



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

Table 1 – Patients, disease and transplant characteristics (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 spermatogenic cord; GVHD: Graft-versus-host disease.

common pre-transplant and transplant variables. All pathologic analyses were reviewed, and diagnosis was confirmed at the institution.

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

Table 2 – Mortality within 100 days after transplant.

Patient	1	2	3	4	5
Age (years)	50	46	47	24	41
Gender	M	F	F	M	M
Disease	Follicular	Lymphocytic	Follicular	CLL	Follicular
Time from diagnosis to transplant (months)	25	186	16	28	14
Conditioning	CyMel	CyMel	FluTBI	CyTBI	FluTBI
Disease status	Refractory	Refractory	Refractory	Refractory	Refractory
Infection	VRE, candidemia	none	none	Fusarium	Pseudomonas
Days to death after transplant	32	33	24	53	81
Cause of death	Gastrointestinal bleeding, sepsis	Lung bleeding	VOD	Sepsis	perforated acute abdomen caused by necrosis of the tumor

M: male; F: female; CyMel: cytarabine and melphalan; FluTBI: fludarabine and total body irradiation; CLL: chronic lymphocytic leukemia; VRE: vancomycin-resistant enterococci; VOD: venous occlusive disease.

chronic GVHD based on clinical criteria.^{20,21} Both these events were summarized by the corresponding cumulative incidence estimate, with death without the development of GVHD as the competing risk. The World Health Organization criteria were used to define the histologic classification of NHL after 2001.

Transplant procedures

Thirteen patients received RIC [fludarabine and total body irradiation ($n=9$), fludarabine and cyclophosphamide ($n=2$), fludarabine and busulfan ($n=1$) or carmustine, etoposide, cytarabine and melphalan – BEAM ($n=1$)], and 16 received a MA regimen [cyclophosphamide and melphalan ($n=8$), busulfan and cyclophosphamide ($n=6$), or cyclophosphamide and total body irradiation ($n=2$)]. There was only one unrelated donor stem cell transplantation. All patients received GVHD prophylaxis with a calcineurin inhibitor and either methotrexate (MA regimen) or mycophenolate mofetil (RIC regimen).

Supportive care

All patients received standard supportive care as per institutional guidelines. Standard antimicrobial prophylaxis, surveillance cultures, and treatment were administered as per protocol.

Statistical analysis

Variables are described as medians and range for continuous variables, and percentage of total for categorical variables (Table 1). Occurrence of acute and chronic GVHD, relapse and mortality were calculated using cumulative incidence estimates, adjusted for the competing risk. Probabilities of progression free survival (PFS) and overall survival (OS) were estimated from the time of transplantation using Kaplan-Meier analysis. Univariate analysis was performed with disease and transplant-related variables to see the effect on long-term outcome of patients. The chi-square test was used to determine the relationship between all categorical variables. The Mann-Whitney *U* rank sum test was used to identify associations between continuous variables and categories. All reported *p*-values are two-sided with statistical

significance declared at a *p*-value <0.05 . Statistical analyses were performed using the Statistical Package for the Social Sciences software (version 20; IBM-SPSS, Chicago, IL, USA).

Results

Variables related to the patient, disease, and transplant outcomes are presented in Table 1. Twenty-nine eligible patients who underwent allo HSCT for advanced indolent lymphoproliferative disorders from January 1997 to December 2010 were included in this analysis. The median age was 44 years (range: 24–53 years). Half of the patients had follicular NHL. All patients were staged as Ann Arbor IVA or IVB. Most patients received less than three therapeutic regimens before allo HSCT, and only 21% had received rituximab. The median time from diagnosis until transplant was 24 months. Seventy-six percent of patients had partial response or stable disease at the time of the transplant. MA conditioning was used in 59%, especially in the first years of this study.

TRM was associated with refractory disease in the five patients that died before 100 days (Table 2). Sixteen patients had some grade of cutaneous, hepatic and gastrointestinal aGVHD, but only four had grade III or IV (Table 3). Of 24 patients, 18 had cGVHD, although just 12 with moderate or severe one. Four died of infection or other immunosuppression complications (Table 4). The OS and disease free survival (DFS) at 42 months were 56.7% and 45.4%, respectively (Figure 1). Age, gender, and conditioning regimen had no impact on the OS (*p*-value=0.0091, *p*-value=0.123 and *p*-value=0.290, respectively). Only less time between the diagnosis and transplantation improved the OS (*p*-value=0.031 – Figure 2). The median time from diagnosis to transplant was two years (range: 8–186 months). Younger patients have better

Table 3 – Acute graft-versus-host disease in 29 patients.

