Biol Blood Marrow Transplant 21 (2015) 281–287

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Long-Term Outcomes of Patients with Persistent Indolent B Cell Malignancies Undergoing Nonmyeloablative Allogeneic Transplantation

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Article history:
Received 11 September 2014
Accepted 28 October 2014

Key Words:
Indolent lymphoma
Nonmyeloablative transplantation
Radioimmunotherapy

A B S T R A C T

Relapse is least common in patients with indolent B cell (iB) malignancies (ie, iB non-Hodgkin lymphoma [NHL]) who undergo nonmyeloablative allogeneic transplantation (NMAT) in complete remission (CR). However, for the many patients unable to achieve this state, outcomes are poorly described and methods to improve results are unknown. We sought to describe the long-term follow-up and predictive factors for these poor-risk patients unable to achieve CR before NMAT. We identified and evaluated patients with iB-NHL including chronic lymphocytic leukemia treated with fludarabine/total body irradiation–based NMAT that had evidence of persistent disease before NMAT. From December 1998 to April 2009, 89 patients were identified, most commonly with small/chronic lymphocytic lymphoma (n = 62) and follicular lymphoma (n = 24). Pretransplant anti-CD20 radioimmunotherapy (RIT) using standard yttrium-90-ibritumomab tiuxetan was administered to 18 patients (20%) who more frequently had chemoresistant disease (81% versus 39%, $P = .003$), disease bulk > 5 cm (61% versus 15%, $P < .001$), thrombocytopenia < 25k/μL (33% versus 7%, $P = .002$), and Hematopoietic Cell Transplant Comorbidity Index scores ≥ 3 (72% versus 37%, $P = .006$). After adjusting for these imbalances, RIT-treated patients had improved rates of progression-free survival (PFS) (hazard ratio [HR] = .4; 95% confidence interval [CI], .2 to .9, $P = .02$) and overall survival (OS) (HR = .3; 95% CI, .1 to .8, $P = .008$) compared with the non-RIT group. The 3-year adjusted estimates of PFS and OS for the RIT and non-RIT groups were 71% and 87% versus 44% and 59%, respectively. The use of RIT was the only factor independently associated with improved PFS and OS. Rates of nonrelapse mortality and graft-versus-host disease (GVHD) were similar between the 2 groups, although over 70% of patients developed clinically significant acute or chronic GVHD. In conclusion, despite relatively high rates of GVHD, patients with persistent iB-NHL can derive durable benefit from NMAT.

INTRODUCTION

Nonmyeloablative allogeneic hematopoietic cell transplantation (NMAT) is frequently cited as the only potentially curative intervention for advanced-stage indolent B cell non-Hodgkin lymphomas (iB-NHL) and chronic lymphocytic leukemia (CLL). These results have been demonstrated consistently in a number of series, with long-term relapse-free survival rates ranging from about 40% to 80% [1-7]. Furthermore, low rates of regimen-related toxicity and nonrelapse mortality (NRM) after NMAT make it feasible for older and/or more medically infirm patients. Improved methods of HLA typing and medical prophylaxis have also reduced the rates of severe graft-versus-host disease (GVHD), the most common complication of this treatment [8,9].

Financial disclosure: See Acknowledgments on page 286.

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http://dx.doi.org/10.1016/j.bbmt.2014.10.024
1083-8791/

Despite these successes, NMAT has limitations. Disease relapse remains the major concern after NMAT, particularly for patients with persistent/refractory disease at the time of transplantation with bulky disease sites [1,5]. Thus, it is believed that being in complete remission (CR) at the time of NMAT yields lower rates of relapse [2]. However, for patients with chemotherapy-refractory disease, the use of high-dose chemotherapy-based conditioning may be contemplated to achieve this goal. Unfortunately, identifying a regimen with effective antitumor activity in this setting remains challenging. Moreover, the risk of NRM may be prohibitive for such an approach, which can be estimated with tools such as the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) [10].

