Biol Blood Marrow Transplant 22 (2016) S15–S18

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Reprint of: 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

Article history:
Received 27 October 2015
Accepted 2 November 2015

Key Words:
Global Activity Survey
Haplo-transplantation
Haplo-HSCT
Beijing Protocol
Europe
United States

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

DOI of original article: http://dx.doi.org/10.1016/j.bbmt.2015.11.001.
☆ This article is reprint of a previously published article. Fir citation purposes, please use the original publication details: Bio Blood Marrow Transplant. 2016;22:23–26.
Financial disclosure: See Acknowledgments on page S18.
* 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).

http://dx.doi.org/10.1016/j.bbmt.2016.01.006
1083-8791/

have increased to 16,000 per year. The results of allo-HSCT 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