



Haploidentical HSCT

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65.1 Introduction

Haploidentical hematopoietic stem cell transplantation (haplo-HSCT) is now considered a clinical therapeutic option in patients candidate to allo-HSCT. Primary prevention and treatment of GvHD have been a major challenge in this peculiar major HLA-mismatched setting. Two main platforms have been developed: ex vivo TCD and unmanipulated graft transplantation. Overall, the primary objective of a stable haploidentical hematopoietic engraftment at a low GvHD rate resulted feasible in both platforms in

a significant proportion of patients undergoing haplo-HSCT for any clinical indication.

The great interest in transplantation from haploidentical donors arises from the immediate availability of a suitable one-haplotype mismatched donor for virtually all patients in the appropriate timing. In the absence of a HLA full-matched donor, alternative family haploidentical donors have been intensively investigated in the past decade.

Primary prevention and treatment of GvHD have been a major challenge in this peculiar HLA-mismatched setting of HSCT. Two main clinical platforms have been developed: ex vivo TCD and more recently unmanipulated graft transplantation.

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65.2 Ex Vivo TCD Platforms

The physical removal of donor T-cells from the graft has been pioneered by the group of Perugia in the late 1990s (Aversa et al. 1998). The original concept was to prevent GvHD through a graft with a T-cell content not exceeding a total T-cell graft dose of 1×10^4 /kg of recipient body weight.

65.2.1 Positive CD34 Selection

The most experienced ex vivo manipulation has been the positive selection of CD34+ cells realized by CliniMACS® CD34 System Miltenyi,

providing a TCD graft with high cell dose of CD34+ cells starting from G-CSF-mobilized PBSC graft of family haploidentical donors (Aversa et al. 1998; Ciceri et al. 2008; Reisner et al. 2011). This profound TCD graft required the development of conditioning regimens aimed at a maximal host IS through the use of ATG, full-dose TBI, and the combination of intensive IS, FLU, and TT.

Despite the application of intensive immunoblastic regimens, the rate of graft rejection has been 10–15% requiring a salvage subsequent second HSCT providing an overall engraftment rate >95%. According to the primary objective, ex vivo TCD by CD34+ selection allows a stable engraftment with a GvHD rate <10% in the absence of any additional post transplant IST.

Unfortunately, this intense graft TCD translated into a slow post transplant immune recovery with a prolonged and profound T-cell lymphopenia (Reisner et al. 2011; Perruccio et al. 2005). In this clinical platform, TRM have been observed in a significant proportion of recipients (Ciceri et al. 2008). Leading causes of deaths reported were opportunistic infections occurring even as late as 1-year post transplant in the absence of GvHD and any IST. The improvement of post transplant immune reconstitution while controlling GvHD prompted the concurrent development of several additional strategies of cell therapy (Perruccio et al. 2005; Di Ianni et al. 2011; Ciceri et al. 2009). Particularly in the pediatric population, virus-specific T-cells have been a promising tool (Leen 2009; Feucht 2015). Donor T-cells genetically modified to express HSV-thymidine kinase suicide gene (Zalmoxis®) have been recently registered by the European Medicines Agency as adjunctive therapeutic tool post haploidentical HSCT.

65.2.2 CD3/CD19 Negative Selection

A partial T-cell depletion less profound than CD34+ selection can be provided by alternative selections, such as CD3/CD19 negative selection. The CliniMACS CD3/CD19 Product Line was developed for the simultaneous depletion of

unwanted T- and B-cells in combination with the CliniMACS System. This approach keeps stem and progenitor cells untouched and leaves immune effector cells, such as NK cells and dendritic cells, in the cellular product (Bethge et al. 2006; Federmann et al. 2011; Federmann et al. 2012). Starting from G-CSF-mobilized PBSC in adults, grafts contained a median of 7.0×10^6 CD34+ cells/kg, 4.2×10^4 CD3+ T-cells/kg, and 2.7×10^7 CD56+ cells/kg; incidence of grade II–IV acute GVHD and chronic GVHD was 46% and 18%, respectively, requiring the post transplant use of a CNI as additional GvHD prophylaxis in adult patients.

65.2.3 TCR α/β and CD19 Depletion

More recently, Miltenyi developed CliniMACS TCR α/β and CD19-depleted stem cell grafts from haploidentical donors for HSCT in children and adults. The ex vivo protocol has been designed to selectively remove donor T-cells with TCR α/β that are recognized to mediate GvHD. Preliminary clinical experience in children showed a very low rate of skin GvHD and no visceral acute or chronic GVHD (Bertaina et al. 2014; Li Pira et al. 2016).