Site	Grade I-IV	Grade III or IV
Cutaneous	8	2
Hepatic	8	3
Gastrointestinal tract	7	1
Total	16 (55%)	4 (14%)

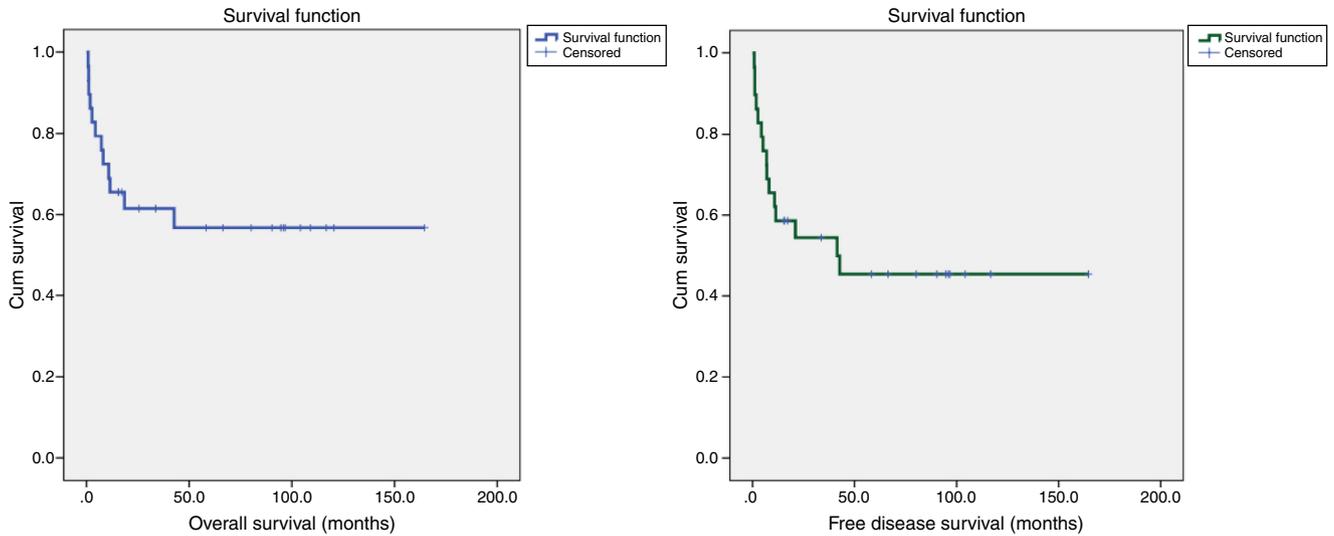


Figure 1 – Overall and disease free survival in advanced lymphoproliferative disorders and non-Hodgkin lymphoma after allogeneic hematopoietic stem cell transplantation.

