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REVIEW ARTICLE

Haploidentical stem cell transplantation for patients with lymphoma: a position statement from the Lymphoma Working Party-European Society for Blood and Marrow Transplantation

Sascha Dietrich[1] · Peter Dreger[1] · Olivier Hermine[2] · Chara Kyriakou[3] · Silvia Montoto[4] · Steve Robinson[5] · Norbert Schmitz[6] · Harry C Schouten[7] · Anna Sureda[8] · Alina Tanase[9]

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Abstract

Allogeneic stem cell transplantation (alloSCT) continues to be the only potentially curative treatment for patients with refractory lymphomas or relapsing after autologous stem cell transplantation. Until recently, alloSCT was restricted to patients who had a matched donor, sibling or unrelated. In the past years, substantial progress in haploidentical transplantation (haploSCT) has resulted in a significant increase in the number of patients treated with this procedure, worldwide. Given the fact that an HLA haplo-identical donor can be found within the immediate family for almost any patient, virtually every patient can receive an haploSCT. Another reason to use haploSCT, especially in diseases like lymphomas where the decision to perform an alloSCT is being taken sometimes late in the course of the disease, is the considerable delay to find a matched unrelated donor (MUD), when an HLA-identical sibling (MSD) is not available. In this paper, we summarize available evidence supporting the use of haploSCT in lymphoma patients and share current recommendations of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation (EBMT) on how to integrate haploSCT in this population.

Introduction

The mainstay of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) treatment is still chemotherapy (in combination with anti-CD20 antibody in B-cell lymphomas). Although chemo-(immuno)-therapy has a curative potential for a significant proportion of patients with HL or aggressive NHL, the percentage of chemo-refractory patients increases with each relapse and line of treatment. Allogeneic stem cell transplantation (alloSCT) is a valuable treatment option with curative potential for patients with relapsed or refractory NHL [1–7] and HL [8–12].

The potential of alloSCT to cure patients even with chemorefractory lymphoma is based on the powerful immune-mediated mechanism termed graft vs. lymphoma (GvL) effect. Unfortunately, the curative potential of alloSCT is counterbalanced by graft vs. host disease (GVHD), the main cause of non-relapse mortality (NRM). Thus, in daily practice alloSCT is generally reserved for patients relapsing after autologous stem cell transplant (ASCT) [13, 14].

Historically, alloSCT was restricted to young patients with an HLA-identical sibling donor, but the decreasing

✉ Alina Tanase
alina.tanase@icfundeni.ro

1 Department Medicine V, University of Heidelberg, Heidelberg, Germany
2 Department of Hematology, Necker University Hospital, Paris, France
3 Department of Haematology, University College London Hospital and London North West University Heathcare NHS Trust, London, UK
4 Department of Haemato-oncology, St Bartholomew's hospital, Barts Health NHS Trust, London, UK
5 BMT Unit, University Hospital Bristol NHS Foundation Trust, Bristol, UK
6 Department of Hematology, Oncology, and Stem Cell Transplantation, Asklepios Hospital St Georg, Hamburg, Germany
7 University Hospital Maastricht, Maastricht, The Netherlands
8 Hematology Department, Institut Català d'Oncologia–Hospitalet, Barcelona, Spain
9 Fundeni Clinical Institute, Bucharest, Romania

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availability of sibling donors in small families reduces the likelihood to find a matched identical sibling donor (MSD). HLA-matched unrelated donors (MUD) represent a very important alternative to sibling donors. The development of international stem cell donor registries, with currently more than 26 million potential unrelated donors, has enormously improved donor availability. Through such registries, more than 90% of patients of Caucasian origin will find a suitable donor, but depending on the ethnic background, 10–50% of patients in need of an alloSCT cannot find an HLA-matched donor, or an unrelated donor search cannot be awaited due to fast progression of the disease. These patients may be considered for an alloSCT using donors mismatched at one or two HLA alleles, but each additional mismatch decreases survival by ~10% [15, 16]. Therefore, alternative stem cell sources such as umbilical cord blood or HLA-haploidentical blood or marrow emerged to fill the void for patients lacking HLA-matched donors. Potential haploidentical donors include patients' biological parents or children, and each sibling or half-sibling of a patient has a 50% chance of being HLA-haplo-identical to the patient. Thus, almost every patient will have an HLA haploidentical donor within the immediate family. Evolution of the haploSCT procedure using post-transplant cyclophosphamide (PT-Cy) in order to avoid tedious in vitro manipulation of the graft and at the same time lowering toxicity and decreasing complications has resulted in a significant increase in the use of this donor type [17]. Another advantage of haploSCT is the shorter time necessary to identify a suitable donor in comparison with a MUD search. This is potentially more relevant in diseases like some types of lymphoma, in which the indication to perform an alloSCT is being made sometimes late in the course of the disease.

