Biol Blood Marrow Transplant 22 (2016) 119–124

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Clinical Research: Alternative Donors

Haploidentical T Cell–Replete Transplantation with Post-Transplantation Cyclophosphamide for Patients in or above the Sixth Decade of Age Compared with Allogeneic Hematopoietic Stem Cell Transplantation from an Human Leukocyte Antigen–Matched Related or Unrelated Donor

Didier Blaise [1,2,3,4,*], Sabine Fürst [1,2], Roberto Crocchiolo [5], Jean El-Cheikh [1,2], Angela Granata [1,2], Samia Harbi [1,2], Reda Bouabdallah [2], Raynier Devillier [1,2], Stephania Bramanti [5], Claude Lemarie [6], Christophe Picard [7], Christian Chabannon [3,4,6,8], Pierre-Jean Weiller [1,2,4], Catherine Faucher [1,2], Bilal Mohty [1,2], Norbert Vey [2,3,4], Luca Castagna [1,2,5]

[1] *Transplant and Cellular Therapy Unit, Institut Paoli Calmettes, Marseille, France*
[2] *Hematology Department, Institut Paoli Calmettes, Marseille, France*
[3] *Centre de Recherche en Cancérologie de Marseille (CRCM), Marseille, France*
[4] *Aix-Marseille University (AMU), Marseille, France*
[5] *Transplant unit, Department of Hemato-oncology, Humanitas Cancer Center, Milano, Italy*
[6] *Cell Therapy Facility, Institut Paoli Calmettes, Marseille, France*
[7] *HLA immunogenetic Laboratory, Blood Bank, Marseille, France*
[8] *Inserm CBT-510, Clinical Investigation Center in Biotherapy, Institut Paoli Calmettes, Marseille, France*

Article history:
Received 29 April 2015
Accepted 20 August 2015

Key Words:
Haplo-identical
Elderly
Allogeneic
Unrelated donor
Related donor

A B S T R A C T

It has recently been shown that a T cell–replete allogeneic (allo) hematopoietic stem cell transplantation (HSCT) from a haploidentical donor (haplo-ID) could be a valid treatment for hematological malignancies. However, little data exist concerning older populations. We provided transplantation to 31 patients over the age of 55 years from a haplo-ID and compared their outcomes with patients of the same ages who underwent transplantation from a matched related (MRD) or an unrelated donor (UD). All 3 groups were comparable, except for their conditioning. Patients in haplo-ID group received 2 days of post-transplantation high-dose cyclophosphamide followed by cyclosporine A and mycophenolate mofetil, whereas patients in other groups received pretransplantation antithymocyte globulin, cyclosporine A, and additional mycophenolate mofetil in case of 1-antigen mismatch. All patients but 1 in the haplo-ID group engrafted. The incidence of grades 2 to 4 acute graft-versus-host disease (GVHD) was not statistically different between recipients from haplo-ID (cumulative incidence, 23%) and MRD (cumulative incidence, 21%) transplantations but it was lower than after UD HSCT (cumulative incidence, 44%). No patient in the haplo-ID group developed severe chronic GVHD, compared with cumulative incidences of 16% and 14% after MRD ($P = .02$) and UD ($P = .03$) grafts, respectively. The cumulative incidences of relapse were similar in the 3 groups, whereas nonrelapse mortality after UD HSCT was 3-fold higher than after haplo-ID or MRD HSCT. Overall, 2-year overall survival (70%), progression-free survival (67%), and progression and severe chronic GVHD–free survival (67%) probabilities after haplo-ID did not statistically differ from MRD transplantation (78%, 64%, and 51%, respectively), although they were higher than after UD transplantation (51% [$P = .08$], 38% [$P = .02$], and 31% [$P = .007$]). We conclude that T cell–replete haplo-ID HSCT followed by post-transplantation high-dose- cyclophosphamide in patients over 55 years is associated with promising results, similar to MRD HSCT, and is deserving prospective evaluation.

