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Haploidentical Hematopoietic Stem Cell Transplantation: A Global Overview Comparing Asia, the European Union, and the United States

Jane Apperley [1], Dietger Niederwieser [2], Xiao-jun Huang [3], Arnon Nagler [4], Ephraim Fuchs [5], Jeff Szer [6], Yoshihisa Kodera [7,*]

[1] *Haematology Department, Imperial College, Hammersmith Hospital, London, United Kingdom*
[2] *Division of Hematology and Medical Oncology, University of Leipzig, Leipzig, Germany*
[3] *Peking University Institute of Hematology, Peking University People's Hospital, Beijing Key Laboratory of HSCT, Beijing, Peoples Republic of China*
[4] *Hematology Division BMT and Cord Blood Bank, Chaim Sheba Medical Center, Tel-Hashomer, Israel*
[5] *Sidney Kimmel Comprehensive Cancer Center, Blood and Bone Marrow Cancers Program, The Johns Hopkins University, Baltimore, Maryland*
[6] *Department of Clinical Haematology & BMT Service, The Royal Melbourne Hospital, Melbourne, Australia*
[7] *Department of Promotion for Blood and Marrow Transplantation, Aichi Medical University School of Medicine, Nagakute, Aichi, Japan*

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A B S T R A C T

One of the major projects of the Worldwide Network for Blood and Marrow Transplantation (WBMT) is to promote hematopoietic stem cell transplantation (HSCT) in emerging countries in the world. For these countries, HLA haploidentical HSCT (haplo-HSCT) from family members is an attractive approach because of its cost effectiveness. To learn the current status, including recent trends, of haplo-HSCT, the WBMT invited speakers from major transplant centers in 3 regions (Asia, Europe, and North America) to present at its annual WBMT Joint Session. This article represents the direct reports from these 3 speakers in addition to introductions by 2 WBMT speakers who address data from the Global Transplant Activity survey. It must be emphasized, however, that certain promising results of haplo-HSCT presented in this article were obtained at well-experienced institutes.

INTRODUCTION

One of the major projects of the Worldwide Network for Blood and Marrow Transplantation (WBMT) is to promote hematopoietic stem cell transplantation (HSCT) in emerging and developing nations. For these countries, HLA haploidentical HSCT (haplo-HSCT) from family members is an attractive approach because of its cost effectiveness. To understand the current status and the future trends of haplo-HSCT, the WBMT/Tandem Joint Session invited experts from major transplant centers in 3 regions, Asia, Europe, and North America. This article is the synthesis of reports from these individuals. It must be emphasized, however, that the optimism surrounding the outcomes of haplo-HSCT presented in this article were the result of studies conducted and analyzed at institutes with significant experience in the field.

Allogeneic HSCT (allo-HSCT) is a potentially curative treatment of a wide variety of malignant and nonmalignant disorders of hematopoiesis. Since the first HSCT in the late 1950s, more than 1 million procedures have been completed worldwide, and the annual transplant rate is now close to 70,000 per annum without any evidence of a plateau. Of these, approximately 45% are allogeneic, and major indications include leukemia (82%), lymphomas (11%), and bone marrow failure (6%).

Historically, the best outcomes of allo-HSCT have been obtained when the donor is an HLA-matched sibling [1]. Unfortunately, each sibling of a patient has only a 25% chance of being HLA-matched, and with the small family sizes seen in the many nations, patients have only about a 30% chance of having an HLA-matched sibling donor. With the expansion of the unrelated donor pool to now more than 26 million donors worldwide, the numbers of unrelated allo-HSCTs have increased to 16,000 per year. The results of allo-HSCT

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* Correspondence and reprint requests: Yoshihisa Kodera, Aichi Medical University School of Medicine, 1-1 Yazakokarimata, Nagakute, Aichi, 480-1195, Japan.
E-mail addresses: ykodera@river.ocn.ne.jp, ykodera@aichi-med-u.ac.jp (Y. Kodera).

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from closely matched unrelated adult donors have improved dramatically over the last 25 years, and the overall and event-free survival rates after matched unrelated donor stem cell transplantation (HSCT) rival those seen after HLA-matched sibling transplantation. Nevertheless, well-matched donors cannot be found for many patients, and many other patients either relapse or become too ill while waiting for a donor to be identified.