The panel members of the Lymphoma Working Party (LWP) of the European Society for Blood and Marrow Transplantation (EBMT) reviewed the literature available and critically assessed the reported efficacy of haploSCT in patients with lymphoma. In this paper we discuss the results of haploSCT in lymphoma, focusing on HL, high-grade B-cell lymphoma (HG-NHL), follicular lymphoma (FL) and mantle cell lymphoma (MCL) providing a position statement of the LWP-EBMT.

Development of haploSCT

HaploSCT was introduced into the clinical setting in the mid-1990s, and was considered an experimental treatment for patients who lacked an HLA-identical donor. Bidirectional alloreactivity of T-cells from the host and the donor leading to a high incidence of both graft failure and GVHD prohibited crossing the HLA barrier when an HLA-identical donor was not available [18–20]. Transplantation of "mega doses" of CD34+ enriched stem cells from peripheral blood (PB) after myeloablative conditioning and prevention of GVHD by T-cell depletion of the stem cell product was investigated to overcome the problem [21]. Significant regimen-related toxicities, delayed immune reconstitution and a high incidence of opportunistic infections were serious consequences of this approach. The group from Perugia observed that patients with acute myeloid leukemia receiving a haploSCT with a killer-cell immunoglobulin-like receptors (KIR)-ligand mismatch of natural killer (NK) cells had a lower risk of relapse without an increased risk of GVHD [22], but whether this is also the case in lymphomas has to be explored. A Chinese group led by Xiao Jun Huang developed a strategy for ex-vivo graft manipulation, which builds on haploidentical blood and/or bone marrow (BM) primed with granulocyte-colony stimulating factor (G-CSF) and on intensified immunological suppression with anti-human thymocyte immunoglobulin This strategy, using the 'GIAC' protocol, shows acceptable NRM and a favourable disease-free survival following T-cell repleted haploSCT with BM, but was associated with high rates of GVHD. It has to be mentioned that no data on this strategy in patients with lymphoma is available thus far [23]. The Johns Hopkins group established an alternative strategy, based on the observation that cyclophosphamide administration after stem cell transplant preferentially targets alloreactive T-cells, while sparing stem cells and the peripheral memory T-cells [24]. Luznik et al. developed a clinical protocol which involves high-dose PT-Cy to prevent graft rejection and GVHD after non-myeloablative conditioning and T-cell replete BM transplantation from partially HLA-mismatched (haploidentical) related donors [25]. This strategy has quickly been adopted by many centers in the Western world because PT-Cy after haploSCT avoids ex-vivo graft manipulation and can be easily and safely performed by most transplant centers. The discussion on whether to use BM or peripheral blood stem cells (PBSC) is still open. Most haploSCT studies have used BM, but in recent years PBSC are increasingly used. A large CIBMTR study [26] compared transplant outcomes after haploSCT in patients with hematologic malignancies according to the source of stem cells (BM or PBSC). There were no significant differences in OS, but the risk of grade II-IV acute and chronic GVHD were significant lower with BM in comparison with PBSC. In contrast, in a joint collaborative program at two European transplant centers [27] haploSCT with PT-Cy using PBSC grafts resulted in a low incidence of GVHD with promising disease control, making PBSC a valuable alternative to BM graft. Although initially described using BM as the preferred graft source, the use of PBSC has grown and now exceeds BM, at least in Europe [28].

Following these developments, the number of haploSCT performed in Europe for lymphoid malignancies continues to grow (Fig. 1).

HaploSCT for Hodgkin lymphoma

In recent years, multiple studies have been published supporting the efficacy of haploSCT in patients with advanced HL. Most of these studies suggest that the outcomes of patients with HL after haploSCT and after conventional alloSCT are, at least, comparable. The results after haploSCT can be influenced by disease status and high comorbidity index before transplant, as in all types of transplant; Marani et al. [29] showed, in a study on 41 patients with relapsed/refractory HL undergoing haploSCT with PT-Cy, that pre-transplant FDG-PET with a Deauville score ≥4 and HCT-CI ≥3 identified patients at high risk of relapse.

