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Unrelated Transplantation for Poor-Prognosis Adult Acute Lymphoblastic Leukemia: Long-Term Outcome Analysis and Study of the Impact of Hematopoietic Graft Source

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Adults with high-risk acute lymphoblastic leukemia (HR-ALL) have a poor outcome with standard chemotherapy and usually undergo unrelated stem cell transplantation (SCT) if a matched sibling donor is not available. We analyzed the outcome of adult patients with unrelated SCT for HR-ALL and studied the possible effect of the hematopoietic stem cell source of the transplant. A total of 149 adult patients (median age, 29 years, range, 15-59 years) with HR-ALL underwent unrelated SCT in 13 Spanish institutions between 2000 and 2007. Patients in first complete remission (CR1) at transplantation had at least one adverse prognostic factor (advanced age, adverse cytogenetics, hyperleukocytosis, or slow response to induction therapy). ALL was in CR1 in 81 patients (54%), in second CR (CR2) in 37 patients (25%), in third CR (CR3) in 11 patients (7%), and with overt disease in 20 patients (13%). The hematopoietic source was unrelated cord blood (UCB) in 62 patients and an unrelated donor (UD) in 87 patients. The patients undergoing UCB-SCT and UD-SCT were comparable in terms of the main clinical and biological features of ALL, except for a higher frequency of patients with more overt disease in the UCB-SCT group. There was no statistically significant difference in overall survival (OS) or disease-free survival (DFS) at 5 years between the 2 groups. Treatment-related mortality (TRM) was significantly lower in the UCB-SCT group ($P = .021$). The probability of relapse at 1 year was 17% (95% confidence interval [CI], 7%-27%) for the UD-SCT group and 27% (95% CI, 14%-40%) for the UCB-SCT group ($P = .088$), respectively. Only disease status at transplantation (CR1, 41% [95% CI, 18%-64%] vs CR2, 51% [95% CI, 17%-85%] vs advanced disease, 66% [95% CI, 46%-86%]; $P = .001$) and the absence of chronic graft-versus-host disease (74% [95% CI, 46%-100%] vs 33% [95% CI, 17%-49%]; $P = .034$) were significant factors for relapse. All unrelated transplantation modalities were associated with high treatment-related mortality for adult HR-ALL patients without a sibling donor. UCB-SCT and UD-SCT were found to be equivalent options. Disease status at transplantation and chronic GVHD were the main factors influencing relapse in both transplantation modalities.

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INTRODUCTION

Adults with acute lymphoblastic leukemia (ALL) with high-risk features at diagnosis, recurrent disease, or slow response have a poor outcome with standard chemotherapy. Autologous stem cell transplantation (SCT) has not proved to provide any advantage for ALL patients in complete remission (CR), because of a high frequency of relapse [1,2]. Despite a high frequency of treatment-related mortality (TRM), allogeneic SCT remains the best therapeutic option in high-risk ALL [3-8]. High-risk adult ALL patients have a very poor outcome, with an expected disease-free survival (DFS) of only 35%-45% in many trials [9,10]. Consequently, in most transplantation centers, these patients are considered for alternative-donor SCT when a matched sibling donor is not available [11-14]. The alternative hematopoietic source can be a nonidentical relative, an unrelated donor (UD), or unrelated cord blood (UCB) units [15-22].

Long-term results of UD-SCT in adult patients are scarce, and the best unrelated progenitor source remains unclear. To date, no comparative study on the outcomes of adult ALL patients in Western countries who underwent UD-SCT based on the stem cell source has been published; the only related study is a recent report comparing unrelated bone marrow (BM) and UCB-SCT in Eastern adult patients with acute leukemia [23].

We retrospectively analyzed the outcome of adult patients undergoing unrelated SCT for poor-prognosis ALL in 13 transplantation centers in Spain between 2000 and 2007, focusing on the hematopoietic stem cell (HSC) source.

