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Stem cell transplantation - Section 17

Unmanipulated haploidentical transplantation for adult patients with hematological malignancies

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Take home messages

- The number of patients transplanted using Haplo-HSCT is increasing consistently in Europe and United States.
- Haplo-HSCT with the use of PTCy for GVHD prophylaxis, allows low incidence of grade III to IV acute GVHD, chronic GVHD, and comparable survival with HLA-matched unrelated and cord blood transplantation.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) represents a curative treatment for different hematological disease. HSCT from a human leukocyte antigen (HLA)-matched sibling donor (MSD) is the standard of care for treating those patients, however only 25% to 30% of the patients in need have a MSD available. Even with the use of large unrelated donor registries, 25% of Caucasian patients are unable to find an HLA matched unrelated donor (MUD), and this percentage increases to 50% to 85% for individuals of other ethnicities.[*1]

Historically, the use of mismatched related donor was limited by the high level of HLA disparities, rendering this strategy such an alternative, using a "megadose of CD34+ selected graft" after ex-vivo T-cells depletion, to avoid severe graft versus host disease (GVHD). However, this approach was associated with high risk of graft failure, relapse and delayed immune recostitution.[2]

More recently, the use of novel strategies without ex-vivo T-cell depletion made the use of unmanipulated haploidentical transplants (haplo-HSCT) feasible, allowing a continuous increase in its use in different countries.[*3]

Current state of the art

Haplo HSCT are attractive because do not require any graft manipulation, and allow important reduction of costs, making the procedure affordable for the majority of transplant centers. In addition, family donors are easily available and highly motivated, the procedure may be organized fast, avoiding delay. There are several platforms of haplo-HSCT available, and among them, two main approaches were developed in the last decades with different platform of GVHD-prophylaxis, based either on anti-thymocyte globulin (ATG)[4] or on post-transplant cyclophosphamide (PT-Cy).[5] Details on the recent studies available are showed in Table 1.

ATG allows extensive in vivo T-cell depletion and induces tolerance with expansion of regulatory T-cells. ATG effectively reduce GVHD incidence after both MSD and MUD HSCT.[6] The Beijing group[4] firstly reported the efficacy of the "GIAC protocol" in haplo-HSCT, using intensified immunosuppression through ATG, cyclosporine (CSA), mycophenolate-mofetil (MMF), short-course methotrexate, and monoclonal antibodies. On the other hand, Luznik et al[5] introduced the use of high dose PT-Cy for GVHD prophylaxis in the combination with reduced-intensity conditioning regimen (RIC) and bone marrow (BM) as stem-cell source. In the absence of prospective trials comparing the different platforms of haplo-HSCT, most of the data come from single centers or registries reports.

The PT-Cy is more frequently associated with calcineurin inhibitors and MMF, however some authors reported the efficacy of the PT-Cy in combination with rapamycin to enhance regulatory T-cells,[7] showing low rates of acute GVHD and NRM, and favorable immune reconstitution profile.

Despite the low incidence of acute and chronic GVHD and the low NRM also for older patients reported with RIC PT-Cy, disease recurrence is rather high, partially due to the high risk disease in most of the transplanted patients.[8]

The broad HLA disparities in the haplo setting was a limitation to the use of peripheral blood stem cell (PBSC). With the intent to

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Table 1
Results of haploidentical HSCT with PTCy in hematological malignancies