An important multicenter retrospective analysis pointing in this direction was published by Burroughs et al. [30], who compared the outcomes of non-myeloablative (NMA) alloSCT with MSD, MUD, and haploSCT for relapsed/refractory HL (r/r HL). Haploidentical donor transplants appeared to have significantly better progression-free survival (PFS) than MSD and MUD transplants. The 2-year PFS was 51% (haploSCT), 23% (MSD), and 29 % (MUD), respectively. NRM was also significantly lower for HLA-haploidentical compared to HLA-matched related recipients. The incidences of grade III–IV acute GVHD and extensive chronic GVHD (cGVHD) were 11 and 35% for haploSCT, 16 and 50% for MSD and 8 and 63% for MUD. This study (using only BM grafts) suggests that outcomes after haploSCT are better than after MSD / MUD transplants.

More recently, and following the introduction of PT-Cy as GVHD prophylaxis, a number of studies, most of them including a relatively small number of patients (26–98), have been published (Table 1). NRM at 1 year is around 20%. The cumulative incidence (CI) of relapse at 2 years ranges from 24 to 40%. Grade II–IV acute GVHD (aGVHD) at 100 days is 23–43% and 2-year cGVHD, 4–35%. Two-year PFS is around 50% with a 2-year OS 58–67%. Some of the studies identified prognostic factors, some of them associated with disease or patients characteristics (such as advanced disease and high comorbidity index having a poor impact on OS) [31] and some related to the procedure (PB is associated with a better OS and PFS and a lower CI of relapse) [32].

The Center for International Blood and Marrow Transplant Research (CIBMTR) performed two separate retrospective analyses of haploSCT for patients with lymphoma including HL and NHL. The first one, published by Kanate

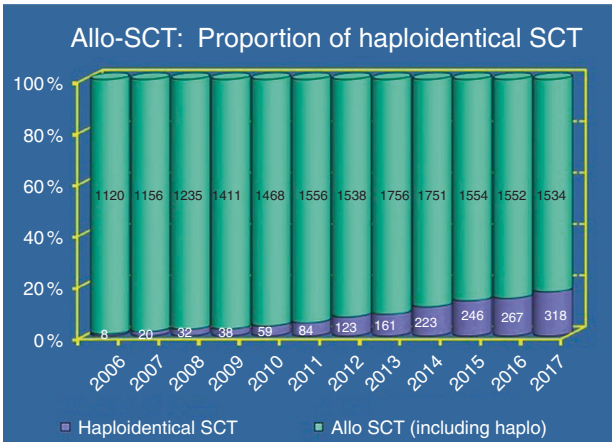

Fig. 1 HaploSCT performed in Europe for lymphoid malignancies

et al. [33], analyzed RIC transplantation for lymphomas using haploidentical related donors vs. MUD (split into two separate groups: with or without ATG). The graft source was predominant BM for haplo (93%) and PB for MUD (93–94%). Of 185 patients with lymphoma who received a haploSCT, 46 patients had r/r HL; for these patients, PFS at 3 years was 45%, compared with 45% for MUD without ATG and significantly better than for MUD with ATG at 34%. However, this study showed a clear difference in the risk of grade III–IV aGVHD and cGVHD between the haploidentical transplants and MUD transplants without ATG, with a significantly lower incidence of severe aGVHD and cGVHD with haploidentical donors compared with MUD (aGVHD: 8 vs. 17%; and cGVHD: 13 vs. 51%). Relapse risk and NRM were similar after haploSCT and MUD transplants [33].

The second study from the CIBMTR, published by Ghosh et al. [34], compared the outcome of patients with lymphoma undergoing haploSCT using PT-Cy-based GVHD prophylaxis with that of patients undergoing a MSD transplant. Of 180 lymphoma patients who received a haploSCT, 44 had HL. Considering all types of lymphomas, there were no statistically significant differences in 3-year NRM (15 vs. 13%), 2-year CI of relapse (37 vs. 40%), 3-year PFS (48 vs. 48%) or 2-year OS (61 vs. 62%), suggesting very similar outcomes between haploSCT and MSD cohorts. The 100-day CI of grade II–IV aGVHD was similar between the two groups, but the 1-year CI of cGVHD was significantly lower after haploSCT (12 vs. 45%) [34].