Patients lacking an HLA-matched sibling or unrelated donor have 3 different options for graft sources: partially HLA-mismatched unrelated adult donors, unrelated donor umbilical cord blood [2], and partially HLA-mismatched or HLA-haploidentical, related donors [3,4]. An HLA-haploidentical donor is a related donor who shares exactly 1 HLA haplotype and differs by a variable number of HLA genes on the unshared haplotype. Mendelian genetics dictate that each biological parent and each biological child of a patient is HLA-haploidentical; each sibling, half-sibling, aunt, or uncle has a 50% likelihood of being HLA-haploidentical; and each cousin, niece, or nephew has a 25% chance of being HLA-haploidentical. Herein lies the greatest advantage of the haploidentical donor option: A haploidentical donor can be found for nearly every patient that is referred for allo-HSCT. Further, graft acquisition costs are modest compared with unrelated donor options, and the donor is readily available to donate more stem cells or lymphocytes in the event of graft failure or relapse, respectively.

Historically, the major limitation of haplo-HSCT has been intense, bidirectional alloreactivity resulting in unacceptably high incidences of graft failure, graft-versus-host disease (GVHD), and nonrelapse mortality and poor rates of overall and event-free survival [5-7]. Beginning in the 1990s, the picture for haplo-HSCT brightened with the development of "megadose" T cell–depleted haplo-HSCT by the group led by Massimo Martelli Perugia, Italy [4]. Currently, 3 main approaches control GVHD after haplo-HSCT:

1. The megadose HSCT approach using peripheral blood stem cell grafts positively selected for $CD34^+$ cells, depleted of $CD3^+$ and $CD19^+$ cells, or depleted of T cells bearing the T cell receptor.
2. The GIAC protocol, pioneered in China, comprising *G*ranulocyte-colony-stimulating factor stimulation of the donor; *I*ntensified immunosuppression through post-transplantation cyclosporine, mycophenolate mofetil, and short-course methotrexate; *A*ntithymocyte globulin added to conditioning to help prevent GVHD and aid engraftment; and *C*ombination of peripheral blood stem cell and bone marrow allografts.
3. High-dose, post-transplantation cyclophosphamide (PTCy).

THE ASIAN EXPERIENCE

Haplo-HSCT is an important alternative transplant option for most patients with hematological disease and is available without search or acquisition costs to the patient. However, the success of haplo-HSCT was previously hindered by high incidences of GVHD and graft rejection. A number of studies were undertaken to devise strategies to overcome the immunological barrier, in which G-CSF (filgrastim) was recognized as a novel mediator of T cell tolerance, by polarization of T cells from Th 1 to Th 2 phenotype, regulatory T cell/Th 17 balance toward regulatory T cells, and modulation of non-T regulatory cells such as dendritic cells and myeloid-derived suppressor cells, among others.

Over the past 15 years, by using a combination of G-CSF–mobilized bone marrow and peripheral blood cells, as well as antithymocyte globulin administration for the prophylaxis of GVHD and graft rejection, the Beijing group initiated one of the earliest clinical trials to explore unmanipulated myeloablative haplo-HSCT for leukemia [8]. The Beijing Protocol was shown to be a reliable treatment strategy for patients without a suitable HLA-matched donor for the following reasons: graft rejection was reduced with 99% of patients achieving sustained myeloid engraftment and 92% platelet engraftment; the risk of lethal GVHD was not increased when compared with HLA-matched allogeneic HSCT (grades III to IV acute GVHD was 11% to 14% and extensive chronic GVHD 19% to 23%); haplo-HSCT achieved similar clinical efficacy as allo-HSCT from an HLA-identical sibling donor or matched unrelated donor and was found to be superior to cord blood transplantation in the treatment of children with hematological malignances and chemotherapy in treatment of intermediate/high-risk acute myelogenous and acute lymphoblastic leukemias in first complete remission; and the health-related quality of life and the cumulative incidence of late effects was found to be similar or even better for patients receiving haplo-HSCT compared with allo-HSCT from identical sibling donor.

In recent years the Beijing Protocol has been improved in many aspects and developed into an integrated haplo-HSCT system. The indications for haplo-HSCT have been extended from hematological malignancy to include nonmalignant disease such as severe aplastic anemia and inherited disorders. A series of new conditioning regimens were introduced, including total body irradiation–based regimens and other optimized regimens for certain groups of patients. Selected older patients aged >50 years with low hematopoietic cell transplantation–specific comorbidity index and good performance status have been shown to safely undergo haplo-HSCT. Donor selection based on non-HLA systems, such as donor-specific antibodies, KIR, and family relationship, now play a predominant role in haplo-HSCT. It has been suggested that choosing young, male, NIMA-mismatched donors is a reasonable strategy, whereas transplants from older multiparous women and NIPA-mismatched donors should probably be avoided. Donor-specific antibodies were indicated to be associated with primary graft failure, transplant-related mortality, and inferior overall survival after haplo-HSCT. Using a combination of reliable biomarkers (minima; residual disease detection, leukemia initiating cells, chimerism) and powerful intervention strategies (donor lymphocyte infusion, IFN-□) using pre- and post-transplant risk stratification directed interventions has reduced relapse risk after haplo-HSCT.