Overall, ex vivo TCD is a platform clinically useful to provide hematopoietic engraftment with low GvHD in haploidentical setting. Furthermore, the different cell population selection in the graft provides a unique clinical setting to dissect the biology of different immune cells as NK, TCR α/β , and TCR γ/δ T-cells in the clinical post transplant immune reconstitution and antitumor and immune protective in vivo effects (Ruggeri et al. 2002; Aversa et al. 2005; Locatelli et al. 2013).

65.2.4 Regulatory T-Cells

The Perugia group has recently presented a variation of ex vivo TCD, with the addition of regulatory T-cells, followed by mature T-cells (Martelli et al. 2014): preferential migration of regulatory T-cells to the lymph nodes, but not the bone mar-

row, 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 (Martelli et al. 2014).

65.3 Unmanipulated Haploidentical HSCT

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-HSCT (Fig. 65.1).

65.3.1 Anti-thymocyte Globulin (ATG) Based

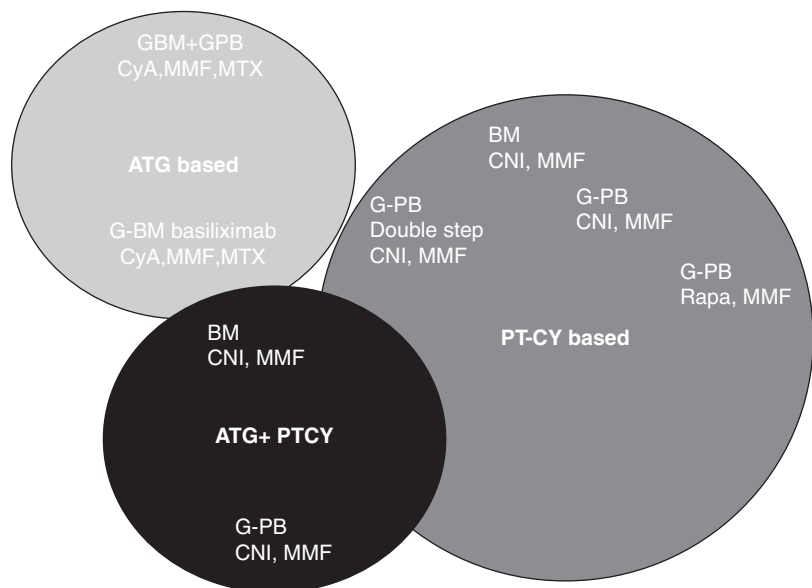
In 2006 the Chinese group led by Dao-Pei Lu compared the outcome of 158 leukemia patients grafted from HLA-identical siblings with 135 leukemia patients grafted from HLA-haplotype mismatch family members, after a MAC regimen (Lu et al. 2006; Fig. 65.1: ATG-based; GBM + GPB +

CSA + MMF + MTX). The results were surprising, with the OS and DFS identical for both groups. The conditioning therapy consisted of Ara-C (4 g/m²/day, on days -10 to -9), BU (4 mg/kg/day, orally on days -8 to -6 before January 2008 and 3.2 mg/kg/day, IV on days -8 to -6 after January 2008), CY (1.8 g/m²/day, on days -5 to -4), 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (Me-CCNU) (250 mg/m², once on day -3), and ATG (2.5 mg/kg/day, rabbit; Sanofi Genzyme, France, days -5 to -2).

All patients received CSA, MTX, and MMF; the HLA-mismatch group received in addition ATG (Lu et al. 2006). The graft source was a combination of G-CSF (G)-mobilized bone marrow (G-BM) and G-mobilized PB. The cohort in HLA-haplotype mismatch group had a higher risk of acute GvHD ($P = 0.02$) and of TRM ($P = 0.05$), but OS was comparable ($P = 0.6$). This was the first report on a large number of family mismatched grafts, showing survival identical to sibling HLA-matched grafts, and this led to the emergence of other programs.

Another group of Chinese investigators developed an ATG-based program with unmanipulated G-BM alone (Ji et al. 2005; Fig. 65.1, G-BM + CSA + MMF + MTX + basiliximab). They included intensive GvHD prophylaxis with ATG,

Fig. 65.1 Different modalities of haplo-HSCT. See text for details abbreviations: *ATG* anti-thymocyte globulin, *GBM* G-CSF-mobilized bone marrow, *MTX* methotrexate, *PT-CY* post transplant cyclophosphamide, *CNI* calcineurin inhibitor, *MMF* mycophenolate, *Rapa* rapamycin



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): acute GvHD grade II–IV and III–IV was, respectively, 24% and 5%, which is extremely low for family HLA-haplotype mismatch, T-cell-replete transplants. The TRM was not negligible, being 30% for “standard” and 45% for “high-risk” patients (Di Bartolomeo et al. 2010). Overall 3-year survival was 54% for standard and 33% for high-risk patients. Di Bartolomeo et al. used for most patients a conditioning regimen combining TT, IV BU, and FLU (TBF), originally described by Sanz and coworkers for cord blood transplants (Sanz et al. 2012).