The EBMT performed one of the largest retrospective registry-based analysis comparing the results of alloSCT for HL using MSD (338), MUD (273), or haploSCT with PT-Cy (98) [35]. There were no significant differences in OS or PFS between haploSCT and MSD or MUD transplants. Two-year OS and PFS were 67 and 43% for haploSCT, 71 and 38% for MSD, and 62 and 45% for MUD, respectively. Although survival was comparable among all three types of

Table 1 Haplo SCT in Hodgkin Disease using PTCy

	Pts (*n*)	Conditioning	Type of graft BM/PBSC%	Disease status SD/PD %	Prior AutoSCT %	CI II–IV aGVHD	CI III–IV aGVHD	CI cGVHD	PFS	GRFS	OS	CI Relapse	NRM%
Burroughs 2008 [26]	28	NMA	100	43	89	43 100 d	11 100 d	35 2y	2y/51	NA	2y/58	2y/40	2y/9
Kanate 2016 [30]	185 (HL 46)	NMA	93/7	5	72	27 100 d	8 100d	13 1y	3y/47	NA	3y/60	3y/36	3y/17
Ghosh 2016 [31]	180 (HL 44)	NMA/RIC	93/7	6	38	27 100 d	8 100 d	15 1y	3y/48	NA	3y/61	3y/37	3y/15
Gayoso 2016 [28]	43	RIC	28/72	NA	79	39 100 d	14 100 d	19 2y	2y/48	NA	2y/58	2y/24	1y/21
Gauthier 2017 [29]	34	NMA/RIC	50/50	11	77	28 100d	3 100 d	15 2y	3y/66	3y/52	3y/75	3y/25	3y/9
Martinez 2017 [32]	98	RIC/NMA	61/39	15	77	33	9	26 1y	2y/43	NA	2y/67	2y/39	1y/17
Castagna 2017 [27]	62	NMA/RIC	63/37	13	40	23 100 d	4 100 d	16 167 d	3y/59	NA	3y/63	3y/21	1y/20
Mariotti 2017 [43]	26	NMA/RIC	-	59	tandem	23 1y	0	4 2y	3y/55		2y/61	3y/28	1y/16.6.
Mariotti 2018 [33]	30	NMA/RIC/MA	-	73	100	23 1 year	13 1 year	3 2y	3y/60	3y/47	3y/56	3y/13	1y/26

*NMA*nonmyeloablative conditioning regimen, *RIC*reduced intensity conditioning, *SD*stable disease, *PD*progressive disease, *Auto SCT*autologous stem cell transplant, *aGVHD*acute graft vs. host disease, *cGVHD*chronic graft vs. host disease, *PFS*progresion free survival, *GRFS*GvHD-free relapse-free survival, *OS*overall survival, *NRM*non-relapse mortality

alloSCT, cGVHD was less common in the haploSCT group than in the MUD group. Extensive GVHD and relapse-free survival (GRFS) was significantly better for haploSCT (40%) compared with MSD (28%) and similar to MUD (38%) [35]. In multivariable analysis, relative to MSD, NRM was similar after haploSCT and higher after MUD, and the CI of relapse was lower in both haploSCT and MUD. Disease status at transplantation and chemorefractory disease appeared to be the most important prognostic factors in these patients.

Gauthier et al. [36] reported a study on behalf of the French Society of Bone Marrow Transplantation and Cellular Therapy analyzing the results of 98 patients with HL who underwent a RIC or NMA alloSCT from an alternative HLA mismatched donor at 24 French and Belgian centers. Transplants from the three different donor types (haploSCT, mismatched unrelated donors and cord blood graft) had similar results regarding OS, PFS, relapse, and NRM. However, a lower CI of cGVHD and grade III-IV aGVHD were observed in the haploSCT group, resulting in a significantly higher GRFS at 3 years. Disease status at transplant was the only independent risk factor that correlated with a lower OS ($p < 0.001$).

Mariotti J et al. performed a retrospective study on 64 patients with HL relapsing after ASCT in order to compare the outcome after MSD or haploSCT with PT-Cy [37]. Results for haploSCT appeared to be significantly advantageous relative to MSD transplant, in particular with a reduced 3-year CI of relapse (13 vs. 62%), reduced incidence of cGVHD (3 vs. 32%) and improved GRFS (47 vs. 17%).

