Leukemia Research 59 (2017) 1–7

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

Prognostic factors on graft-versus-host disease-free and relapse-free survival after allogeneic hematopoietic stem cell transplantation for adults with acute leukemia

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ARTICLE INFO

Keywords:
Prognostic factors
Hematopoietic stem cell transplantation
Acute leukemia
Graft-versus-host disease
Graft-versus-host disease-free and relapse-free survival

ABSTRACT

The cure of acute leukemia by allogeneic hematopoietic stem cell transplantation (allo-HSCT) is closely linked to major complications leading to adverse outcomes, including graft-versus-host disease (GVHD), disease relapse and death. This study retrospectively investigated a consecutive series of 312 adult patients with acute leukemia receiving allo-HSCT by using a novel concept of GVHD-free/relapse-free survival (GRFS), and further evaluated the impact of clinical factors on GRFS. Results indicated that the 1- and 2-year GRFS were 54.8% and 51.5%, respectively. In multivariable analysis, recipient age > 35 years (HR 1.676; p = 0.006), diagnosis of acute lymphoblastic leukemia (HR 1.653; p = 0.027) and acute biphenotypic leukemia (HR 2.175; p = 0.010), advanced disease (HR 2.702; p < 0.001), and donor age > 35 years (HR 1.622; p = 0.008) were significantly associated with inferior GRFS post-HSCT. GRFS of haploidentical-related donor transplant was comparable to that of matched sibling donor or matched unrelated donor transplant. Furthermore, prophylactic donor lymphocyte infusion (DLI) had an overall beneficial effect on GRFS (HR 0.645, p = 0.044). Collectively, with a better understanding of these significant prognostic factors which impacted on GRFS, we can effectively evaluate the risk and probability of real recovery after allo-HSCT, further optimizing the therapeutic avenues for acute leukemia.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative therapy for many hematologic malignancies. The outcome of the treatment is usually determined by two critical factors: relapse-related mortality and transplantation-related morbidity or mortality (TRM) [1]. Despite recent progress, it is difficult to mitigate one cause of mortality while without compromising the other. For instance, efforts at reducing TRM with reduced-intensity condition (RIC) and T-cell depletion of allograft may lead to increased risk of relapse [2–5]. Likewise, intensified chemotherapy can lower relapse-related motility, but in the meantime, it can significantly raise the risk of fatal organ damage, graft-versus-host disease (GVHD) or infection [3]. Consequently, HSCT cannot be effectively evaluated fully by focusing on TRM or relapse alone.

To address this problem, the Blood and Marrow Transplant Clinical Trails Network proposed a composite outcome of GVHD-free/relapse-free survival (GRFS) in trails of allogeneic HSCT, in which the endpoint events included grade 3–4 acute GVHD (aGVHD), systemic treatment-requiring chronic GVHD (cGVHD), relapse, and death. To this end, GRFS represents real recovery without ongoing morbidity [6,7]. To further understand the clinical factors which can effectively impact on GRFS in patients with acute leukemia after HSCT, we retrospectively reviewed 312 adult patients with acute leukemia treated with HSCT between 2008 and 2014 in our institution, and further investigated overall GRFS, disease-free survival (DFS), and overall survival (OS) at 1 and 2 years after HSCT. Through this way, we aim to identify reliable prognostic factors which can effectively predict the outcome of acute leukemia patients treated with HSCT in order to optimize therapeutic avenues.

2. Patients and methods

2.1. Study design and patient population

A consecutive series of 312 adult patients (age ≥18 years) with acute leukemia receiving allogeneic HSCT between Mar 2008 and October 2014 in our institution was enrolled in this retrospective

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http://dx.doi.org/10.1016/j.leukres.2017.05.011
Received 10 February 2017; Received in revised form 20 April 2017; Accepted 12 May 2017
Available online 12 May 2017
0145-2126/

Table 1
Clinical characteristics of patients.