Author, Journal	n	Disease (%)	CR (%)	FU,y	Conditioning	Graft Type	Median Age,y	Engraft-ment	aGVHD Gr II–IV	aGVHD Gr III–IV	cGVHD	Relapse	NRM	PFS	OS
Martelli et al. Blood 2014	43	AML 77% ALL23%	CR1 58%	3.8	MAC	TCD PBSC	40	95%	15%	NA	2.4%	4.9%	40%	1.5y 56%	NA
Ciceri et al. Blood 2008	173	AML 65%	CR1 29%	3.9	MAC	TCD PBSC	37	91%	100 d5%	NA	2 y10%	2 y16%	2 y66%	2 y48%	NA
	93	ALL 35%	39%	2.4	MAC	TCD PBSC	21	91%	100 d18%	NA	2 y 19%	2 y26%	2 y44%	2 y13%	NA
Di Bartolomeo et al. Blood 2013	80	AML 56%	56%	1.5	MAC 80%	BM	37	93%	100 d24%	5%	2 y 17%	1 y 21%	1 y 36%	3 y 44%	3 y 54%
Ciurea et al. Blood 2015	NM 88	AML 100%	82%	3.3	NM PTCy	BM 88%	>51	93%	3 m 19%	3 m 2%	3 y 34%	3 y 58%	3 y 9%	N/A	3 y 46%
	MAC 104	AML 100%	68%	2.5	MAC PTCy	BM 82%	21–50	90%	3 m 16%	3 m 7%	3 y 30%	3 y 44%	3 y 14%	N/A	3 y 45%
Mc Curdy et al. Blood 2015	372	AL 31% MDS/MPN 9%	84%	4.1	NM PTCy	BM	55	92%	3 m 32%	3 m 4%	2 y 13%	3 y 46%	3 m 8%	3 y 40%	3 y 50%
Kasamon et al. JCO 2015	271	AML 24%, MDS 13%, ALL 3%	84%	4	NM PTCy	BM	61	94%	6 m 33%	6 m 3%	1 y 10%	3 y 52%	6 m 8%	3 y 37%	3 y 46%
Gaballa et al. Cancer 2016	60	AML/MDS 67%, ALL 12%	67%	2	NM PTCy	BM	45	97%	100 d 28%	100 d 3%	2 y 24%	2 y 24%	2 y 23%	2 y 53%	2 y 55%
Santoro et al. JHO 2017	208	ALL 100%	CR1 44%	2.5	NM 34%	BM 57%	32	92%	100 d 31%	100 d 11%	3 y 29%	3 y 37%	3y 32%	3 y 31%	3 y 33%
Bashey et al. JCO 2017	BM 481	AML 39%,ALL14%	63%	2.9	NM 82%	BM	58	91%	6 m 25%	6 m 7%	2y 20%	2y 45%	2y 17%	2y 41%	2y 54%
	PB 190	AML 56%,ALL15%	57%	1.6	NM 42%	PBSC	47	88%	6 m 42%	6 m 10%	2y 41%	2y 28%	2y 16%	2y 54%	2y 57%
Ruggeri et al. Cancer 2018	BM 260	AML 75%	CR1 67%	1.8	MAC 61%	BM	46	92%	100 d 22%	100 d 4%	2y 36%	2y 27%	2y 23%	2y 49%	2y 55%
	PB 191	AML 71%	CR1 69%	1.5	MAC 49%	PBSC	44	95%	100 d 38%	100 d 14%	2y 32%	2y 22%	2y 23%	2y 54%	2y 56%
Santoro et al. Cancer 2019	MAC 373	AML 100%	CR 1 48%	2.5	MAC	BM 54%	55	91%	100 d 25%	100 d 8%	100 d 27%	2 y 25%	2 y 31%	2 y 44%	2 y 48%
	NM 539	AML 100%	CR 1 47%	2.1	NM	BM 41%	61	92%	100 d 32%	100 d 10%	100 d 27%	2 y 29%	2 y 30%	2 y 41%	2 y 44%

aGVHD, acute graft vs host disease; AL, acute leukaemia; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BM, bone marrow; cGVHD, chronic graft vs host disease; CR, complete remission; d: day(s); m: months(s); MAC, myeloablative; MDS, myelodysplastic syndrome; NA, not available; NM, non-myeloablative; NRM, non relapse mortality; OS, overall survival; PBSC, peripheral blood stem cell; PFS progression free survival; PTCy, post-transplant cyclophosphamide; TCD, T cell depletion; y: year(s).

overcome the relapse rate some centers explored PBSC in the unmanipulated haplo-HSCT. Recently, 2 independent studies by CIBMTR[9] and EBMT[10] compared transplant outcomes of BM and PBSC recipients. Bashey et al[9] reported 681 haplo-HSCT with different hematological malignancies receiving either PBSC or BM as stem cell source with PT-Cy. Results were comparable with, however, higher risk of acute and chronic GVHD in PBSC recipients. The ALWP-EBMT registry, analyzed 451 patients with AML and ALL.[10] Overall survival and LFS as well chronic-GVHD and relapse risk were not different using BM versus PBSC, while acute GVHD grade 2–4 was significantly higher in PBSC recipients. Together, these two retrospective confirmed the increased risk of grade 2–4 aGVHD with comparable survival outcomes using PBSC or BM with PT-Cy.

