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Favorable Outcomes from Allogeneic and Autologous Stem Cell Transplantation for Patients with Transformed Nonfollicular Indolent Lymphoma

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A B S T R A C T

The role of allogeneic (allo-) and autologous stem cell transplantation (auto-SCT) in the management of patients with transformed indolent nonfollicular non-Hodgkin lymphoma is unknown. This is a multicenter, retrospective cohort study of patients with biopsy-proven indolent B cell nonfollicular non-Hodgkin lymphoma and simultaneous or subsequent biopsy-proven aggressive histology transformation who were treated with allo-SCT or auto-SCT between 1996 and 2013. All patients received myeloablative conditioning regimens. Outcomes were compared with a cohort of 246 patients with transformed follicular lymphoma who also underwent allo-SCT (n = 47) or auto-SCT (n = 199) across the same institutions and time frame. Thirty-four patients were identified with the following underlying indolent histologies: 15 (44%) marginal zone lymphoma, 11 (32%) chronic lymphocytic leukemia, 6 (18%) small lymphocytic lymphoma, and 2 (6%) lymphoplasmacytic lymphoma. Patients received various anthracycline or platinum-containing chemotherapy regimens for transformation, incorporating rituximab in 25 (74%). Twelve (35%) subsequently underwent allo-SCT, whereas 33 (65%) underwent auto-SCT. The 3-year overall survival rate after transplantation was 67% (allo-SCT 54%, auto-SCT 74%), and 3-year progression-free survival rate was 49% (allo-SCT 40%, auto-SCT 54%). The 3-year nonrelapse mortality rate was 14% (allo-SCT 15%, auto-SCT 7%). Transplant-related mortality at 100 days was 17% for allo-SCT and 0% for auto-SCT. Adjusted for type of stem cell transplantation, 3-year overall survival, progression-free survival, and nonrelapse mortality rates were similar to those of patients with transformed follicular lymphoma receiving allo-SCT and auto-SCT ($P = .38$, $P = .69$, and $P = .54$, respectively). Allo-SCT and auto-SCT may be reasonable treatments for selected patients with transformed nonfollicular indolent lymphoma, although medium-term outcomes and toxicity appear to be more favorable with auto-SCT.

INTRODUCTION

Patients with indolent non-Hodgkin lymphomas may experience disease transformation to aggressive histology

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lymphoma during the course of their disease. This risk is approximately 2% to 3% per year in patients with follicular lymphoma (FL) [1-4]. The incidence and clinical course of patients with other nonfollicular indolent histologies experiencing transformation appear to be similar based on limited data [5-8].

Several studies suggest that certain patients with transformed indolent lymphomas may benefit from allogeneic (allo-) or autologous stem cell transplantation (auto-SCT). However, these studies have included only patients with transformed FL [9-16] or a minority of patients with other indolent histologies [17-25]. No large studies have evaluated SCT strategies exclusively in patients with transformed non-FL, with the exception of Richter's transformation in chronic lymphocytic leukemia [26-28]. Therefore, the purpose of this study was to evaluate outcomes after allo-SCT or auto-SCT in patients with transformed non-FL and to compare them with a similar population of patients with transformed FL undergoing the same treatments.

METHODS

Patient Identification

This is an international, multicenter cohort study of patients with transformed non-FL who were treated with allo-SCT or auto-SCT during 1996 to 2013. Canada has no centralized transplant data repository, and therefore all transplant centers in the Canadian Blood and Marrow Transplant Group were contacted. These transplant centers reported all cases with transformed indolent lymphoma treated with SCT, which were combined into a database of 391 patients. Results for the subgroup of patients with transformed FL were previously published [14] but not for those with transformed nonfollicular indolent histologies. In Australia, there is a voluntary but complete registration and reporting process to a national stem cell transplantation registry. However, for this study, data for all eligible similar transplant cases treated only at Peter MacCallum Cancer Centre, Melbourne, Australia, were collected from the institutional database.

Adult patients with biopsy-proven indolent non-Hodgkin lymphoma and subsequent biopsy-proven aggressive histology B cell lymphoma transformation treated with allo-SCT or auto-SCT were included. Patients who initially presented with simultaneous indolent and aggressive histologies (discordant or composite) were excluded. Patients transplanted for a subsequent diagnosis of Hodgkin lymphoma or T cell lymphoma and those with a clinical diagnosis of transformation without biopsy confirmation were excluded. Patients with an initial diagnosis of aggressive lymphoma with a subsequent indolent histology relapse were also excluded. Pathology was reviewed at each academic center for transformed lymphoma cases before SCT.