The Beijing Protocol has been widely incorporated into clinical practice in China, including modified protocols such as haplo-HSCT with G-CSF–mobilized peripheral blood instead of bone marrow plus peripheral blood and the use of low-dose antithymocyte globulin; haplo-HSCT has become the largest donor source compared with identical sibling donor from 2013 and now is used in almost 48% of allo-HSCT in China. Furthermore, cooperation between the major transplant centers of China has enabled successful implementation of several multicentered studies for haplo-HSCT. In other countries, modified haplo-HSCT protocols with reduced-intensity conditioning have been carried out in Japan and Korea, and modified protocols with G-CSF–primed

bone marrow have been replicated with promising results in Europe. It has been estimated that more than half of the HLA haplotype mismatched transplantations performed worldwide will follow the Beijing Protocol [9]. With the development of international multicenter clinical trials between Asia and the West along with advances in translational research, haplo-HSCT may well become the dominant form of HSCT.

THE EUROPEAN EXPERIENCE

Allo-HSCT represents the only possible cure for adult patients with high risk acute leukemia. In the absence of an HLA-matched donor, haplo-HSCT is an attractive alternative that provides the possibility of transplantation to almost all patients needing an allo-HSCT. The numbers of haplo-HSCT in Europe are constantly increasing, with a steep rise in recent years reaching about 8% of all allo-HSCT in 2013. In view of the slow immune reconstitution leading to a high incidence of both life-threatening infections and relapse after T cell–depleted haplo-HSCT (unless regulatory T cells/Tcon or other modes of post-transplant adoptive cellular immunotherapies are given), currently most haplo-HSCTs in Europe are performed with a T cell–replete approach. However, many questions are still open, and most reports of haplo-HSCTs are from single centers and with rather short follow-up periods in a limited number of patients.

The Adult Leukemia Working Party of the European Group for Blood and Marrow Transplantation took advantage of large registry data and performed several retrospective registry studies in the last few years, trying to address these open issues in the field. Specifically, T cell–replete haplo-HSCTs were compared with cord blood transplantation in acute leukemia to address the topic of alternative donor transplants [10]. Similarly, in 2 separate studies, T cell–replete haplo-HSCT has been compared with matched and mismatched unrelated allo-HSCT (S. Piemontese, personal communication) and autologous transplantations for patients with acute leukemia [11]. Theoretically, there was the idea that the broad HLA disparity involved in haplo-HSCT would result in a stronger graft-versus-leukemia effect in comparison with HLA-matched transplants. This question has been addressed in another study from the European Group for Blood and Marrow Transplantation [12]. Other studies have researched myeloablative versus reduced-intensity conditioning for unmanipulated haplo-HSCT. Finally, very recently the impact of HLA disparities on the outcomes after haplo-HSCT in acute leukemia has been examined.

THE U.S. EXPERIENCE

PTCy is a special case of the more general phenomenon of drug-induced immunological tolerance, first developed by Schwartz and Dameshek [13]. In drug-induced immunological tolerance, an animal is exposed to an antigen for the first time and shortly thereafter treated with a drug that is selectively toxic to dividing cells. Because an immunogenic antigen exposure induces the activation and proliferation of antigen-specific B cells and T cells, a properly timed administration of the cytotoxic drug will selectively inactivate the antigen-responsive lymphocytes while sparing lymphocytes specific for other antigens. Berenbaum [14] found that cyclophosphamide could prolong the survival of rat skin allografts if the drug was administered approximately 1 to 3 days after graft placement.

In a series of pioneering experiments, Mayumi et al. [15] found that complete tolerance to minor histocompatibility antigens could be induced by infusing mice intravenously with a high dose of spleen cells bearing these antigens followed in 48 to 72 hours by intraperitoneal injection of a high dose of cyclophosphamide. Luznik et al. [16] achieved tolerance and durable chimerism with MHC-incompatible cells by conditioning mice with fludarabine and 200 cGy total body irradiation, transplanting marrow on day 0, and giving high dose cyclophosphamide on day 2. This basic regimen was then translated to the clinic. Initial studies used a single dose of cyclophosphamide 50 mg/kg i.v. on day 3, but subsequent trials used this dose of drug on each of days 3 and 4 after transplantation.