These studies suggest that haploSCT with PT-Cy is an effective treatment option for r/r HL. The majority of these retrospective analyses showed no significant differences in NRM, CI of relapse, PFS or OS between haploSCT and HLA matched transplants. In addition, there is a suggestion of a significantly lower risk of cGVHD which can in turn result in a better GRFS.

- The outcomes following haploSCT with PT-Cy for r/r HL seem to be comparable to those reported for MSD or MUD. In the absence of an MSD or 10/10 MUD donor, a haploSCT is the preferred alternative donor source.
- There is not enough evidence to recommend a haploSCT over a MSD or 10/10 MUD. The only circumstance in which it might be appropriate to use a haploSCT rather than starting a MUD search is if there is an urgency to find a donor.
- Prospective studies must clarify if haploidentical donor transplants should be preferred to other types of donors.
- There is no clear evidence of the superiority of one source of stem cells (BM or PBSC) over the other. Ideally, prospective studies should clarify this issue.

HaploSCT for Non-Hodgkin lymphoma

Whereas data on haplo-HSCT using PT-Cy across a variety of standard indications, such as acute leukemia and HL is accumulating, information on the efficacy of this approach in NHL is still limited. This is partly due to the advent of CAR-T cells therapy, which is focusing the attention of researchers; however, alloSCT remains an adequate treatment option in patients with HG-NHL. Patients with relapsed HG-NHL should be ideally enrolled in controlled trials comparing alloSCT with CAR-T-cells, to evaluate long-term results, if available.

The results obtained with PT-Cy-based haploSCT in patients with advanced NHL have been reported in two small single center studies (Table 2) [38, 39]. Zoellner et al. showed, in a small group of patients, that sequential therapy combining clofarabine and T-cell-replete haploSCT is feasible and effective and provides an acceptable toxicity profile in high-risk non-remission NHL [39].

The EBMT-Lymphoma Working Party reported that patients with lymphoma (including FL, DLBCL, MCL, and PTCL) who received PT-Cy-based haploSCT had outcomes comparable to those of MSD and MUD transplants; outcome after haploSCT seemed superior to cord blood transplants and to haploSCT using immunosuppressive strategies other than PT-Cy [40]. This study reported a 1-year OS and PFS after PT-Cy haploSCT of 68 and 52%, respectively. In addition, it provided a transplant-specific risk factor analysis, which identified previous autoSCT and advanced age as significant variables associated with an inferior prognosis after haploSCT. Importantly no difference between BM stem cells and PB stem cells as the graft source was observed on OS and PFS.

These promising results were confirmed by a registry analysis of the CIBMTR, comparing the outcome of 185 patients with lymphoma who had undergone a haplo-SCT with that of 732 patients who had a MUD transplant [33]. Of 185 patients with lymphomas, 139 had NHL (FL, DLBCL, MCL, PTCL). In that study, haplo-SCT turned out to be comparable for all survival and disease-specific end points, but was again associated with a lower risk of cGVHD. The CIBMTR published a study comparing haploSCT vs. MSD in patients with lymphoma, includin 134 NHL, but the results were presented for the whole series of 180 patients with no details on histological subtypes (results discussed in the HL section) [34].

In a large retrospective study, Dreger et al. [41] compared long-term outcomes of haploSCT using PTCy with those of MSD and MUD with or without T-cell depletion in 1428 patients with relapsed diffuse large B-cell lymphoma (DLBCL), from the EBMT and CIBMTR databases. Three-year OS, PFS, NRM, and relapse/progression incidence after haploSCT was not significantly different from

Table 2 HaploSCT in NonHodgkin Lymphomas using PT-Cy

	Pts (*n*)	Conditioning	Type of Graft BM/PBSC%	Disease Status SD/PD %	Prior AutoSCT %	II-IV aGVHD	III-IV aGVHD	cGVHD	PFS	OS	Relapse	NRM
Zoellner 2014 [39]	16	RIC	87,5/12.5	75	50	37%	6%	25%	2y/50	2y/69	36%	1y/19
Garciaz2015 [38]	26	NMA	50/50	0	61	34	15	15	2y/65	2y/77	19%	15%
Ghosh 2016 [34]	180 (NHL136)	NMA/RIC	93/7	6	38	27 100 d	8 100 d	15 1y	3y/48	3y/61	3y/37	3y/15
Kanate 2016 [33]	185 (139 NHL)	NMA	93/7	5	72	27 100 d	8 100 d	13 1y	3y/47	3y/60	3y/36	3y/17
Dietrich 2016 [40]	59	22% MAC 78% RIC	NA	39%	54%	NA	11%	19%	2y/50	2y/56	2y/27	2y/23

outcomes of matched donor transplants, but PTCy-based haplo-HCT resulted in a lower risk of cGVHD compared with matched donors.

