or no GvHD (Anderson et al. 2003). In the last decade, few groups have implemented the use of CD45RA+ depletion targeting naïve T cells to reduce the risk of GvHD in mismatched HCST (Triplett et al. 2018; Gasior Kabat et al. 2021; Maschan et al. 2017).

65.2 Unmanipulated Haploidentical HCT

The number of unmanipulated HLA haploidentical transplants has been rapidly increasing over the past 15 years (Passweg et al. 2012), due to the successful prevention of two major problems: lethal GvHD and graft rejection. There are currently three main platforms to perform unmanipulated haplo-HCT:

ATG based → together with CSA, MMF, and MTX (Lu et al. 2006),

PTCy based → together with FK/CSA, MMF (Luznik et al. 2008), and

ATG + PTCy → together with other in vivo immunosuppressants (DeZern et al. 2017; Duléry et al. 2018)

65.2.1 Anti-Thymocyte Globulin (ATG) Based

Following the pioneering work of Dao Pei Lu (Lu et al. 2006), the ATG-based prophylaxis has been shown to allow significant engraftment and control of GvHD, in recipients of haplo-HCT, such that the outcome is comparable with recipients of HLA-matched grafts (Wang et al. 2013).

The Beijing protocol consists of a myeloablative conditioning regimen (ARA-C, BU 4 days and CY 2 days), together with rabbit ATG 2.5 mg/kg/day (Fig. 65.1). GvHD prophylaxis is based on 4 drugs (ATG, CSA, MTX, MMF) (Fig. 65.1). The stem cell source is a combination of G-CSF (G)-mobilized bone marrow (G-BM) and G-mobilized PB. A modification of the Beijing protocol has used unmanipulated G-BM alone (Ji et al. 2005) and included intensive GvHD prophylaxis with ATG, CSA, MTX, and MMF with the addition of basiliximab, an anti-CD25 antibody. The same GvHD prophylaxis has been reported by an Italian consortium (Di Bartolomeo et al. 2010), with a different conditioning regimen (thiotepa, busulfan, fludarabine) (TBF), originally described by Sanz and coworkers for cord blood transplants (Sanz et al. 2012).

65.2.2 Post-transplant Cyclophosphamide (PT-Cy) Based

The use of PT-Cy on day +3 and +4 after an unmanipulated haplo-HCT has been pioneered by the Baltimore group (Fig. 65.2). It is based on the combination of FLU Cy and low dose TBI (2 Gy), followed by unmanipulated haplo BM; GvHD prophylaxis consists of high-dose CY on day +3 +4 (50 mg/kg) combined with a CNI and MMF (Fig. 65.2).

It is based on the idea that high-dose Cy (50 mg/kg) will kill alloreactive T cells proliferating on day +3 and +4 after the transplant, whereas stem cells would be protected because they are not proliferating and with a high concentration of aldehyde dehydrogenase. In 2008, the Baltimore group published their first clinical study and showed that PT-Cy was able to protect patients from GvHD after haplo-HCT (Luznik et al. 2008). not only GvHD could be prevented, but GvL seemed superior, at least in patients with HL.

There have been numerous variations of the Baltimore protocol, with use of G-PB instead of BM (Bashey et al. 2017), rapamycin, instead of a CNI (Cieri et al. 2015), the use of a MAC regi-