INTRODUCTION

Patients presenting with hematological malignancies have a median age of 66 years [1]. Over the last decade, reduced-intensity (RIC) or low-toxicity conditionings have

Financial disclosure: See Acknowledgments on page 123.
* Correspondence and reprint requests: Didier Blaise, MD, Transplant and Cellular Therapy Unit, Department of Hematology, Institut Paoli Calmettes, 232 Boulevard Sainte Marguerite, 13009 Marseille, France.
E-mail address: blaised@ipc.unicancer.fr (D. Blaise).

http://dx.doi.org/10.1016/j.bbmt.2015.08.029
1083-8791/

been associated with reduced regimen-related mortality, allowing for HLA identical allogeneic (allo) hematopoietic stem cell transplantation (HSCT) [2] in unfit or older patients who were previously not considered for allo-HSCT [3]. However, most transplantation-eligible patients lack a suitable matched related (MRD) donor [4]. In addition, MRD to elderly patients are elderly themselves, with frequent conditions contraindicating donation. Matched (MUD) or 1-antigen mismatched (MMUD) unrelated donors are frequently used when a suitable MRD is lacking, with publications reporting similar results. However, these publications have mainly described younger patients receiving myeloablative conditioning and lack data from older populations [5,6]. In addition, MMUD is not always found [4]. Presently, other alternative graft sources, such as unrelated cord blood or 1 haplotype–matched related donor (haplo-ID) are seldom used in older patients because these are perceived as too toxic. Overall, this translates to a low rate of allo-HSCT performed in a population with the highest incidence of hematologic malignancies, who usually present with the poorest prognosis unless allo-HSCT can be performed. Thus, to meet this unmet medical need, it is critical to develop innovative efficient therapeutic strategies.

Recently, several teams successfully introduced T cell–replete haplo-ID transplantation combining RIC or ablative conditioning and new schemes for graft-versus-host disease (GVHD) prophylaxis, reducing transplantation toxicities and, in turn, increasing the number of patients who can benefit from an allo-HSCT. Because of decreased toxicity documented with this transplantation technology when compared with previous haplo-ID transplantation attempts, this possibility may represent a real breakthrough in allowing for an expanded number of patients needing an allo-HSCT who can be offered an allo-HSCT. However, the suitability of haplo-ID HSCT in the patients over age of 55 and who usually present with more comorbidities remains unknown.

In this perspective, we report here a series of 31 patients ages of 55 years or beyond with high-risk hematological malignancies treated with an allo-HSCT from a related haplo-ID using high-dose post-transplantation cyclophosphamide, as previously described by the Johns Hopkins group [7]. This cohort is compared to 2 series of patients with the same characteristics who underwent transplantation from an MRD or an unrelated donor (UD).

PATIENTS AND METHODS

From January 2011 until November 2013, 31 consecutive patients older than 55 years underwent T-cell replete haplo-ID allo-HSCT for a hematological malignancy in institut Paoli Calmettes, Marseille and were included in this analysis.

During the same period and in the same institution, 110 patients older than 55 years received allo-HSCT from an MRD (n = 47) or UD (n = 63 of whom 13 presented with 1-antigen mismatch) with all patients receiving a similar RIC regimen [3,8]. Informed consent was obtained from all patients included in this study approved by our institutional review board.

Inclusion Criteria

For patients with an allo-HSCT indication, our strategy according to French standards was to first try to identify an HLA identical or 1 antigen–mismatched related or UD. In case such a donor was not identified, patients were eligible for a haplo-ID allo-HSCT. Previous autologous and allo HSCT were not considered contraindications. In case of previous allo-HSCT, the initial donor was considered as ineligible for a second donation.

Overall patients were ineligible for allo-HSCT if they had uncontrolled infections, active central nervous system disease, a Karnofsky performance status <60%, or severe organ dysfunction, as previously reported [3,9].

The comorbidity index of each patient was calculated using the hematopoietic cell transplantation–specific comorbidity index [10]. Disease risk index was retrospectively assessed, according to Armand et al. [11].