The regimen that has been used in over 500 patients at Johns Hopkins in Baltimore consists of the following; Cy 14.5 mg/kg/day on days −6 and −5; fludarabine 30 mg/m^2/day on days −6, −5, −4, −3, and −2; total body irradiation 200 cGy on day −1; Cy 50 mg/kg/day on days 3 and 4 followed by G-CSF 5 μg/kg/day, mycophenolate mofetil 15 mg/kg/day, and tacrolimus. The incidences of acute and chronic GVHD were remarkably low, and nonrelapse mortality was acceptable at 17% in the long term. Overall and event-free survival rates at 5 years after transplantation were in the range of 40% and 30%, respectively. When adjusted for disease risk index according to the methodology developed by Armand [17], outcomes of reduced-intensity conditioning and haploidentical bone marrow transplantation with PTCy are roughly equivalent to the outcomes of patients receiving grafts from HLA-matched donors. These results suggest that high dose, post-transplant Cy substantially mitigates alloreactivity after haploidentical bone marrow transplantation, to the point that outcomes are equivalent to those seen when using HLA-matched donors.

Roughly equivalent outcomes of HLA-matched and haploidentical bone marrow transplantation with PTCy have been reported in single-center retrospective comparisons by other groups [18-21]. More recently, a case-control study from the Center for International Blood and Marrow Transplant Research showed equivalent outcomes for acute myeloid leukemia patients receiving either HLA-matched unrelated donor stem cells or haploidentical bone marrow with PTCy. High dose PTCy for GVHD prophylaxis has now been used with good results after myeloablative [19] and nonmyeloablative [18] conditioning and with filgrastim-mobilized stem cells as well as with bone marrow as the graft source [22].

Although haplo-HSCT with PTCy is now in widespread use in the United States, as well as in France, Italy, Australia, and elsewhere [18,21,23], this approach may ultimately have its greatest impact in developing countries, where economic resources are more limited. Unrelated donor registries and cord blood banks are expensive to set up and maintain. In contrast to haplo-HSCT strategies that require graft manipulation, no special expertise or cell separation devices are required. Many centers that have adopted the use of PTCy for GVHD prophylaxis have achieved results comparable with those obtained at Johns Hopkins, the center that pioneered this approach. This result suggests no significant “learning curve” and that similar results can be expected as new centers adopt this strategy. Still, major questions about the PTCy approach remain. How dose PTCy compare with megadose stem cell transplantation or to the GIAC protocol for haplo-HSCT? How does haplo-HSCT with PTCy compare with unrelated umbilical cord blood transplantation, to matched unrelated donor HSCT, or to matched sibling HSCT? Can haplo-HSCT with PTCy be extended on a large scale to treat

other diseases, such as hemoglobinopathy [24], aplastic anemia [25], immunodeficiency, or even autoimmune disease? Can PTCy be used to induce hematopoietic chimerism and tolerance to solid organ transplants [26]? Many of these questions are being actively investigated, and results should be available within the next 5 years.

CONCLUSION

Haplo-HSCT is clearly increasing in activity and provides a clear path to identifying a potential donor for an HSCT recipient candidate where no other exists or is feasible because of immunological or financial factors, thus providing the promise of a donor for almost every eligible patient. The safe use of these donors in regions with newly developing transplant programs will require careful mentoring by centers and individuals experienced in allo-HSCT.

