Biol Blood Marrow Transplant 20 (2014) 370–374

Antithymocyte Globulin in Reduced-Intensity Conditioning Regimen Allows a High Disease-Free Survival Exempt of Long-Term Chronic Graft-versus-Host Disease

Raynier Devillier [1,2,3], Sabine Fürst [1], Jean El-Cheikh [1], Luca Castagna [1,4], Samia Harbi [1,2], Angela Granata [1], Roberto Crocchiolo [1,4], Claire Oudin [1,2], Bilal Mohty [1], Reda Bouabdallah [1], Christian Chabannon [2,3,5,6], Anne-Marie Stoppa [1], Aude Charbonnier [1], Florence Broussais-Guillaumot [1], Boris Calmels [3,5,6], Claude Lemarie [5,6], Jèrôme Rey [1], Norbert Vey [1,2,3], Didier Blaise [1,2,3,*]

[1] *Hematology Department, Transplantation Program, Institut Paoli Calmettes, Marseille, France*
[2] *Aix-Marseille Université, Marseille, France*
[3] *Centre de Recherche en Cancérologie de Marseille (CRCM), Marseille, France*
[4] *Hematology Unit, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Milano, Italy*
[5] *Cell Therapy Facility, Institut Paoli Calmettes, Marseille, France*
[6] *Inserm CBT-510, Centre d'Investigations Cliniques en Biothérapie, Institut Paoli Calmettes, Marseille, France*

Article history:
Received 27 October 2013
Accepted 29 November 2013

Key Words:
Allogeneic stem cell transplantation
Reduced-intensity conditioning
Antithymocyte globulin

A B S T R A C T

Nonmyeloablative (NMA) regimens allow the use of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients considered unfit for standard myeloablative conditioning (MAC) regimens using high-dose alkylating agents with or without total body irradiation (TBI). Reduced-intensity conditioning (RIC) regimens, based on fludarabine (Flu), busulfan (Bu), and rabbit antithymocyte globulin (r-ATG), represent an intermediate alternative between NMA and MAC regimens. This platform was subsequently optimized by the introduction of i.v. Bu and the use of 5 mg/kg r-ATG, based on the hypothesis that these modifications would improve the safety of RIC allo-HSCT. Here we report a study conducted at our institution on 206 patients, median age 59 years, who underwent allo-HSCT after conditioning with Flu, 2 days of i.v. Bu, and 5 mg/kg r-ATG (FBx-ATG) between 2005 and 2012. The prevalence of grade III-IV acute graft-versus-host disease (GVHD) was 9%, and that of extensive chronic GVHD was 22%. Four-year nonrelapse mortality (NRM), relapse, and overall survival (OS) rates were 22%, 36%, and 54%, respectively. NRM tended to be influenced by comorbidities (hematopoietic cell transplantation–specific comorbidity index [HCT-CI] <3 versus HCT-CI ≥ 3: 18% versus 27%; $P = .075$), but not by age (<60 years, 20% versus ≥60 years, 25%; $P = .142$). Disease risk significantly influenced relapse (2 years: low, 8%, intermediate, 28%, high, 34%; very high, 63%; $P = .017$). Both disease risk (hazard ratio [95% confidence interval]: intermediate, 2.1 [0.8 to 5.2], $P = .127$; high, 3.4 [1.3 to 9.1], $P = .013$; very high, 4.0 [1.1 to 14], $P = .029$) and HCT-CI (hazard ratio [95% confidence interval]: HCT-CI ≥3, 1.7 (1.1 to 2.8), $P = .018$) influenced OS, but age and donor type did not. The FBx-ATG RIC regimen reported here is associated with low mortality and high long-term disease-free survival without persistent GVHD in both young and old patients. It represents a valuable platform for developing further post-transplantation strategies aimed at reducing the incidence of relapse, particularly in the setting of high-risk disease.

© 2014 American Society for Blood and Marrow Transplantation.

INTRODUCTION

Nonmyeloablative (NMA) regimens allow the use of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients unfit for standard myeloablative conditioning (MAC) regimens, such as cyclophosphamide (Cy) and full-dose total body irradiation (TBI; 12 Gy) or Cy and busulfan (Bu). NMA regimens are associated with reduced nonrelapse mortality (NRM) and exert disease control relying solely on the allogeneic graft-versus-tumor immune reaction [1,2].

