Biology of Blood and Marrow Transplantation 12:641-647 (2006)

1083-8791/06/1206-0006$32.00/0
doi:10.1016/j.bbmt.2005.12.040

Does Follicularity in Large Cell Lymphoma Predict Outcome after Autologous Stem Cell Transplantation?

Amrita Krishnan, Auayporn Nademanee, Henry Fung, Maria Angelopoulou, Arturo Molina, Karl Gaal, Andrew Dagis, Joycelynne Palmer, Joseph Alvarnas, Marilyn Slovak, Neil Kogut, Leslie Popplewell, Roberto Rodriguez, Jeffrey Schriber, Sean Wang, Stephen J. Forman

Division of Hematology/Hematopoietic Cell Transplantation, City of Hope Comprehensive Cancer Center, Duarte, California

Correspondence and reprint requests: Amrita Krishnan, MD, FACP, City of Hope Comprehensive Cancer Center, Division of Hematology/Hematopoietic Cell Transplantation, 1500 E. Duarte Rd., Duarte, CA 91010 (e-mail: akrishnan@coh.org).

Received June 20, 2005; accepted December 28, 2005

ABSTRACT

The purpose of this study was to evaluate whether follicular histology in large cell lymphoma influences treatment outcomes after autologous stem cell transplantation (ASCT). It remains an area of controversy whether the natural history of follicular large cell lymphoma (FLCL) is akin to diffuse large cell lymphoma (DLCL) with curative potential or is more similar to indolent follicular lymphomas with a pattern of late relapses after intensive chemotherapy. Although ASCT is a potentially curative treatment for patients with recurrent DLCL, the effectiveness of this approach in patients with FLCL is unclear. We undertook a retrospective analysis of 332 patients with large cell lymphoma who underwent ASCT at the City of Hope Comprehensive Cancer Center. With a median follow-up of 31 months, the projected 10-year overall survival and disease-free survival were similar between patients with FLCL and DLCL. Analysis of prognostic factors demonstrated that although age, chemotherapy refractoriness, and disease status at the time of ASCT were predictive of overall survival/disease-free survival, follicularity did not influence the outcome. Furthermore, the similar plateau in the survival curve for the DLCL and FLCL patients suggests that the behavior of FLCL is similar to that of DLCL and that FLCL is potentially curable with ASCT.

KEY WORDS

Follicular large cell lymphoma • Transplantation

INTRODUCTION

Over the past 20 years, several classification schemes have been developed for non-Hodgkin lymphoma (NHL) that are based on the observation that the clinical behavior of various follicular lymphomas can be highly variable and on the need for a more precise and reproducible system to guide clinicians. At present, the curative potential of follicular large cell lymphoma (FLCL), otherwise known as follicular grade 3 NHL in the Revised European-American classification (REAL) schema, remains an area of controversy [1]. Some series suggest that FLCL behaves as an indolent lymphoma characterized by late relapses after chemotherapy [2]. Other investigators have demonstrated high complete remission rates and plateaus in disease-free survival (DFS) when these patients were treated with an anthracycline-based regimen [3-5].

The role of autologous stem cell transplantation (ASCT) for this histologic subtype is also unclear. For patients with relapsed NHL, a prospective randomized study has demonstrated that high-dose chemotherapy/radiotherapy with ASCT is superior to conventional salvage therapy [6]. However, the number of patients with FLCL included in the study was small; hence, this question remain unanswered: is ASCT curative, or are there continued late relapses, as occur with other follicular histologic categories [7]? Several retrospective series have addressed this question, but with conflicting results [8,9]. In the Nebraska series, patients with good-prognosis FLCL had an improved survival compared with a similar group of patients

with diffuse large cell lymphoma (DLCL) [8]. In contrast, the series from Princess Margaret Hospital found no prognostic significance to FLCL versus DLCL histological findings [9]. Because of these conflicting results, we evaluated this question in a larger series of patients with sufficient long-term follow-up to capture late relapses.