Conditioning Regimen and GVHD Prophylaxis

For haplo-ID HSCT, the intensity of the conditioning regimen was progressively increased over time when experience with haplo-HSCT associated with the original nonmyeloablative conditioning (NMAC) regimen was felt to be insufficient for tumor control in high-risk patients, notably for patients with myeloid malignancies. Thus, the initial NMAC consisted of cyclophosphamide (Cy) (14.5 mg/kg/day on days −6 and −5), fludarabine (30 mg/m^2/day from days −6 to −2), and 2 Gy total body irradiation (day −1) [12]. After this, RIC included Cy (14.5 mg/kg/day on days −7 and −6), fludarabine (30 mg/m^2/day from days −6 to −2), and i.v. busulfan (130 mg/m^2/day on days −3 and −2). After this, thiothepa (5 mg/kg on day −6) was introduced instead of pretransplantation Cy. In all cases, Cy (50 mg/kg/day) was administered on days +3 and +4. Further GVHD prophylaxis consisted of cyclosporine A and mycophenolate mofetil initiated on day +5, as initially reported [9,12].

RIC for MRD- or UD-based allo-HSCT was identical for all patients as previously reported [3,8]. Fludarabine (30 mg/m^2/day from day −6 to day −2), i.v. busulfan (130 mg/m^2/day on days −4 and −3), and antithymocyte globulin (2.5 mg/kg on days −3 and −2) (Thymoglobulin; Genzyme, St. Germain-en-Laye, France). GVHD prophylaxis consisted of cyclosporine A starting on day −1, and mycophenolate mofetil was added in case of 1-antigen–mismatched transplantation.

Stem Cell Sources and Donors

For haplo-ID HSCT, potential family members were typed at the HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 loci at a high-resolution level. All the donor/recipient pairs exhibited a median of 4 mismatches (range, 2 to 5) on the unshared haplotype. HLA antibody screening was performed in the patient, as previously reported [9], to help determine donor choice. Zero to 1-antigen–mismatched donors shared 6 or 5 of 6 antigens with the patient (high-resolution molecular typing of HLA-A, -B, -DRB1) when related, or 10 or 9 of 10 antigens (high-resolution molecular typing of HLA-A, -B, -Cw, -DRB1, and -DQ) when unrelated.

For the few donors who underwent bone marrow harvest under general anesthesia, the target dose was 4×10^8 nuclear cells/kg of recipient weight. Otherwise, most donors were mobilized with granulocyte colony–stimulating factor (Granocyte; Chugai, France) with a CD34$^+$ cells target of 4×10^6/kg. Both harvest modalities have been previously described [9]. Grafts were infused unmanipulated on day 0 except in case of ABO incompatibility.

Supportive care has been previously reported [3,9].

Engraftment and GVHD Evaluation

Neutrophil and platelet engraftment were defined as previously reported [9]. Acute and chronic GVHD (aGVHD and cGVHD, respectively) were graded as previously reported [9], according to international criteria [13,14].

Statistical Methods

We analyzed the cumulative incidences of aGVHD and cGVHD, nonrelapse mortality (NRM), and relapse or progression using competing risk analysis and Gray test for comparison among groups [15]. Death without evidence of relapse was considered as a competing event for the incidence of relapse. Similarly, the occurrence of relapse was considered as a competing event for the incidence of NRM, whereas relapse, progression, and deaths were treated as competing risks when analyzing the incidence of GVHD. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method, and results were compared using the log-rank test [16]. A P value $< .05$ was considered significant. We also compared the 3 groups using a composite endpoint integrating the probability of survival without progression or development of extensive cGVHD, as previously described [17]. All survival analyses were computed on the R 3.1.0 statistical software (http://www.R-project.org). Data from haplo HSCT group were compared with those from MRD and UD HSCT groups.

RESULTS

Patient and transplantation characteristics are reported in Table 1. UD were more often cytomegalovirus negative. Peripheral blood stem cells were more often collected from MRD than from haplo-ID ($P = .02$) and NMAC was more often used in haplo-ID HSCT recipients ($P < .0001$, see Table 1 for further details).

All but 1 patient engrafted with a longer time to reconstitute platelets counts after haplo-ID HSCT (Table 2).