Biol Blood Marrow Transplant 23 (2017) 140–146

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Late Complications and Quality of Life after Reduced-Intensity Conditioning Allogeneic Stem Cell Transplantation

Aline Clavert [1,†], Zinaida Peric [1,*,‡], Eolia Brissot [1], Florent Malard [1], Thierry Guillaume [1], Jacques Delaunay [1], Viviane Dubruille [1], Steven Le Gouill [1,2,3,4], Beatrice Mahe [1], Thomas Gastinne [1], Nicolas Blin [1], Jean-Luc Harousseau [1,2,3,§], Philippe Moreau [1,2,3], Noel Milpied [1,5,‖], Mohamad Mohty [1,6,7,¶], Patrice Chevallier [1]

[1] *Service d'Hématologie Clinique, Centre Hospitalier et Universitaire (CHU) de Nantes, Nantes, France*
[2] *Université de Nantes, Nantes, France*
[3] *INSERM CRNCA UMR 892, Nantes, France*
[4] *Centre d'Investigation Clinique en Cancérologie (CI2C), CHU de Nantes, Nantes, France*
[5] *Université de Bordeaux, Bordeaux, France*
[6] *Universite Pierre & Marie Curie, Paris, France*
[7] *INSERM UMRs 938, Paris, France*

Article history:
Received 18 July 2016
Accepted 12 October 2016

Key Words:
Reduced-intensity conditioning
Long-term effects
Quality of life

A B S T R A C T

Late complications (LC) and quality of life (QOL) were analyzed in 110 adult patients who underwent reduced-intensity conditioning (RIC) allogeneic stem cell transplantation (allo-SCT) and were alive for more than 2 years after allo-SCT. Overall survival of these patients was 93% (95% confidence interval [CI], 88% to 99%) and 81% (95% CI, 71% to 94%) at 5 and 10 years, respectively. The primary cause of death was a recurrence of primary malignancy. With a median follow-up of 4.6 years (range, 2 to 12.1), chronic graft-versus-host disease (cGVHD) was the most prevalent late effect, with a cumulative incidence of 66% (95% CI, 57% to 74%) at 10 years. Cardiovascular complications were the most prevalent LC with a cumulative incidence of 47% (95% CI, 35% to 59%), followed by pulmonary complications with a cumulative incidence of 33% (95% CI, 21% to 46%) and renal impairment with a cumulative incidence of 34% (95% CI, 25% to 43%) at 10 years. Secondary malignancies occurred with a cumulative incidence of 11% (95% CI, 5% to 20%) at 10 years. In this series, 61 patients (55%) responded to QOL survey. With the use of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 and Functional Assessment of Cancer Therapy–Bone Marrow Transplant questionnaires, most of the patients reported good to excellent QOL and patients with cGVHD had significantly lower QOL than patients without cGVHD. In conclusion, QOL after RIC is comparable to that seen after myeloablative conditioning, while the natural history of LC after RIC appears to be different from that described in the standard myeloablative setting, warranting further research in this field.

INTRODUCTION

Expanding indications and increasing eligibility have led to a growing number of allogeneic stem cell transplantations (allo-SCT) being performed yearly worldwide. Moreover, improvements in transplantation techniques and supportive care have resulted in a reduction of transplantation-related mortality and a growing number of long-term allo-SCT survivors. However, mortality rates among allo-SCT patients remain higher than those for the general population for at least 10 years after transplantation [1-4]. These risks are related to the late complications (LC) and long-term effects, which occur secondary to treatment exposures before and during allo-SCT. These complications not only

Financial disclosure: See Acknowledgments on page 145.

* Correspondence and reprint requests: Zinaida Peric, MD, PhD, School of Medicine, University of Zagreb, Salata 3, 10 000 Zagreb, Croatia.
E-mail address: zina_peric@yahoo.com (Z. Peric).
† Current address: Aline Clavert: Service d'Hématologie, CHU d'Angers, Angers, France.
‡ Current address: Zinaida Peric: School of Medicine, University of Zagreb, Zagreb, Croatia.
§ Current address: Jean-Luc Harousseau: Centre Régional de Lutte contre le Cancer (CRLCC) René Gauducheau, Nantes, France.
‖ Current address: Noel Milpied: Service d'Hématologie, CHU de Bordeaux, France.
¶ Current address: Mohamad Mohty: Service d'Hematologie Clinique et Therapie cellulaire, Hopital Saint-Antoine, Paris, France.

http://dx.doi.org/10.1016/j.bbmt.2016.10.011
1083-8791/

contribute to late mortality but also cause substantial morbidity and impair long-term health-related quality of life (QOL). Information about QOL is now considered to be an index of the effectiveness of treatment because it provides a broader understanding of the patient's status beyond simple disease-free survival. It is a multidimensional construct comprised of several related domains including physical, emotional, social, and role functioning, as well as a person's overall evaluation of his or her well-being and ability to function [5,6].

Most of the research on LC and QOL in long-term survivors has been performed among patients receiving myeloablative conditioning therapy (MAC) before allo-SCT [4,7-9]. However; allo-SCT is being increasingly performed with reduced-intensity-conditioning (RIC), especially in elderly or frail patients not eligible for standard MAC. The natural history of LC and QOL after RIC-allo SCT tends to be similar to those observed with myeloablative treatments, but data are still sparse in this setting. A recent study by Madden et al. described LC in children who underwent RIC-allo SCT for nonmalignant disorders [10].