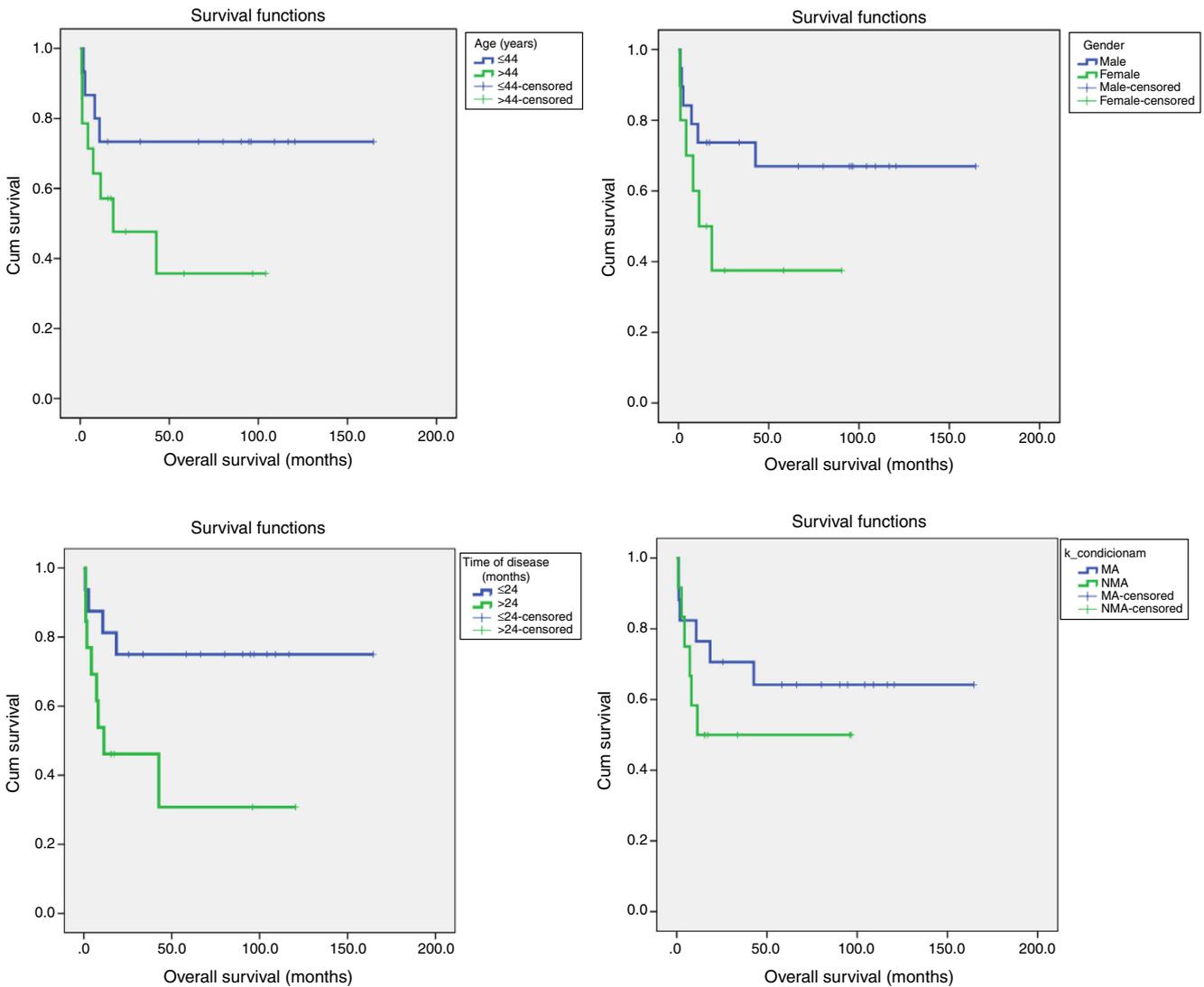


Figure 2 – Impact of age, gender, time of disease and conditioning on the overall survival.

Table 4 – Outcomes at five years of 24 patients in relation with chronic graft-versus-host disease (GVHD).

GVHD			
No (n=6)	Alive n=3		
	Dead n=3	Day + 129 (pneumonia)	
		Day + 218 (refractory, pneumonia) Day + 1280 (myocardial infarction)	
Yes (n=18)	Alive n=14	No treatment n=3	
		Under treatment n=11	
		Dead n=4	
	Day + 244 (refractory, sepsis) Day + 324 (severe pulmonary chronic GVHD, pneumonia) Day + 343 (accident on passage of catheter)		
		Day + 555 (chronic renal failure, infection)	

OS and men had better responses than women (p -value >0.05 for both).

Discussion

In the present study, 29 patients with advanced indolent lymphoproliferative disorders were analyzed after allo HSCT in two transplant centers in Brazil between April 1997 and October 2010. About 42 months after the transplant, 56.7% were alive and the DFS was 45.4%.

Indolent lymphoproliferative disorders, mainly NHL, comprise a variety of diseases with different incidence patterns in populations. Approximately 390,000 new cases and 199,000 NHL deaths were estimated in the world in 2012. There were 9800 new cases just in Brazil in 2014, that is, about five new cases for every 100,000 inhabitants.²² Like most cancers, the risk of NHL increases with age, often when patients are unable to get HSCT.