Disease and Treatment Data

Standard staging investigations, including computed tomography scans and bone marrow biopsies, were completed at the time of diagnosis and transformation. 18-F deoxyglucose positron emission tomography scans were not routinely performed. Advanced stage at transformation was defined as Ann Arbor stage III or IV or stage I or II with B symptoms or bulky disease ($\geq$10 cm).

At the time of transformation, patients received at least 1 cycle of combination chemotherapy, most commonly anthracycline or platinum-containing, with or without rituximab. Response to chemotherapy was retrospectively interpreted by participating physicians according to the 1999 International Working Group criteria [29]. Patients underwent allo-SCT or auto-SCT for any episode of transformation (first or subsequent relapse) and were selected for SCT primarily on the basis of chemosensitivity. Similar criteria were applied for response evaluation after allo-SCT or auto-SCT. The choice of chemotherapy regimens, SCT type, stem cell source and mobilization procedures, graft-versus-host disease prophylaxis, and supportive care followed individual institutional standards.

Statistical Analysis

Overall survival (OS), calculated from the date of allo-SCT or auto-SCT to the date of last follow-up or death from any cause, was the primary endpoint. Progression-free survival (PFS), calculated from the date of allo-SCT or auto-SCT to the date of last follow-up (censored observations) or subsequent progression, relapse, or death from any cause (events), was a secondary endpoint. Nonrelapse mortality (NRM) was calculated from the date of allo-SCT or auto-SCT to the date of last follow-up (censored observations) or death from any cause before lymphoma relapse or progression (events). Death within 100 days of transplant was considered as transplant-related mortality.

Outcomes were also compared with a cohort of 246 patients with transformed FL treated with either allo-SCT (n = 47) or auto-SCT (n = 199) across the same institutions, countries, and time period, identified within the databases described above. Patient characteristics at diagnosis, transformation, and transplantation were compared between groups using Fisher's exact test for discrete variables and Student's *t*-test for continuous variables. Three-year OS, PFS, and NRM rates were estimated using the Kaplan-Meier method and compared using the log-rank test [30]. Data were analyzed using SPSS version 14.0 for Windows (SPSS Inc., Chicago, IL).

Table 1
Patient Characteristics at Time of Diagnosis of Indolent Lymphoma and Transformation

Characteristics	Allo-SCT (n = 12)		Auto-SCT (n = 22)		*P*
	n	%	n	%	
At diagnosis of indolent lymphoma					
Country					
Canada	10	84	15	68	.30
Australia	2	17	7	32	
Male gender	4	33	10	46	.72
Age at diagnosis, yr					
Median	48		53		.29
Range	24-64		32-64		
Indolent histology at original diagnosis					.05
Marginal zone lymphoma	3	25	12	55	
Chronic lymphocytic leukemia	6	50	5	23	
Lymphoplasmacytic lymphoma	2	17	0	0	
Small lymphocytic lymphoma	1	8	5	23	
Systemic regimens for iNHL					.90
0	3	25	4	18	
1	6	50	12	55	
2-3	3	25	6	27	
Pretransformation radiotherapy	1	8	5	23	.39
At diagnosis of transformation					
Year of transformation					1.0
1996-2005	7	58	12	55	
2006-2013	5	42	10	45	
Years from iNHL to transformation					.12
Median	2.1		2.9		
Range	.6-7.7		.4-18.3		
Transformation histology					.35
Diffuse large B cell lymphoma	11	92	22	100	
Burkitt-like lymphoma	1	8	0	0	
Advanced stage	12	100	19	86	.54
Elevated LDH*	3/7	43	12/19	63	.41
Systemic regimens for transformation					.85
1	8	67	14	64	
2	3	25	7	32	
3	1	8	1	4	
Last line of chemotherapy					.08
CHOP	7	58	5	27	
Platinum-containing	3	25	14	64	
Other†	2	17	3	14	
Last chemotherapy with rituximab	7	58	18	82	.22

iNHL indicates indolent non-Hodgkin lymphoma; LDH, lactate dehydrogenase; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone.

* Number of patients/number of patients with available data.

† Other regimens such as carmustine, etoposide, cytarabine, melphalan (mini-BEAM) and cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, methotrexate (hyper-CVAD).

RESULTS

Patient Characteristics

Patient and treatment characteristics are described in Tables 1 and 2. Thirty-four patients (25 Canada, 9 Australia) were identified with the following underlying indolent histologies: 15 (44%) marginal zone lymphoma, 11 (32%) chronic lymphocytic leukemia, 6 (18%) small lymphocytic