	Whole cohort (N = 312)	MSD recipients (N = 139)	MUD recipients (N = 98)	HRD recipients (N = 75)	P
Median age. Years (range)	30 (18–61)	33 (18–61)	28 (18–54)	27 (18–54)	0.011
Gender					0.135
Male	199 (63.8%)	85 (61.2%)	59 (60.2%)	55 (73.3%)	
Female	113 (36.2%)	54 (38.8)	39 (39.8%)	20 (26.7%)	
Diagnosis					0.674
AML	142 (45.5%)	68 (48.9%)	39 (39.8%)	35 (46.7%)	
ALL	124 (39.7%)	54 (38.8%)	44 (44.9%)	26 (34.7%)	
ABL	29 (9.3%)	11 (7.9%)	10 (10.2%)	8 (10.7%)	
CML-BP	17 (5.4%)	6 (4.3%)	5 (5.1%)	6 (8.0%)	
Status					0.020
CR	233 (74.7%)	113 (81.3%)	72 (73.5%)	48 (64.0%)	
NR	79 (25.3%)	26 (18.7%)	26 (26.5%)	27 (36.0%)	
genetics					0.661
unfavorable	91 (29.2%)	37 (26.6%)	30 (30.6%)	24 (32.0%)	
other	221 (70.8%)	102 (73.4%)	68 (69.4%)	51 (68.0%)	
Conditioning					0.336
Myeloablative-TBI	198 (63.5%)	84 (60.4%)	68 (68%)	46 (61.3%)	
Myeloablative-chemotherapy	114 (36.5%)	55 (39.6%)	30 (30.6%)	29 (38.7%)	
Cell source					< 0.001
PBSC	241 (77.2%)	133 (95.7%)	98 (100%)	10 (13.3%)	
BM + PBSC	71 (22.8%)	6 (4.3%)	0 (0%)	65 (86.7%)	
Donor/recipient sex combination					0.001
male donor to male recipient	111 (35.6%)	40 (28.8%)	45 (45.9%)	26 (34.7%)	
Female donor to male recipient	71 (22.8%)	29 (20.9%)	30 (30.6%)	12 (16.0%)	
Female donor to female recipient	42 (13.5%)	25 (18.0%)	9 (9.2%)	8 (10.7%)	
Female donor to male recipient	88 (28.2%)	45 (32.4%)	14 (14.3%)	29 (38.7%)	
Age of Donor					< 0.001
35 years	197 (63.1%)	78 (56.1%)	80 (81.6%)	39 (52.0%)	
> 35 years	115 (36.9%)	61 (43.9%)	18 (18.4%)	36 (48.0%)	
Time interval					0.112
< 12 months	274 (87.8%)	128 (92.1%)	82 (83.7%)	64 (85.3%)	
> 12 months	38 (12.2%)	11 (7.9%)	16 (16.3%)	11 (14.7%)	
DLI					0.656
no	223 (71.5%)	96 (69.1%)	73 (74.5%)	54 (72.0%)	
yes	89 (28.5%)	43 (30.9%)	25 (25.5%)	21 (28.0%)	

investigation. All living patients had been routinely followed until October 2016. Clinical data including gender, age, donor type, diagnosis of disease, status of disease, GVHD, conditioning regimens, and other clinical characteristics and complications were gathered. DFS was defined as the period after the last transplantation until death or relapse of the underlying malignancy was detected; OS was defined as the period from transplantation to death. Advanced leukemia was defined as disease status of NR before HSCT was performed. GRFS events were defined as grade 3–4 aGVHD, cGVHD requiring systemic immunosuppressive treatment, disease relapse, or death from any cause during the first 12 and 24 months after allogeneic HSCT. For GRFS events, all data were considered as the first posttransplant event during 12 and 24 months. The impact of each clinical factor on 1- and 2-year GRFS was investigated. This retrospective study was approved by our institutional ethical review boards according to the revised Helsinki Declaration.

2.2. Donor type and conditioning regimens

High-resolution molecular typing for HLA-A, −B and −C, as well as HLA-DRB1 and −DQB1 were detected in all recipients and donors. Donors' type included matched sibling donor (MSD), matched unrelated donor (MUD), and haploidentical-related donor (HRD).

Five approaches of myeloablative conditioning regimens were adopted as described previously [8], including Bu (busulfan) + Flu (fludarabine), Bu + Cy (cyclophosphamide), TBI (total body irradiation) + Cy, TBI + Cy + etoposide (intensified myeloablative conditioning), and Flu + cytarabine + TBI + Cy + etoposide (sequential intensified conditioning). In general, conditioning regimens were selected on the basis of diagnosis, disease status and clinical situations at transplantation. Bu + Cy or Bu + Flu was administered to patients with acute myeloid leukemia (AML) in CR; TBI + Cy + etoposide or TBI + Cy was administered to patients with acute lymphoid leukemia (ALL) in CR; Flu + cytarabine + TBI + Cy + etoposide or TBI + Cy + etoposide was administered to patients with acute biphenotypic leukemia (ABL), blast phase of chronic myeloid leukemia (CML-BP) or advanced leukemia.

2.3. GVHD prophylaxis and prophylactic donor lymphocyte infusion (DLI)

CsA (Cyclosporine A) or CsA + MTX (methotrexate) was adopted for patients treated with HLA-matched sibling donor transplants; CsA + MTX + ATG (antithymocyte globulin) with or without mycophenolate was used in patients treated with unrelated donor or haploidentical transplants [8–10]. Grading of aGVHD was based on the scoring system of Glucksberg and Thomas, whereas the severity of cGVHD was identified by the scoring system of NIH [11,12].

Patients who were in NR regardless of minimal residual disease (MRD) or patients in CR and MRD were positive post-transplantation received prophylactic DLI in the circumstance that they did not suffer from aGVHD of grade 2 or above. After meeting the above conditions by day 60+ post-transplantation, the initial G-CSF-primed prophylactic DLI was treated at a median dosage of 1.0 (range 0.7–1.4) × 10^8