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Report

Proceedings from the Second Haploidentical Stem Cell Transplantation Symposium—Haplo2014, San Francisco, California, December 4, 2014

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A B S T R A C T

Significant progress has been made over the past decade in haploidentical transplantation, with the development of novel methods to control intense alloreactive reactions generated in the major HLA-mismatched setting. Application of post-transplantation cyclophosphamide has gained worldwide acceptance as an effective and low-cost way to perform this type of transplantation, with outcomes now similar to those from HLA-matched unrelated donors. These advances have resulted in improved treatment-related mortality, whereas disease relapse has emerged as the most common cause of treatment failure. In addition, improvements in immunologic reconstitution after transplantation are much needed, not only in haploidentical transplantation but in all forms of stem cell transplantation. This symposium has focused on some of the most promising methods to control alloreactivity in this form of transplantation and application of cellular therapy to prevent disease relapse after transplantation, as well as understanding immunologic reconstitution and foreseeable approaches to improve immune recovery after transplantation.

INTRODUCTION

HLA–half-matched related donors are increasingly utilized as source of stem cells because of lower acquisition cost, widespread availability regardless of race of recipient, fast procurement of stem cells, and availability of donors to collect additional cells. Haploidentical transplantation outcomes have improved primarily because of the use of

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post-transplantation cyclophosphamide (PTCy) for graft-versus-host disease (GVHD) prevention; however, novel methods using partial T cell depletion are equally exciting. As treatment-related mortality (TRM) has decreased with these approaches, prevention of disease relapse has now become the most important target to further improve transplantation outcomes. Haploidentical transplantation (HaploSCT) represents an optimal setup to accomplish this because of accessibility to donor cells and because the HLA-mismatch setting may provide enhanced graft-versus-tumor effects if graft-versus-host reactions can be controlled. Cellular therapy with T cell subsets or modified T cells may provide an opportunity to tilt the balance of favor of the graft-versus-tumor effect and holds promise to improve relapse rates and transplantation outcomes. Improving immunologic reconstitution remains of paramount importance, as it represents the key to further decreasing toxicity and TRM in any form of transplantation.

This report summarizes recent developments in haploidentical transplantation that were presented at the Second Symposium on Haploidentical Transplantation, Haplo2014, held in San Francisco, California. This symposium was divided into 3 sections dedicated to conditioning and graft manipulation, current clinical trials in haploidentical transplantation, and cellular therapy and immunologic reconstitution after transplantation.

The meeting started with an overview presentation by Dr. Mary Horowitz on recent Center for International Blood and Marrow Transplant Research (CIBMTR) trends in the use of HLA-matched and alternative donor transplantation. First, a growing number of first allogeneic transplantations continues to be noted in the United States, from approximately 6000 transplantations in 2010 to almost 7500 transplantations in 2013. The increase was mostly based on increase in unrelated donor and haploidentical transplantations. The 1-year survival in patients with acute leukemia in remission or myelodysplastic syndrome (MDS) younger than 50 years old using myeloablative conditioning with matched unrelated donor (MUD) was 70% in 2011. There was steady increase in survival of 8% (95% confidence interval [CI], 7% to 9%) per year from 1990 until 2011. Since 2009, a growing number of alternative donor transplantations was noted, with a significant increase in haploidentical transplantations of approximately 200 in 2010 to approximately 400 in 2013. Of 1646 alternative donor transplantations performed in 2010, 41%, 25%, 20%, and 14% used mismatched unrelated, double-unit cord blood, single-unit cord blood, and haploidentical donors, whereas from 1825 transplantations performed in 2013, 43%, 13%, 22%, and 22% used mismatched unrelated, double-unit cord blood, single-unit cord blood, and haploidentical donor transplantations, respectively. Not unexpectedly, the use of an alternative donor was more pronounced in minority groups (African-American for example) than in the Caucasian population.

Historically, in MUD transplantations, a single-allele mismatch at HLA-A, -B, -C, or -DRB1 was associated with worse overall survival; this difference disappeared in advanced or high-risk disease [1]. However, such differences do not appear to be the case for haploidentical transplantations performed with PTCy, where using a full haplotype–mismatched transplant does not appear to produce higher TRM. Moreover, early registry data from CIBMTR comparing outcomes between patients with acute myeloid leukemia (AML) receiving a transplant from a haploidentical donor or a MUD showed similar results [2]. Progression-free survival for AML patients at 3 years adjusted for age and disease risk was similar between MUD and haploidentical donor transplantations when either myeloablative (50% versus 45%; hazard ratio, .93; 95% CI, .7 to 1.22; $P = .58$) or reduced-intensity conditioning (RIC)/nonmyeloablative conditioning was used (44% versus 46%; hazard ratio, 1.06; 95% CI, .79 to 1.43; $P = .70$) [2].

Conditioning and Graft Manipulation

Dr. Stefan Ciurea discussed recent developments in haploidentical transplantation performed with PTCy. Several groups reported very good outcomes using PTCy, tacrolimus, and mycophenolate mofetil (MMF) as GVHD prevention in this setting with different conditioning regimens [3-9]. In addition, different single-institution studies reported comparative outcomes between haploidentical and HLA MUD transplantations. Different groups published data on haploidentical transplantation outcomes using several conditioning regimens other than fludarabine (Flu), cyclophosphamide (Cy), and total body irradiation (TBI). Although very low TRM was noted with this regimen, a higher relapse rate (in excess of 50%) for patients with acute leukemia prompted several groups to explore more intense conditioning regimens for these patients, with very good results. Several myeloablative conditioning regimens have now been established as safe and effective, including Flu with busulfan and thiotepa [5], Flu with melphalan and thiotepa or TBI [7], and Flu with ablative TBI doses [8]. In these studies, relapse rates for patients with myeloid malignancies varied from 20% to 40% at 1 year. In addition, these groups also compared outcomes of haploidentical transplantation performed with PTCy with HLA-matched transplantations (including matched related and unrelated) [7,10,11], and found similar transplantation outcomes for patients with hematological malignancies who had haploidentical and HLA-matched transplantations. To confirm these findings, we did a larger CIBMTR retrospective analysis comparing transplantation outcomes in an uniform group of patients with AML who had transplantation with a haploidentical or an 8/8 HLA MUD. This study showed almost identical survival at 3 years for patients who received either myeloablative (41% versus 42%, $P = .87$) or RIC/nonmyeloablative conditioning (35% versus 37%, $P = .89$) [2]. These encouraging results suggested that prospective comparative clinical trials are needed to appreciate outcomes between haploidentical transplantations performed with PTCy and HLA-matched transplantations, mostly with MUD transplantations, which, in general, take longer time to perform, during which patients with more advanced disease may progress and miss the opportunity to receive this life-saving procedure.

Dr. Rupert Handgretinger discussed the evolution of haploidentical transplantation, from complete T cell depletion to a partial depletion of alloreactive T cells, and its potential use as a platform to apply post-remission therapy. Depletion of $\alpha\beta$ T cells is associated with lower incidence of acute GVHD (aGVHD) and more rapid immune reconstitution of donor's immune system in the setting of no post-transplantation immunosuppressive therapy. Historically, effective T cell depletion of mobilize peripheral blood stem cells (PBSC) was based on positive $CD34^+$ selection of pure stem cells developed in the late 1990s. This was found to be associated with higher rates of graft failure, infectious complications, and TRM, as well as a higher rate of disease relapse [12-14]. In 2003, CD3/19 depletion was introduced as a step forward with the advantage of preserving natural