The optimal conditioning intensity regimen is another debated topic. The ALWP[11] recently reported equivalent outcomes after MAC or RIC on 912 AML patients older than 45 years. RIC may offer the possibility of lowering early toxicity and enhance post-transplantation maintenance therapy to prevent relapse, therefore in the absence of prospective trials, the appropriate regimen should be chosen according to disease risk features, patients' comorbidities, and transplant center experience.

Another important risk factor for haplo-HSCT outcomes is the presence of donor-specific anti-HLA antibodies (DSA). DSA are an important barrier against successful engraftment of donor cells, and can affect transplant survival. Before haplo-HSCT, recipient screening for detection of DSA and desensitization strategies, in case of absence of different donor, are recommended.[12]

Several prospective trials comparing haplo-HSCT with other donors are currently ongoing (NCT01597778, NCT03250546, NCT03275636, NCT01751997). So far, the retrospective studies available by single centers experience and registries, reported that the toxic profile and survival outcomes of haplo-HSCT are similar to HSCT from MUD or UCBT.[13,*14]

Comparison between haplo-HSCT and MSD resulted in the advantage of MSD-HSCT, mainly for decreased GVHD and NRM.[15] To date, HSCT from MSD remain the standard of care for patient with an available fully matched related donor.

Future prospective

The use of unmanipulated haplo grafts may provide access to HSCT virtually to all patients in need also in elderly population.[16] Although, relapse remains one of the major cause of transplant failure, in the haplo-HSCT the antigenic disparities between donor and recipient can strengthen the immunological response against the original disease. Furthermore, the rapid availability of donors, makes haplo-HSCT an ideal platform to develop further strategies of immunomodulation after HSCT[17,*18] or with donor lymphocyte infusion (DLI) in patients with minimal residual disease (MRD) or relapse. Some authors reported the use of DLI without severe toxicity of fatal GVHD in the haplo-HSCT setting[19,20] for relapse treatment or as pre-emptive strategies, as reported in other donor setting. Ideally, DLI after haplo-HSCT should be performed in the setting of clinical trials.

In conclusion, haplo-HSCT is an effective strategy for patients lacking a MSD-HSCT. The use of haplo-HSCT with PT-Cy is rapidly increasing due to the easy graft procurement, and the low cost of graft acquisition and manipulation. Indeed, the donor accessibility could allow reduction of time to proceed to HSCT and help in decreasing the risk of disease recurrence, in patients with impending relapse, also with strategies of post-transplant immunotherapy.

References

*1. Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. *N Engl J Med.* 2014;371:339–348.

Analysis of donor availability across different ethnicities using the large US registry.

2. Aversa F, Tabilio A, Velardi A, et al. Treatment of high-risk acute leukemia with T-cell–depleted stem cells from related donors with one fully mismatched HLA haplotype. *N Engl J Med*. 1998;339:1186–1193.

*3. Passweg JR, Baldomero H, Bader P, et al. Is the use of unrelated donor transplantation leveling off in Europe? The 2016 European Society for Blood and Marrow Transplant activity survey report. *Bone Marrow Transplantation*. 2018;53:1139–1148.

Global European survey showing the transplant activities in EBMT centers with the indication for HSCT and the increasing use of haplo-HSCT

4. Huang X, Liu D, Liu K, et al. Haploidentical hematopoietic stem cell transplantation without in vitro T cell depletion for treatment of hematologic malignancies in children. *Biol Blood Marrow Transplant*. 2009;15:91–94.

5. Luznik L, Jalla S, Engstrom LW, et al. Durable engraftment of major histocompatibility complex-incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplantation cyclophosphamide. *Blood*. 2001;98:3456–3464.

*6. Kröger N, Solano C, Wolschke C, et al. Antilymphocyte globulin for prevention of chronic graft-versus-host disease. *N Engl J Med*. 2016;374:43–53.