A crucial problem faced in all transplantation settings is relapse of the original disease. This is particularly relevant for patients with aggressive lymphomas, where a large proportion of patients receive a transplant with active disease [6, 42].

- The available, retrospective data on the use of haploSCT in NHL data suggests, similar to HL data, that PT-Cy might help to establish haploSCT as a safe and effective alternative to standard MSD and 10/0 MUD transplants in patients with advanced NHL.

Evidence of disease control: donor lymphocyte infusions following haploSCT for patients with lymphoma

Although alloSCT is a procedure with curative intent to treat hematologic malignancies, disease recurrence remains a concern, in particular for patients with relapsed/refractory lymphoma. As with alloSCT in general, therapeutic strategies may be needed after haploSCT to prevent or treat disease progression [43]. In such situation, donor lymphocytes infusions (DLI) can be an option trying to enhance the GVL effect. DLI is an established therapeutic option for relapsed disease after MSD or MUD blood or marrow transplantation, but it is associated with significant risk of GVHD [44]. Due to the expected higher incidence of GVHD in the presence of HLA mismatches, few series have reported on DLI following haploSCT so far [45].

The Baltimore group [46] published the results of DLI in 40 patients who relapsed after haploSCT with PT-Cy. Eleven patients had lymphomas (six NHL and five HL). The median time from relapse to first DLI administration was 56 days. The first DLI dose was 1×10^5 CD3+ cells/kg with subsequent escalation. No GVHD prophylaxis was administered after DLI. Out of the 40 patients who received DLI, 10 developed aGVHD (25%), eight patients had grade II–IV aGVHD (20%), and 6 had grade III–IV aGVHD (15%). Grade II–IV aGVHD occurred after DLI doses higher than of 1×10^6 CD3+/kg. Twelve (30%) patients achieved a CR with a median response duration of 12 months.

Another study reported by Ghiso et al. [47] investigated DLI in 42 patients relapsing after unmanipulated BM haploSCT with PT-Cy. DLI were given at escalating doses from 1×10^3, without GVHD prophylaxis. Of 42 patients, 10 had relapsed HL, grafted with a NMA regimen and received DLI following 1–4 courses of chemotherapy, with a median interval between chemotherapy and DLI of 9 days (range 5–21). The CI of aGVHD II–IV in the HL group was 10%, at a median interval of 17 days (range, 7–47) following DLI, with a response rate of 70% with 40% PET negative CR. The median duration of response was 9 months with a 2-year actuarial OS of 80% [47].

Cauchois et al. [48] reported 36 patients (17% with lymphomas) who received prophylactic DLI after haploSCT, with 34% cumulative incidence of requiring-systemic steroids GVHD and 14% cumulative incidence of relapse at 1 year after pDLI.

Recommendations and conclusion—a position statement from the Lymphoma Working Party-European Society for Blood and Marrow Transplantation

1. Based on current data, haploSCT is a valid and safe option for patients with NHL or HL lacking an HLA 10/10 matched donor.
2. There is not yet evidence to prefer haploSCT over a MSD or 10/10 MUD. The only circumstance in which it might be appropriate to use haploSCT rather than starting a MUD search is if there is an urgency to find a donor or in cases of ethnic minorities.
3. PT-Cy haploSCT demonstrates outcomes comparable to MSD and MUD, with a lower incidence of cGVHD.
4. Although BM is more frequently used as the graft source in most studies, haploSCT with either BM or PB as the stem cell sources can be safely performed.
5. HaploSCT followed by PT-Cy represent the most used platform worldwide and can be safely and effectively performed in patients with lymphoma.
6. There is insufficient data to support either a RIC or a MAC strategy for haploSCT in patients with lymphoma. Conditioning regimens should be adapted to disease status and recipient fitness.

Critical areas to investigate in prospective studies:

- if haploSCT should be preferred to other types of donors as first line
- if PB graft have the same results as BM graft in haploSCT
- if RIC/NMC represent a better option as conditioning before haploSCT
- if haploSCT have better results in selected type of lymphoma

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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