Reduced-intensity conditioning (RIC) regimens deliver a higher degree of myeloablation than NMA regimens but a lower level than MAC regimens. RIC regimens usually include an intermediate dose of alkylating agents, and thus retain a direct antitumor effect, with the risk of higher NRM [3,4]. We previously reported that an RIC regimen composed of an intermediate dose of oral Bu and a low dose of r-ATG resulted in higher disease control, but also in higher NRM compared with a 2-Gy TBI NMA conditioning regimen, with similar overall outcomes [5,6]. We found that with such a conditioning regimen, both graft-versus-host disease (GVHD) and NRM could be satisfactorily controlled without loss of disease control by only a marginal increase in r-ATG dose and a switch from oral to i.v. Bu [7,8].

Here we report the outcome of the first 206 consecutive patients who were treated with this protocol before undergoing allo-HSCT from an HLA-identical related donor or an unrelated donor. With a minimal follow-up of 7 months and a median follow-up of 28 months, our results strongly suggest that although the population is characterized by high-risk features, this protocol allows for an encouragingly high survival rate without disease recurrence or persistent debilitating chronic GVHD.

PATIENTS AND METHODS

Selection Criteria

Patients with the following criteria were included in our analyses: (1) allo-HSCT performed between 2005 and 2012; (2) RIC based on Flu, i.v. Bu

Financial disclosure: See Acknowledgments on page 373.

* Correspondence and reprint requests: Didier Blaise, MD. Institut Paoli Calmettes, 232 boulevard Sainte Marguerite, 13009 Marseille, France
E-mail address: blaised@ipc.unicancer.fr (D. Blaise).

1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.11.030

(Bx), and r-ATG (FBx-ATG); (3) allo-HSCT from a matched related donor (MRD) or 10/10 HLA-matched unrelated donor (MUD); and (4) peripheral blood stem cells (PBSCs) as the graft source. Our Institutional Review Board approved this study, and all patients provided informed consent in accordance with the Declaration of Helsinki.

Conditioning Regimen and GVHD Prophylaxis

The FBx-ATG conditioning regimen was started on day -6 and included Flu (Fludara; Bayer, Puteaux, France) 30 mg/m^2 daily from day -5 to day -1, Bx (Busilvex, Pierre Fabre, Boulogne-Billancourt, France) 130 mg/m^2 once daily on days -4 and -3, and r-ATG (Thymoglobuline, Genzyme, St. Germain-en-Lay, France) 2.5 mg/kg once daily on days −2 and −1 or on days −3 and −2, as reported previously [9]. Cyclosporine A (Sandimmun; Novartis, Bâle, Switzerland), started on day −1, was used for postgraft immunosuppression. Stem cell harvesting and supportive care were performed as described previously [5].

Stratification of Risk of Relapse and NRM

The risk of relapse in our cohort of patients with different hematologic diseases was characterized using the disease risk index (DRI) as described by Armand et al. [10]. Comorbidities were assessed using the hematopoietic cell transplantation–specific comorbidity index (HCT-CI) [11].

Study Endpoints and Statistical Analysis

The cumulative incidence of GVHD was calculated as described previously [12,13]. NRM and relapse were determined using the Prentice estimation and the Gray test, which allow consideration of competing events [14,15]. Progression-free survival (PFS) and OS were calculated with the Kaplan-Meier method and the log-rank test [16]. In patients who survived without disease recurrence, the prevalence of immunosuppressive treatments served as a surrogate marker of quality of life. Time to events was calculated from the date of allo-SCT. Cox regression was used to analyze the impact of pretransplantation covariates in multivariate analyses of PFS and OS [17]. All survival analyses were performed using R version 2.13.1 (http://www.R-project.org).

RESULTS

Patient and Transplantation Characteristics

A total of 206 consecutive patients were included in our analyses. Baseline patient and transplantation characteristics are described in Table 1. The median patient age was 59 years (range, 19 to 71 years), and 32 patients were age ≥65 years. One hundred and twenty-four patients (60%) underwent transplantation from an MRD. Only 25 patients (12%) presented with a low disease risk index, and 90 patients (46%) had an HCT-CI ≥3. Seventy-six patients (37%) were not in complete remission at the time of transplantation. The median duration of post-transplantation follow-up was 28 months (range, 7 to 76 months).