This study shows the results of the prospective randomized trial on the use of ATG in the setting of related and unrelated donor transplantation.

7. Cieri N, Greco R, Crucitti L, et al. Post-transplantation cyclophosphamide and sirolimus after haploidentical hematopoietic stem cell transplantation using a treosulfan-based myeloablative conditioning and peripheral blood stem cells. *Biol Blood Marrow Transplant*. 2015;2:1506–1514.

8. Kasamon YL, Bolaños-Meade J, Prince GT, et al. Outcomes of nonmyeloablative HLA-haploidentical blood or marrow transplantation with high-dose post-transplantation cyclophosphamide in older adults. *J Clin Oncol*. 2015;28:3152–3161.

9. Bashey A, Zhang MJ, McCurdy SR, et al. Mobilized peripheral blood stem cells versus unstimulated bone marrow as a graft source for T-cell–replete haploidentical donor transplantation using post-transplant cyclophosphamide. *J Clin Oncol*. 2017;35:3002–3009.

10. Ruggeri A, Labopin M, Bacigalupo A, et al. Bone marrow versus mobilized peripheral blood stem cells in haploidentical transplants using posttransplantation cyclophosphamide. *Cancer*. 2018;124:1428–1437.

11. Santoro N, Labopin M, Ciceri F, et al. Impact of conditioning intensity on outcomes of haploidentical stem cell transplantation for patients with acute myeloid leukemia over 45 years of age. *Cancer*. 2019;[Epub ahead of print].

12. Ciurea SO, Cao K, Fernadez-Vina M, et al. The European Society for Blood and Marrow Transplantation (EBMT) consensus guidelines for the detection and treatment of donor-specific Anti-HLA antibodies (DSA) in haploidentical hematopoietic cell transplantation. *Bone Marrow Transplant*. 2018;53:521–534.

13. Bashey A, Zhang X, Sizemore CA, et al. T-cell-replete HLA-haploidentical hematopoietic transplantation for hematologic malignancies using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. *J Clin Oncol*. 2013;31:1310–1316.

*14. Ruggeri A, Labopin M, Sanz G, et al. Comparison of outcomes after unrelated cord blood and unmanipulated haploidentical stem cell transplantation in adults with acute leukemia. *Leukemia*. 2015;29:1891–1900.

First retrospective analysis in a large series of patients showing comparable results between haplo and unrelated cord blood

15. Salvatore D, Labopin M, Ruggeri A, et al. Outcomes of hematopoietic stem cell transplantation from unmanipulated haploidentical versus matched sibling donor in patients with acute myeloid leukemia in first complete remission with intermediate or high-risk cytogenetics: a study from the acute leukemia working party of the european society for blood and marrow transplantation. *Haematologica*. 2018;103:1317–1328.

16. Santoro N, Labopin M, Giannotti F, et al. Unmanipulated haploidentical in comparison with matched unrelated donor stem cell transplantation in patients 60 years and older with acute myeloid leukemia: a comparative study on behalf of the ALWP of the EBMT. *J Hematol Oncol*. 2018;11:55.

17. Ciceri F, Bonini C, Stanghellini MTL, et al. Infusion of suicide-gene-engineered donor lymphocytes after family haploidentical haemopoietic stem-cell transplantation for leukaemia (the TK007 trial): a non-randomised phase I-II study. *Lancet Oncol*. 2009;10:489–500.

*18. Ciurea SO, Schafer JR, Bassett R, et al. Phase 1 clinical trial using mbIL21 ex vivo-expanded donor-derived NK cells after haploidentical transplantation. *Blood*. 2017;130:1857–1868.

Phase 1 clinical trial exploring the efficacy of adoptive immunotherapy with expanded NK cells after haplo-HSCT to reduce the risk of relapse

19. Zeidan AM, Forde PM, Symons H, et al. HLA-Haploidentical donor lymphocyte infusions for patients with relapsed hematologic malignancies after related HLA-haploidentical bone marrow transplantation. *Biol Blood Marrow Transplant*. 2014;20:314–318.

20. Ghiso A, Raiola AM, Gualandi F, et al. DLI after haploidentical BMT with post-transplant CY. *Bone Marrow Transplant*. 2015;34:1608.