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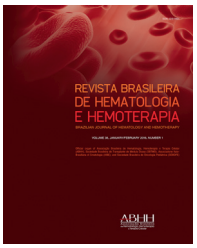

Original article

Allogeneic hematopoietic stem cell transplantation in patients with advanced indolent lymphoproliferative disorders

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ABSTRACT

Background: The role of allogeneic hematopoietic stem cell transplantation for advanced indolent lymphoproliferative disorders remains to be established.
Objective: This paper aims to describe the results of allogeneic hematopoietic stem cell transplantation in patients with advanced indolent lymphoproliferative disorders.
Methods: This article reports on 29 adult patients submitted to allogeneic transplantations from 1997 to 2010.
Results: Most had follicular non-Hodgkin lymphoma ($n = 14$) or chronic lymphocytic leukemia ($n = 12$). The median age was 44 years (range: 24–53 years) and 65% of patients were male. Only 21% had had access to rituximab and 45% to fludarabine. All had advanced disease (stage IV) with partial response or stable disease. Most underwent myeloablative conditioning $n = 17 – 59\%$). In this scenario, refractory disease was observed in seven (24%) patients, the 100-day mortality rate was 17% ($n = 5$) and relapse occurred in four patients (18%). The main cause of death throughout the follow up was refractory disease in six of the 12 patients who died. Moderate and severe chronic graft-versus-host disease was frequent; about 41% of 24 patients analyzed. The overall survival rates and disease free survival at 42 months were 56.7% and 45.4%, respectively. According to Kaplan–Meyer analysis, the median time from diagnosis to transplant predicted the overall survival; however age, gender and conditioning regimen did not predict the prognosis. It was impossible to reach other conclusions because of the small sample size in this study.
Conclusions: The role of allogeneic transplantations should be re-evaluated in the era of targeted therapy.

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Introduction

Hematopoietic Stem cell transplantation (HSCT) is frequently considered for eligible patients with non-Hodgkin lymphoma (NHL).[1–6] Autologous HSCT (auto HSCT) is recommended for patients with either relapsed NHL or those in first remission as consolidative therapy. NHL patients are usually considered for allogeneic HSCT (allo HSCT) because of the high rate of relapse seen even after chemotherapy and auto HSCT, and the potential benefit of a graft-versus-lymphoma (GvL) effect after allo HSCT. The outcomes for these patients in large prospective studies are lacking, and current directions and timing of selection for auto or allo HSCT are influenced by a variety of factors, including patient- or disease-related factors, physician preference, and institutional practices.[7–10]

Allo HSCT in indolent lymphoproliferative disorders allows a GvL effect, and the risk of graft contamination by residual tumor cells is avoided. However, the high transplant-related mortality (TRM) and nonrelated mortality (NRM) associated with myeloablative (MA) allo HSCT greatly limits the use of this approach. Allo HSCT is associated with a lower risk of relapse, but this reduced risk frequently does not translate to a survival benefit because of the excessive TRM.[11–14] Allo HSCT has been used as salvage therapy in relapsed lymphoma after previous auto HSCT; limited success was confined mostly to patients in remission with good performance status and a human leukocyte antigen (HLA)-matched sibling donor.[15]

Reduced-intensity conditioning (RIC) regimens are being increasingly used in patients with NHL.[5,6,16] These lower-intensity conditioning regimens reportedly have lower NRM, and can be used in older patients with comorbidities. Lower-intensity regimens for allo HSCT use lower doses of conditioning chemotherapy and radiation and rely on an immune-mediated GvL effect for disease control.[17,18] In the era of emerging novel therapies, the actual timing, optimal conditioning regimens, and long-term effects of the type of stem cell transplantation are unclear.

In this scenario, this paper describes the results of allo HSCT in 29 patients with advanced indolent lymphoproliferative disorders in two institutions in Brazil from 1997 to 2010.

Materials and Methods

Twenty-nine consecutive over 18-year-old patients with advanced indolent lymphoproliferative disorders who received allo HSCT between April 1997 and October 2010 in Hospital São Paulo (Universidade Federal de São Paulo – UNIFESP) and Hospital Santa Marcelina adult transplant program, were retrospectively included in this study (Table 1) by the analysis of patient medical records. Only 21% of the patients with B cell NHL received planned rituximab-based chemotherapy before allo HSCT. Patients were required to have chemotherapy-sensitive disease (or nonbulky stable disease) documented before allo HSCT and after induction or salvage chemotherapy. This study was approved by the Research Ethics Committees of both institutions. All patients provided informed consent in accordance with the Declaration of Helsinki. Clinical information was reviewed, and baseline characteristics were recorded, including data of common pre-transplant and transplant variables. All pathologic analyses were reviewed, and diagnosis was confirmed at the institution.

Table 1 – Patients, disease and transplant characteristcs (n = 29).

Variable	
Gender, n (%)	
Male	19 (65%)
Female	10 (34%)
Age, median (range), years	44 (24–53)
Diagnosis, n (%)	
Follicular	14 (48%)
CLL/LSC	12 (41%)
Mycosis fungoides	2 (7%)
Hairy cell leukemia	1 (3%)
Ann Arbor Stage IV, n (%)	29 (100%)
Number of prior regimens, n (%)	
≤2	22 (76%)
>2	7 (24%)
Time from diagnosis to HSCT, median (range), months	24 (8–186)
Disease status at time of transplant, n (%)	
Complete response	7 (24%)
Partial response or stable disease	22 (76%)
Prior radiation	3 (10%)
Prior rituximab	6 (21%)
Prior fludarabine	13 (45%)
Type of donor, n	
Matched related donor	28
Unrelated stem cell source	1
Type of conditioning, n (%)	
Reduced-intensity	12 (41%)
Myeloablative	17 (59%)
Moderate and severe GVHD, n (%)	
Acute	4 (14%)

CLL: Chronic lymphocytic leukemia; LSC: lymphoma of the spermatic cord; GVHD: Graft-versus-host disease.

Definitions and response criteria

Response criteria were based on the guidelines of the International Workshop on Non-Hodgkin Lymphoma.[18] Complete remission (CR) was defined as complete radiologic regression of all previous measurable disease and bone marrow involvement. Partial response (PR) was defined as a reduction of 50% in the sum of the products of the longest and perpendicular diameters of measurable lesions. Progression was defined as an increase of 25% or more in the sites of lymphoma or development of new sites of lymphoma at any time after transplantation. Relapse was defined as recurrence of lymphoma after a complete response. Based on these criteria, all data were verified individually regarding the best response status before HSCT.

Other outcomes analyzed include acute and chronic graft versus-host disease (GVHD) and cause of death. Acute GVHD (aGVHD) was defined and graded based on the pattern and severity of organ involvement using established criteria.[19] Chronic GVHD (cGVHD) was defined as the development of any