Table 1
Patient, Disease, and Transplantation Characteristics (n = 206)

Characteristic	Value
Age, yr, median (range)	59 (19-71)
Donor, n (%)	
MRD	123 (60)
MUD	83 (40)
Diagnosis, n (%)	
Acute myelogenous leukemia	70 (34)
Myelodysplastic syndrome	19 (9)
Acute lymphoblastic leukemia	9 (4)
Non-Hodgkin lymphoma	41 (20)
Hodgkin lymphoma	14 (7)
Chronic lymphoblastic leukemia	14 (7)
Multiple myeloma	31 (15)
Myeloproliferative neoplasm	6 (3)
Chronic myelogenous leukemia	2 (1)
Disease risk index, n (%)	
Low	25 (12)
Intermediate	125 (61)
High	48 (23)
Very high	8 (4)
HCT-CI, n (%)	
0-2	107 (54)
≥3	90 (46)
Unknown	9

GVHD, NRM, and Relapse

Post-transplantation events and outcomes of the 206 patients are presented in Table 2. All but 1 patient engrafted. The cumulative incidence of grade III-IV acute GVHD was 9%, and that of extensive chronic GVHD was 22%. The incidence of grade III-IV acute GVHD was higher in patients age ≥60 years (14% versus 5% in those age <60 years; $P = .021$), that of extensive chronic GVHD was similar in the 2 age groups (25% in those age <60 years versus 19% in those aged ≥60 years; $P = .367$). Forty-three patients died of nonrelapse-related causes at a median of 6 months (range, 0.4 to 30 months) after allo-HSCT. NRM was estimated at 5% (95% confidence interval [CI], 2% to 8%) at day +100, 16% (95% CI, 12% to 22%) at 1 year, and 22% (95% CI, 16% to 29%) at 4 years (Figure 1A). NRM was only marginally influenced by comorbidities (18% in patients with HCT-CI <3 versus 27% in those with HCT-CI ≥3; $P = .075$), and was not influenced by age (20% in patients age <60 years versus 25% in those age ≥60 years; $P = .142$). Sixty-three patients experienced disease recurrence, at a median time of 7 months (range, 0.3 to 68 months) after allo-HSCT, for a 2-year cumulative incidence of relapse of 28% (95% CI, 22% to 34%) (Figure 1A). DRI had a significant correlation with the incidence of relapse at 2 years (low, 8%; intermediate, 28%; high, 34%; very high, 63%; $P = .017$).

PFS and OS

One-year PFS was 63% (95% CI, 56% to 70%), and 1-year OS was 73% (95% CI, 67% to 79%) (Figure 1B). The causes of death are listed in Table 3. Multivariate analyses showed that age (<60 versus ≥60 years) or the donor type (MRD versus MUD) did not influence PFS and OS (Table 4). For PFS, DRI was the most significant predictive factor, and the predictive value of HCT-CI was close to significance (Table 4). HCT-CI (2-year OS, 73% for <3 versus 54% for ≥3; $P = .020$; Figure 2A) and DRI (2-year OS, 84% for low versus 68% for intermediate versus 47% for high versus 25% for very high; $P = .008$; Figure 2B) had a significant influence on OS (Table 4).

Immunosuppressive Treatment and GVHD in 1-Year Progression-Free Survivors

At 1 year after allo-HSCT, 122 patients were alive and progression-free. Among these survivors, 96 (79%) were surviving without GVHD without immunosuppressive treatment (IST) (n = 89; 73%) or with tapering IST (n = 7; 6%). Seven patients (6%) were surviving with IST for persistent extensive chronic GVHD.

Table 2
Outcomes after Allo-SCT (n = 206)

Outcome	Value
Acute GVHD, n (%)	
Grade II-IV	23 (17-29)
Grade III-IV	9 (5-13)
Chronic GVHD, n (%)	
Overall	37 (30-44)
Extensive	22 (17-28)
NRM at 4 yr, n (%)	22 (16-29)
Relapse at 4 yr, n (%)	36 (28-44)
PFS at 4 yr, n (%)	41 (34-50)
OS at 4 yr, n (%)	54 (46-64)
Follow-up, mo, median (range)	28 (7-76)

Download English Version:

https://daneshyari.com/en/article/2102018

Download Persian Version:

https://daneshyari.com/article/2102018

Daneshyari.com