In this study, we sought to identify LC and QOL in long-term adult survivors after RIC allo-SCT performed in our institution for both malignant and nonmalignant disorders. The awareness of long-term effects and QOL after RIC allo-SCT is crucial to providing adapted pretransplantation counseling and recommendations for post-transplantation screening, prevention, and early treatment.

MATERIALS AND METHODS

Study Design

This was a single-center retrospective study of consecutive patients who underwent a RIC allo-SCT at the University Hospital of Nantes (CHU de Nantes, Nantes, France) between 1998 and 2008 and were alive at least 2 years after transplantation. The study was approved by the local institutional review board and was performed according to the international ethics standards for human subjects per the Declaration of Helsinki.

Late Effects and Complications Evaluation

All time-related data were measured from the day of allo-SCT. Patients beyond 2 years after allo-SCT and without chronic graft-versus-host-disease (cGVHD) were seen in the outpatient clinic every 6 months for the first 3 years and yearly after that. They had a physical examination and blood was collected for peripheral blood cell counts and tests of immunologic status, liver, kidney, heart, pulmonary, thyroid, and gonadal function. If necessary, radiologic, histologic, or gynecologic evaluations were also undertaken. Patients with cGVHD were followed up more often. Organ- specific specialists were engaged in this outpatient clinic. Per study definition, cardiovascular, pulmonary, renal, endocrine disorders, and secondary cancer were considered as LC, whereas cGVHD, infections, and psychological disorders were evaluated as late effects, separately.

Quality of Life

For evaluation of QOL, all surviving patients received 2 questionnaires at the time of this study. We used 1 general measure questionnaire—European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and 1 allo-SCT–specific questionnaire— Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT). The EORTC QLQ-C30 [11] is a cross-culturally validated questionnaire of 30 questions, which contain 5 multi-item functional scales (physical, role, emotional, cognitive, and social functioning) and a combined global health status/QOL scale. Higher scores on these scales indicate better functioning [11].Three symptom scales measure fatigue, pain, nausea, and vomiting, while 6 single items assess symptoms commonly reported by cancer patients (dyspnea, sleep disturbances, appetite loss, diarrhea, constipation, and financial impact). Higher scores on the symptom scales and single items represent greater symptoms or impairments. The FACT-G (general) [12,13] is a 27-item cancer-specific questionnaire consisting of the following 4 subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being. The FACT-BMT [14] adds a fifth subscale to the FACT-G, which assesses "additional concerns" including overall treatment effects and "regret" related to transplantation. Higher total scores on the FACT-G (range, 0 to 108) and FACT-BMT (range, 0 to 148) indicate better QOL [14,15].

Statistical Methods

All data were computed using the R package [16]. Overall survival was estimated with the Kaplan-Meier method. LC incidences were evaluated using the cumulative incidence method treating death as a competitive risk [17,18], and subgroups were compared using the Gray test [19]. Multivariate regression analysis was done by using the semi-parametric proportional hazards model of Fine and Gray. Comparisons of global QOL, physical, role, and social functioning between patients with or without cGVHD were based on the Mann-Whitney *U* test. A P value < .05 was considered to indicate statistical significance.

RESULTS

Study Population Characteristics

The characteristics of 110 patients included in the study are described in Table 1. Eighty patients received a fludarabine, busulfan, and antithymocyte globulin–based RIC regimen (73%), 11 patients (10%) received fludarabine and low-dose total body irradiation (TBI), and the remaining 19 patients (17%) received different chemotherapy-based RIC regimens. Standard GVHD prophylaxis and supportive care were used as already detailed elsewhere [20].

Table 1
Study Population Characteristics

Characteristic	Value
Patient age, median (range), yr	55 (20-68)
Patient gender	
Male	64 (58)
Female	46 (42)
Donor gender	
Male	57 (52)
Female	53 (48)
Diagnosis*	
Myeloid malignancies	34 (31)
Lymphoid malignancies	74 (67)
Aplastic anemia	2 (2)
Disease status†	
Standard risk	15 (14)
High risk	95 (86)
Stem cell source	
Bone marrow	9 (8)
PBSC	94 (86)
Cord blood	7 (6)
Donor type	
Matched related donor	67 (61)
Matched unrelated donor	35 (32)
Mismatched unrelated donor	8 (7)
Conditioning regimen	
With antithymoglobulin	85 (77)
Without antithymoglobulin	25 (23)
With TBI	23 (21)
Without TBI	87 (79)
GVHD prophylaxis	
CSA alone	64 (58)
CSA + MMF	43 (39)
CSA + MTX	3 (3)
CD 34⁺ cell count, median (range), $\times 10^6$/kg recipient body weight	6.0 (1.7-36.7)
Follow-up, median (range), yr	4.5 (2.0-12.1)

Data presented are n (%) unless otherwise indicated.
PBSC indicates peripheral blood stem cells; CSA, cyclosporine A; Morbus Hodgkin MMF, mycophenolate, mofetil; MTX, methotrexate.
* Myeloid malignancies include 24 acute myeloid leukemia, 3 chronic myeloid leukemia, 7 myelodysplastic syndrome/myeloproliferative syndrome; and lymphoid malignancies include 35 non-Hodgkin lymphoma, 13 Morbus Hodgkin, 14 chronic lymphoid leukemia, 1 acute lymphoid leukemia, 10 multiple myeloma, 1 histiocytosis.
† Patients in complete remission, chronic phase or untreated were considered as a standard risk; all others were considered as high risk.