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REFERENCES

1. Szydlo R, Goldman JM, Klein JP, et al. Results of allogeneic bone marrow transplants for leukemia using donors other than HLA-identical siblings. *J Clin Oncol*. 1997;15:1767-1777.
2. Gluckman E, Broxmeyer HA, Auerbach AD, et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. *N Engl J Med*. 1989; 321:1174-1178.
3. Reisner Y, Kapoor N, Kirkpatrick D, et al. Transplantation for severe combined immunodeficiency with HLA-A, B, D, DR incompatible parental marrow cells fractionated by soybean agglutinin and sheep red blood cells. *Blood*. 1983;61:341-348.
4. 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.
5. Anasetti C, Amos D, Beatty PG, et al. Effect of HLA compatibility on engraftment of bone marrow transplants in patients with leukemia or lymphoma. *N Engl J Med*. 1989;320:197-204.
6. Anasetti C, Beatty PG, Storb R, et al. Effect of HLA incompatibility on graft-versus-host disease, relapse, and survival after marrow transplantation for patients with leukemia or lymphoma. *Hum Immunol*. 1990;29:79-91.
7. Ash RC, Horowitz MM, Gale RP, et al. Bone marrow transplantation from related donors other than HLA-identical siblings: effect of T cell depletion. *Bone Marrow Transplant*. 1991;7:443-452.
8. Bashey A, Zhang X, Sizemore CA, et al. T-cell replete haploidentical transplantation using post-transplant cyclophosphamide results in equivalent non-relapse mortality and disease-free survival compared to transplantation from HLA-identical sibling and matched unrelated donors: a stratified Cox model analysis of two hundred and sixty contemporaneous allogeneic transplants from a single center. *ASH Annu Meet Abstr*. 2011;118:833.
9. Handgretinger R. Haploidentical transplantation: the search for the best donor. *Blood*. 2014;124:827-828.
10. 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.
11. Gorin NC, Labopin M, Piemontese S, et al. T-cell-replete haploidentical transplantation versus autologous stem cell transplantation in adult acute leukemia: a matched pair analysis. *Haematologica*. 2015;100: 558-564.
12. Ringdén O, Labopin M, Ciceri F, et al. Is there a stronger graft-versus-leukemia effect using HLA-haploidentical donors compared with HLA-identical siblings? *Leukemia*. 2015.
13. Schwartz R, Dameshek W. Drug-induced immunological tolerance. *Nature*. 1959;183:1682-1683.
14. Berenbaum MC. Prolongation of homograft survival in mice with single doses of cyclophosphamide. *Nature*. 1963;200:84.
15. Mayumi H, Himeno K, Shin T, Nomoto K. Drug-induced tolerance to allografts in mice. VI. Tolerance induction in H-2-haplotype-identical strain combinations in mice. *Transplantation*. 1985;40:188-194.
16. Luznik L, Jalla S, Engstrom LW, et al. Durable engraftment of major histocompatibility complex-incompatible cells after non-myeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplantation cyclophosphamide. *Blood*. 2001; 98:3456-3464.
17. Armand PG. A disease risk index for patients undergoing allogeneic stem cell transplantation. *Blood*. 2012;120:905-913.
18. Raiola AM, Dominietto A, di Grazia C, et al. Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts. *Biol Blood Marrow Transplant*. 2014;20: 1573-1579.
19. Solomon SR, Sizemore CA, Sanacore M, et al. Haploidentical transplantation using T cell replete peripheral blood stem cells and myeloablative conditioning in patients with high-risk hematologic malignancies who lack conventional donors is well tolerated and produces excellent relapse-free survival: results of a prospective phase II trial. *Biol Blood Marrow Transplant*. 2012;18:1859-1866.
20. Raj K, Pagliuca A, Bradstock K, et al. Peripheral blood hematopoietic stem cells for transplantation of hematological diseases from related, haploidentical donors after reduced-intensity conditioning. *Biol Blood Marrow Transplant*. 2014;20:890-895.
21. Castagna L, Bramanti S, Furst S, et al. Nonmyeloablative conditioning, unmanipulated haploidentical SCT and post-infusion CY for advanced lymphomas. *Bone Marrow Transplant*. 2014;49:1475-1480.
22. Castagna L, Crocchiolo R, Furst S, et al. Bone marrow compared with peripheral blood stem cells for haploidentical transplantation with a nonmyeloablative conditioning regimen and post-transplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2014;20:724-729.
23. Bilmon IA, Kwan J, Gottlieb D, et al. Haploidentical bone marrow transplants for hematological malignancies using non-myeloablative conditioning therapy and post-transplant immunosuppression with cyclophosphamide: results from a single Australian centre. *Intern Med J*. 2013;43:191-196.
24. Bolaños-Meade J, Fuchs EJ, Luznik L, et al. HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. *Blood*. 2012; 120:4285-4291.
25. Jaiswal SR, Chatterjee S, Mukherjee S, et al. Pre-transplant sirolimus might improve the outcome of haploidentical peripheral blood stem cell transplantation with post-transplant cyclophosphamide for patients with severe aplastic anemia. *Bone Marrow Transplant*. 2015;50: 873-875.
26. Leventhal J, Abecassis M, Miller J, et al. Chimerism and tolerance without GVHD or engraftment syndrome in HLA-mismatched combined kidney and hematopoietic stem cell transplantation. *Sci Translat Med*. 2012;4:124-128.