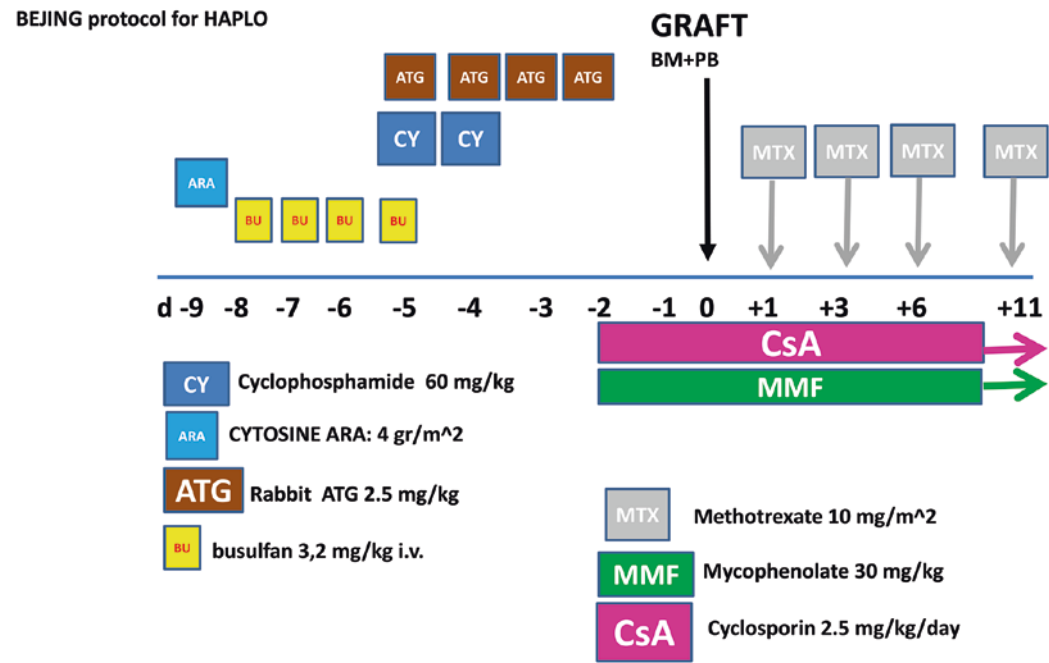


Fig. 65.1 The Beijing protocol, first published in 2006 (Lu et al. 2006), used for patients with hematologic malignancies

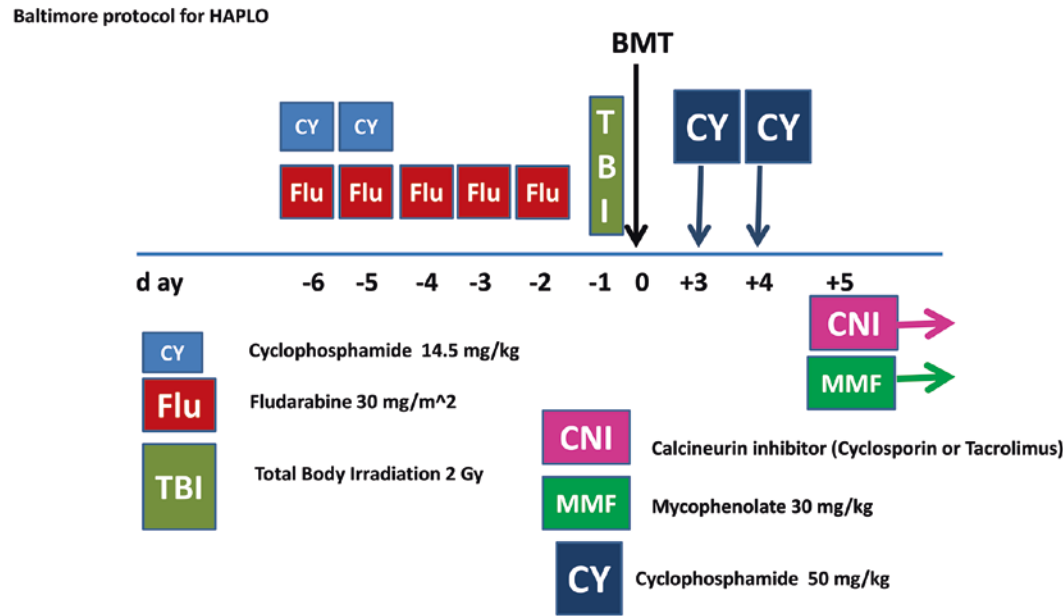


Fig. 65.2 The Baltimore protocol with high-dose Cy post-transplant on days +3 +4

men instead of the NMA regimen of Baltimore (Raiola et al. 2013; Bashey et al. 2017), suggesting a certain degree of flexibility of PTCy-based

platforms. Engraftment is achieved in over 95% of patients, and there is good control of acute and chronic GvHD.