65.3.2 Post transplant Cyclophosphamide (PT-CY) Based

The use of PT-CY on day +3 and +4 after an unmanipulated haplo-HSCT has been pioneered by the Baltimore group. 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 2001, the Baltimore group published their first clinical study and showed that PT-CY was able to protect patients from GvHD after haplo-

HSCT (Luznik et al. 2001). Again, this was not picked up immediately, not until 2008 when a joint Baltimore Seattle study showed that haplo-HSCT in Hodgkin’s lymphoma (HL) produces DFS superior to sibling or unrelated transplants (Chiusolo et al. 2018): 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 (Fig. 65.1) with use of G-PB instead of BM, rapamycin, and MMF, instead of a CNI (Figs. 65.2 and 65.3), the use of a MAC regimen instead of the NMA regimen of Baltimore.

All these platforms seem to achieve a high rate of engraftment, but severe acute GvHD can vary from as low as 3% to as high as 30%. A modified PT-CY regimen has recently been reported in patients with AML (Chiusolo et al. 2018): in this multicenter retrospective study on 150 patients, CSA was administered on day 0, MMF on day +1, and PT-CY on days +3 and +5 (Fig. 65.1). The MA regimen consisted mainly of TBF: the rate of leukemia relapse was extremely low in remission patients (Chiusolo et al. 2018). The major difference here lies in the CSA given before PT-CY and in the two doses of PT-CY spaced on days +3 and +5. It should be noted 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

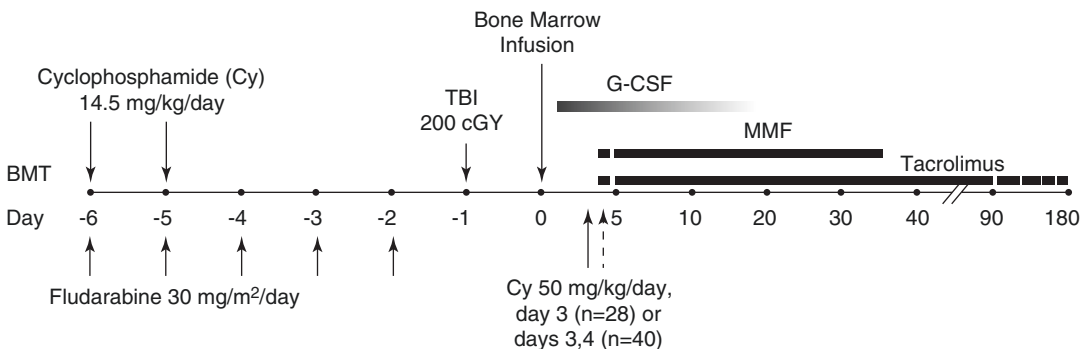
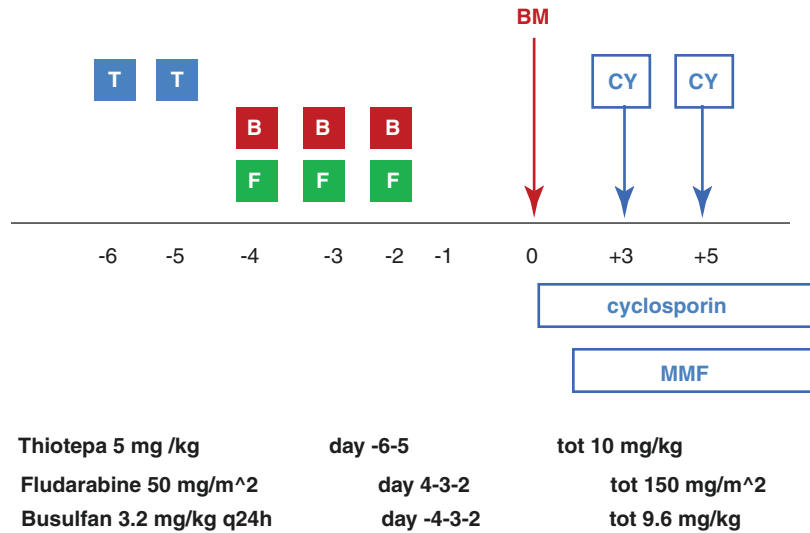