Generally, treatment of indolent NHL in Brazil is through the National Health System. According to the census department of the Brazilian Government, the *Instituto Nacional de Geografia e Estatística* (IBGE), the coverage of health insurance in Brazil is 24.7%. This cover is concentrated regionally, with 64% of insurance in 2012 being in the southeast.²³ There is a delay in the consolidation of the use of new medicines in the Brazilian NHS. Rituximab, for example, widely used in patients with indolent CD20⁺ NHL, was approved by the U.S. Federal and Drugs Administration (FDA) in 1998. In Brazil, the authorization to routinely use this drug was only published in 2009.²⁴⁻²⁶

Registry data from the European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR) show no plateau in relapse rates after autografting.^{11,27,28} Furthermore, the risk of second malignancies after auto HSCT is not insignificant, ranging from 5% to 15% in several studies. Clinical evidence of a GvL effect after allo HSCT is suggested by a plateau in relapse risk that is reached 2–5 years following allo HSCT, indicating that a substantial proportion of lymphoma patients get long-term disease control (10–12 years), and relapses are uniformly low. Even patients with refractory or relapsed lymphoproliferative disorders are

benefited with allo HSCT. Early allo HSCT produces better OS and PFS rates. However, allo HSCT increases post-transplant complications, such as cGVHD. The timing to perform allo HSCT in these patients is not well defined.²⁹⁻³¹ The CIBMTR observed good results in patients with NHL submitted the allo HSCT. On analyzing 1248 over 40-year-old patients after RIC or non-myeloablative regimens (NMA) for aggressive ($n=668$) or indolent NHL ($n=580$), it was noted that allo HSCT is a good therapeutic option even for over 55-year-old patients, giving an OS of 40% in three years. There is an increase in prolonged remission; the report concluded that allo HSCT is underused in this group of patients.³²

In the cohort of advanced indolent lymphoproliferative disorder patients of this study, only the time from diagnosis to transplant was significantly important (p -value = 0.031). The median time from diagnosis to transplant was two years. The therapeutic option of allo HSCT in these patients was only for advanced disease. A fact that may have contributed to the delay in time from diagnoses to transplant was the increased use of rituximab and possible transient disease control. At the beginning of this study, when rituximab was less available, patients were treated with first line therapy, and according to indication, were directly referred for transplant. In the later years, the patients tried to receive rituximab through the court of justice, thereby postponing the transplant.

Younger patients had better, albeit not statistically significant, responses than older patients. Women had worse results than men, but again without statistical significance. This could indicate that men have better home care than women, in this group.

The conditioning was MA in 59% of patients. This represents the period of transition from using MA to RIC in Brazil. TRM was associated with refractory disease in the five patients that died before 100 days than the refractoriness was the most common cause of transplant failure especially in the last years of this study when the RIC had become routine in transplant centers. There was an increase in allo HSCT for refractory and long-term disease, particularly with the possibility of performing transplants in the elderly and in patients with comorbidities. The benefits that could have been visible with the decrease of the NRM, ended up being masked by the change in the profile of transplant patients. Possibly RIC was not enough to treat refractory disease in these cases. A MD Anderson study showed excellent DFS and OS (85% and 83%, respectively) after a median follow-up of five years for relapsed follicular NHL after RIC using fludarabine, cyclophosphamide and rituximab followed by allo HSCT. The incidences of grade II–IV acute and chronic GVHD were 11% and 0%, respectively. They analyzed 47 indolent NHL patients submitted to allo HSCT from March 1999 to April 2005.¹⁷

At the start of immunochemotherapy, most patients had no access to these medicines. It remains to be seen what the response will be after the regular use of these drugs as first line treatment and access to transplant in accordance with institutional standard protocols. It is certain that, as agents that target pathways such as phosphoinositide (PI) kinase, histone deacetylase and immunomodulators gain U.S. FDA approval for various NHL histologies, the role of timing of HSCT will become even more complex. Incorporating these agents as maintenance strategies following RIC and allo HSCT or even

auto HSCT is certainly very attractive. We believe that future clinical trials should aim to consider these novel agents in the transplant and after the transplant period.

Conflicts of interest

The authors declare no conflicts of interest.

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