PTCy dose and timing. There are several open questions: the first is whether the dose of 50 mg/kg $\times$ 2 can be modified. The question is relevant since cardiac toxicity of PTCy 50 mg/kg $\times$ 2 has been reported (Duléry et al. 2021), with clinical consequences such as atrial fibrillation, heart failure, and death. A reduced dose of 40 mg/kg $\times$ 2 (Sugita et al. 2021) as well as 25 mg/kg $\times$ 2 (McAdams et al. 2021) has been reported as effective. It would be clearly very important to assess the minimal effective dose of PTCy, in order to reduce cardiac toxicity, accelerate neutrophil recovery, and maintain protection against GvHD. Another open question is the timing of PTCy. The Baltimore protocol calls for PTCy on days +3 +4 with CNI and MMF starting *after* PTCy (Fig. 65.2). One center has introduced a different timing with PT-Cy on days +3 and +5, together with CSA and MMF starting *before* PT-Cy (Raiola et al. 2013); the feasibility and effectiveness of this timing have been confirmed (Chiusolo et al. 2018). The EBMT has compared the two different options for PTCy: day +3 +4 vs. day +3 +5, in patients with AML (Ruggeri et al. 2020): patients receiving PTCy day +3 +5, had reduced incidence of relapse and improved

DFS. It should be said that this regimen is safe when using BM as a stem cell source, with acute GvHD III–IV rates of 3%; however, it is not known what the outcome would be with PB as a stem cell source, since CSA will protect some T cells from PT-Cy purging, and these may produce a beneficial GvL effect but also cause detrimental GvHD.

65.2.3 ATG + PT-Cy

Some centers are combining the two basic platforms (PT-Cy and ATG), and early results seem promising. The Baltimore group is using this combination for patients with aplastic anemia, in the attempt of avoiding GvHD completely (DeZern et al. 2017, 2020) (Fig. 65.3). The difference here is adding ATG before the conditioning regimen on days -9-8-7, and combining with PTCy, CNI, and MM (4 drug GvHD prophylaxis). Also, the group in Saint-Antoine, Paris, is using a combination of ATG 2.5 mg/kg and PT-Cy, CSA, and MMF for patients with acute leukemia undergoing a MAC haplo-HCT (Duléry et al. 2018).