Fig. 65.2 The original Baltimore protocol consisting of CY 14.5 mg/kg \times 2, fludarabine 30 mg/m² \times 5, and total body irradiation (TBI) 2 Gy day -1. CY 50 mg/kg days

+3 and +4 and CSA, MMF starting day +5. GCSF starts on day +6. From Luznik et al. (2001)

Fig. 65.3 Modified PT-CY regimen. Thiotepe (T), busulfan (B), and fludarabine (F) followed by unmanipulated haploidentical BM. Cyclosporin on day 0, mycophenolate on day +1, and CY 50 mg/kg on days +3 and +5

Raiola et al *BBMT* 2013; 19:117
Chiusolo et al *BBMT* 2018



T-cells from PT-CY purging, and these may produce a beneficial GvL effect but also cause detrimental GvHD.

65.3.3 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 sickle cell disease, in the attempt of avoiding GvHD completely. 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-HSCT (Duléry 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).

The age, CMV status, and ABO matching are general rules which should always be considered: a CMV+ patient should be grafted with a CMV+ donor, if available, and a CMV- patient with a CMV- donor.

Table 65.1 summarizes the most relevant general and immunologic criteria for donor selection in haplo-HSCT.

65.4 Other Relevant Aspects of Haplo-HSCT

65.4.1 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).

Table 65.1 Criteria for donor selection

(a) Immunologic criteria (only in malignancies)	
1.	Presence of NK alloreactivity (KIR/KIR-L mismatch in GvH direction)
2.	Larger size of NK alloreactive subset
3.	KIR haplotype
4.	Higher B content value in B haplotype donors
5.	Presence of educated KIR2DS1 in case of C2+ patient
6.	Higher % NK cells and T lymphocytes
(b) General criteria	
7.	Donor/recipient HCMV serology
8.	Donor age
9.	Donor sex
10.	Donor/recipient body weight

65.4.1.1 Natural Killer (NK)

Natural killer (NK) cells are the first post-HSCT cellular population, reconstituting antiviral and antitumor activity. In this setting, donor NK cell inhibitory receptors mismatched for cognate HLA class I ligands play a key role in the graft-versus-leukemia (GVL) effect. Remarkably, these cells may be uniquely poised to enhance GVL without eliciting GvHD because healthy non-hematopoietic tissues lack activating receptor ligands present on tumor cells.

Over 20 years ago, Moretta et al. 1995 described the concept of NK cells' alloreactivity, showing that defined NK cell subsets were able to kill in vitro allogeneic lymphoblasts. (Ruggeri et al. 2016) first reported the positive impact of KIR ligand-mismatched donor NK cell alloreactivity after TCD haplo-HSCT resulting in a lower risk of relapse and a better OS in adult with AML. Of note, only patients receiving a transplant from a donor who showed NK cell alloreactivity against recipient cells displayed an efficient GVL effect. This happens, for example, in the presence of a KIR-HLA-I (KIR-L) mismatch in the donor-versus-recipient direction. Thus, in donor/patient pairs with KIR-HLA-I mismatch, the event-free survival (EFS) rate was 60%, while in the absence of such mismatch, it was less than 5%.

However, the contribution of NK cell alloreactivity on HSCT outcome is still controversial due to different evaluation criteria, the nature of KIR/KIR ligand genetic combinations studied, and NK cell repertoire size. Given the central role of NK cell alloreactivity in preventing leukemia relapse, in the setting of haplo-HSCT, it is crucial to determine in different potential donors if alloreactive NK cells are present and the size of such alloreactive populations. More recently, in addition to the flow analysis of the alloreactive NK cell populations, other selection criteria have been added (Table 65.1). Among these, the presence of a KIR B haplotype has been shown to be associated with a relevant improvement of the survival in both adult AML and pediatric ALL.

While the antileukemic activity of NK cells and the role of KIR are well known and established by several groups, their impact in preventing graft

failure and/or infections in patients affected by nonmalignant disorders remains unclear.

65.4.2 Comparison of ATG-Based Versus PT-CY-Based Platforms

The EBMT Acute Leukemia Working Party has compared these two platforms in a recent study (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-HSCT.

65.4.3 Bone Marrow or Peripheral Blood

There are now two studies comparing BM versus PB for unmanipulated haplo-HSCT: 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%.

Key Points

- Following the pioneering work of the Perugia group, HLA-haplotype mismatch family transplants are rapidly increasing in numbers, due to improved platforms in both TCD, as well as unmanipulated grafts, with encouraging results in most centers.
- This is true with different stem cell sources, different conditioning regimens, and different GvHD prophylaxes:

in one word, there is more than one way to perform haplo-HSCT.

- One important question is how haplo-HSCT 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 HSCT and should follow clinical protocols.

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.

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