MATERIALS AND METHODS

This was a retrospective study of 332 patients with large cell NHL who underwent ASCT at the City of Hope Comprehensive Cancer Center between December 1987 and November 2002. Fifty-five patients had FLCL, and 277 had DLCL. All biopsy specimens were reviewed at the City of Hope by an expert hematopathologist, and the most recent biopsy sample before ASCT was classified according to the REAL schema. All FLCL patients had either a core biopsy or excisional biopsy for diagnosis, and 14 of these patients underwent another biopsy at time of relapse before transplantation. Patients with T-cell lymphomas were excluded from analysis. Informed consent was obtained from patients, in compliance with institutional standards. Patients were considered eligible for transplantation if they had not achieved an initial complete remission or if they relapsed after attaining a complete remission with standard-dose chemotherapy. In addition, patients in first complete remission who had high-risk features, as defined by the International Prognostic Index (IPI), were also eligible for transplantation [10].

The median age at transplantation was 52 years (range, 27-63 years) and 46 years (range, 12-75 years) for the FLCL group and the DLCL group, respectively ($P = .005$). Other patient and disease characteristics are summarized in Table 1. A higher proportion of patients in the FLCL group had relapsed disease at the time of ASCT. However, both groups had comparable numbers with a chemotherapy-sensitive relapse. Sensitive relapse was defined as at least a 50% reduction in bidimensional measurements of the size of the tumor with the use of conventional salvage therapy. Patients were considered to be in partial remission if they had a >50% reduction in the diameter of all measurable lesions for at least 3 months and resolution of disease-related symptoms. Patients who had <50% reduction, reappearance of disease-related symptoms, or measurable growth of disease during therapy or within 2 months of completion of treatment were considered to have induction failure. There were more patients with bulky disease in the DLCL group, and there was more bone marrow involvement in the FLCL group. The IPI score was known in 143 patients. The median score was 2 in the FLCL group and 3 in the DLCL group. Cytogenetic information was available for 39 of the FLCL patients. Four of these patients had the 14,18 translocation: 2 in bone marrow and 2 in lymph nodes.

Transplantation screening criteria included normal cardiac function (defined as an ejection fraction >50% by either echocardiogram or multiple gated acquisition scan), adequate pulmonary function (diffusion capacity >50% or forced expiratory volume in 1 second >75% of predicted), and adequate renal function (24-hour creatinine clearance >60 mL/min). Patients were screened for hepatitis A, B, and C virus, though this was not an exclusion criterion. They were required to have no bone marrow involvement with lymphoma on their pretransplantation marrow except for patients with discordant lymphoma, who had <5% residual marrow involvement. There was no upper age limit on transplantation.

Bone marrow and/or peripheral blood progenitor cells (PBPCs) were collected. Methods for marrow and PBPC collection have been previously described [11]. No purging was performed of either marrow or PBPCs. Patients with prior bone marrow involvement at diagnosis received PBPCs. Before 1989, patients received a combination of bone marrow and PBPC. Starting in 1991, all patients received PBPCs preferentially.

Patients were treated with 1 of 3 transplant conditioning regimens. The choice of regimen was based on their prior chemotherapy sensitivity, age, and radiation history. The radiation-based regimen consisted of total body irradiation 1200 cGy delivered in split fractions, followed by etoposide 60 mg/kg (adjusted body weight) and cyclophosphamide 100 mg/kg (ideal body

Table 1. *Patient Characteristics*

Variable	FLCL (n = 55)	DLCL (n = 277)	*P* Value
Median age, y (range)	52 (27-63)	46 (12-75)	.005
Disease status	1 CR/1 PR: 11 (20%)	1 CR/PR: 112 (41%)	<.001
	IF 3 (6%)	IF 61 (22%)	
	REL 40 (74%)	REL 101 (37%)	
		Unk 4 (1%)	
Chemosensitive REL	16 (40%)	42 (70%)	.13
Bone marrow involvement at diagnosis	13 (23%)	35 (13%)	.03
FTBI conditioning	25 (66%)	146 (67%)	.92
Bulky disease >10 cm	9 (19%)	92 (39%)	.009

CR indicates complete remission; PR, partial remission; REL, relapse; Unk, unknown; FTBI, fractionated total body irradiation.