De Zern Protocol for HAPLO in SAA

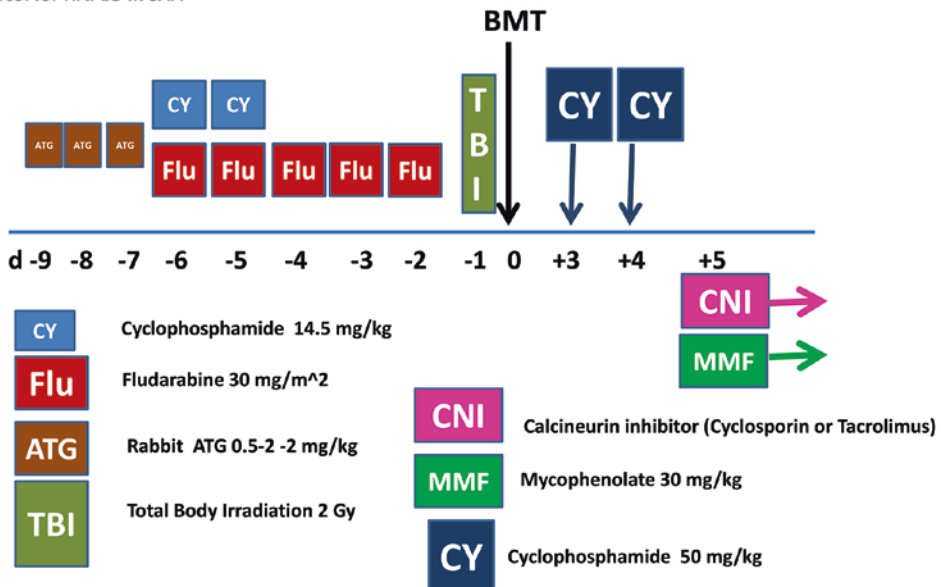


Fig. 65.3 4 drug GvHD prophylaxis (ATG, PTCy, CNI and MMF) for haplo transplants in SAA (De Zern et al 2020). TBI has recently been increased to 4 Gy

65.3 Other Relevant Aspects of Haplo-HCT

65.3.1 Choice of the Best Haploidentical Donor

The EBMT ALWP has established younger donor age and kinship, as a major determinant of outcome for leukemia patients grafted from haploidentical donor (Canaani et al. 2018). The Beijing group has confirmed younger age to be relevant, using their ATG-based platform together with a mismatch for non-inherited maternal antigen (NIMA) (Wang et al. 2014). One report has suggested that NK alloreactivity, together with HLA-DP disparity might identify an optimal haplo donor (Solomon et al. 2018). Other reports have denied an effect of increasing HLA disparity on major outcomes (Wang et al. 2014). There is currently no solid data to choose a haploidentical donor based on HLA disparities.

65.3.2 Comparison of ATG-Based Versus PT-Cy-Based Platforms

The EBMT Acute Leukemia Working Party has compared these two platforms (Ruggeri et al. 2017). In a Cox analysis, ATG-based haplo grafts had a higher risk of failure, in terms of LFS (RR 1.48, $p = 0.03$), GvHD relapse-free survival (RR 1.45, $p = 0.03$), and OS (HR 1.43, $p = 0.06$): there was for all end points a very strong center effect ($p < 0.001$), suggesting that a learning curve is required for optimal results in haplo-HCT.

65.3.3 Bone Marrow or Peripheral Blood

There are two large registry-based studies comparing BM versus PB for unmanipulated haplo-HCT: the EBMT study (Ruggeri et al. 2018) shows increased GvHD II–IV and III–IV with PB, same chronic GvHD, same relapse, and same 2-year OS (55% and 56%). The CIBMTR shows increased GvHD II–IV, but not III–IV with PB grafts, increased chronic GvHD, and reduced

relapse (Bashey et al. 2017): survival at 2 years also in this study is quite similar, 54% vs. 57%. So, it seems that one can use both stem cell sources, with some difference in the short term (more GvHD with PB) and perhaps some differences in the long term (cGvHD and relapse): at the end survival seems comparable.

Key Points

- Following the pioneering work of the Perugia group, HLA-haplotype mismatch family transplants using ex vivo T cell depletion is evolving, with the use of T cell subpopulations and the use of Treg Tcon.
- Unmanipulated haplo-HCT is rapidly increasing in numbers, worldwide, due to the introduction of post-transplant cyclophosphamide (PTCy).
- There are two platforms for unmanipulated haplo-HCT: ATG based or PTCy based.
- ATG can be combined with PTCy, CSA, and MMF, to further reduce GvHD: this is being tested especially in non-malignant disorders.
- One important question is how haplo-HCT compare with unrelated donor grafts, and to answer this question, randomized trials have been designed and are about to start.
- One should consider that HLA-haplotype mismatch transplants remain an alternative donor procedure and should be regarded as such complications, including blood stream infections, invasive fungal disease, viral infections, GvHD, and toxicity may occur with significant frequency and expose the patients to the risk of TRM. For this reason, HLA-haplotype mismatch grafts, whether TCD or unmanipulated, should be performed in centers with expertise in MUD or CB HCT and should follow clinical protocols.

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