Radioimmunotherapy (RIT) is 1 strategy to augment NMAT, which delivers a therapeutic radionuclide to an antigen expressed on tumor cells via a monoclonal antibody. Anti-CD20 RIT-augmented NMAT using yttrium-90 (^{90}Y)-ibritumomab tiuxetan has been studied by our group and others, based on the hypothesis that chemoresistant tumors may remain radiosensitive, and achieving an early post-transplant CR with this approach could lead to better long-term outcomes [11-16]. These studies suggested the best outcomes were in patients with indolent histologies despite frequent high-risk clinical features, such as chemorefractory and bulky disease. However, to date, no formal comparative evaluation has been conducted to determine if such an approach is superior to more standard conditioning regimens.

To address this question and to better understand the utility of NMAT in patients with persistent iB-NHL, we identified a cohort of patients treated at our center meeting eligibility requirements of our prior RIT-NMAT trial but for other reasons did not enroll. These patients could then serve as a fair standard-treatment comparator to the RIT group. Herein, we describe the long-term outcomes for this unique population of patients and evaluate the impact of a RIT-augmented conditioning regimen on results.

METHODS

Study Cohort

We identified patients over age 18 years who presented to the University of Washington and Fred Hutchinson Cancer Research Center between December 1998 and April 2009 for NMAT as treatment for an iB malignancy, including CLL, follicular lymphoma, small lymphocytic lymphoma (SLL), marginal zone lymphoma, and hairy cell leukemia. We further selected patients with detectable disease at the time of NMAT, as assessed by imaging studies according to standard International Working Group definitions [17,18] or via flow cytometric analysis of peripheral blood or bone marrow. We excluded patients without evidence of disease, with large-cell histologic transformation, and who received NMAT from an HLA-mismatched donor. To control for potential imbalances, patients were only included in this analysis if they met the eligibility criteria for the RIT-based NMAT study, regardless of which treatment they received. For patients not treated on the RIT study, reasons they did not enroll included referral for NMAT outside of the enrollment period of this study, insurance denial, or preference of the treating physician or patient. Most patients included in this analysis were also included in prior publications by our group [4,5,13], but this report includes an additional 2 years of patients treated with standard NMAT and up to 5 additional years of post-NMAT follow-up for those studied previously.

All patients received conditioning with fludarabine 30 mg/m^2 for 3 days followed by 200 cGy total body irradiation, as previously described [4]. Patients in the RIT group also received the following, as previously published [13]: On day −21 before transplantation, 250 mg/m^2 of rituximab was administered before an imaging dose of ^{111}In-ibritumomab tiuxetan to ensure expected biodistribution. On day −14, 250 mg/m^2 of rituximab was administered before .4 mCi/kg of ^{90}Y-ibritumomab tiuxetan, with a maximum dose of 32 mCi. Postgrafting immunosuppression varied based on the specific protocol on which patients were treated, but all were based on the combination of a calcineurin inhibitor (ie,

Table 1
Baseline Characteristics of Patents Who Underwent NMAT for Persistent Indolent B Cell Malignancies

Patient Characteristic	Total (N = 89)		RIT Group (n = 18)		Control Group (n = 71)		P^*
	N	%	N	%	N	%	
Gender							.69
Male	66	74	14	78	52	73	
Female	23	26	4	22	19	27	
Age, yr							.95
Median	56		58		55		
Range	30-68		30-68		35-67		
Histology							.08
CLL/SLL	62	70	10	56	52	73	
FL	24	27	6	33	18	25	
Other[†]	3	3	2	11	1	1	
Number of prior therapies							.58
Median	4		4		4		
Range	1-12		3-12		1-11		
Prior rituximab	78	88	18	100	60	85	.07
Prior autologous transplant	16	18	4	22	12	17	.60
Chemoresistant[‡]	38	48	13	81	25	39	.003
Bulky disease (>5 cm)	22	25	11	61	11	15	< .001
HCT-CI score ≥ 3	39	44	13	72	26	37	.006
Unrelated donor	42	47	12	67	30	42	.06
Pre-NMAT platelet count < 25k/μL	11	12	6	33	5	7	.002

FL indicates follicular lymphoma.

[*] *P* values are from comparisons between the RIT and control groups.

[†] RIT group: marginal zone lymphoma (n = 1) and hairy cell leukemia (n = 1); control group: marginal zone lymphoma (n = 1).

[‡] Response to the last systemic therapy administered before NMAT was not available from 9 patients (2 from the RIT group and 7 from the control group).