METHODS

Patients

A total of 149 adult patients (median age, 29 years; range, 15-59 years) with poor- prognosis ALL underwent an unrelated SCT in 13 Spanish institutions between 2000 and 2007. ALL was of precursor B cell lineage in 111 patients (74%), of T cell lineage in 28 patients (19%), and of undetermined lineage in 10 patients (7%). ALL was in first CR (CR1) in 81 patients (54%), in second CR (CR2) in 37 patients (25%), in third CR (CR3) in 11 patients (7%), and with overt disease in 20 patients (13%). Patients were treated with PETHEMA ALL-93 trial [10] or PETHEMA ALL-AR03 trial [24] protocols. After 2003, 39 patients with Philadelphia chromosome–positive ALL were treated with the CSTIBES02 trial protocol and received imatinib in combination with chemotherapy and SCT [25], with 25 undergoing UD-SCT and 14 undergoing UCB-SCT. The median time from diagnosis to SCT was 0.85 years (range, 0.08-16.48 years) for UD-SCT and 0.72 years (range, 0.06-11.10 years) for UCB-SCT. The hematopoietic progenitor source was a single unmanipulated UCB unit in 62 patients (41%), mobilized peripheral blood in 41 patients (28%), and unmodified BM in 46 patients (31%) (Table 1).

Table 1. Patient Characteristics According to Hematopoietic Progenitor Source

	UCB-SCT (n = 62)	UD-SCT (n = 87)	P
Age, years, mean (SD)	29 (9)	31 (11)	.180
Sex, M/F, n	39/23	51/36	.598
Diagnosis, n (%)			.138
B-lineage ALL	43 (69)	68 (78)	
T-lineage ALL	14 (23)	14 (16)	
Unspecified ALL	5 (8)	2 (2)	
No data	0	3 (3)	
Cytogenetics, n (%)	(n = 41)	(n = 66)	.053
Normal	3 (7)	6 (9)	
t(9;22)	26 (63)	39 (59)	
t(4;11)	5 (12)	4 (6)	
Complex	0	3 (5)	
Other abnormality	7 (17)	13 (20)	
No growth	0	1 (2)	
Extramedullary involvement at diagnosis, n (%)	3 (5)	6 (7)	.194
Disease status at transplantation, n (%)			.047
CR1	35 (56)	46 (53)	
CR2	10 (19)	27 (31)	
CR3	3 (5)	8 (9)	
Refractory	6 (10)	3 (3)	
Relapsed	8 (13)	3 (3)	

ALL indicates acute lymphoblastic leukemia; UCB-SCT, unrelated cord blood stem cell transplantation; UD-SCT, unrelated donor stem cell transplant; SD, standard deviation; CR1, first complete remission; CR2, second complete remission; CR3, third complete remission.

High-risk ALL was defined as in PETHEMA ALL-93 trial [10]. The criteria for indicating an unrelated SCT in CR1 was the presence of at least one of the following adverse prognostic factors: aged >30 years, white blood cell count (WBC) $>30 \times 10^9$/L, adverse cytogenetics (t [9; 22], t [4;11] or other 11q23 rearrangements, and t[1;19]), or slow response to induction therapy (defined as >10% blasts in BM on day 15 of induction therapy).

SCT Procedure

Before 2004, UD selection was based on HLA serotyping performed for class I antigens (HLA-A and -B antigens) and high-resolution genotyping for class II antigens (HLA-DR), and required 5 or 6 of 6 identities. After 2004, the requirements included 7 or 8 of 8 allelic identities (HLA-A, -B, -C, and -DR). The requirements for UCB-SCT were 4-6 of 6 HLA-A/-B antigenic and -DR allelic identities.

Conditioning therapy consisted of total body irradiation (TBI) and cyclophosphamide (Cy) in 68 patients (46%), busulfan (Bu) and Cy in 9 patients (6%), thiotepa-Bu-Cy or fludarabine in 60 patients