Biol Blood Marrow Transplant 23 (2017) 53–59

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Phase II Study of Yttrium-90-Ibritumomab Tiuxetan as Part of Reduced-Intensity Conditioning (with Melphalan, Fludarabine ± Thiotepa) for Allogeneic Transplantation in Relapsed or Refractory Aggressive B Cell Lymphoma: A GELTAMO Trial

Monica Cabrero [1], Alejandro Martin [1,*], Javier Briones [2], Jorge Gayoso [3], Isidro Jarque [4], Javier López [5], Carlos Grande [6], Inmaculada Heras [7], Reyes Arranz [8], Teresa Bernal [9], Estefania Perez-Lopez [1], Oriana López-Godino [7], Eulogio Conde [10], Dolores Caballero [1]

[1] *Hematology Department, Hospital Universitario Salamanca and IBSAL (Instituto Biosanitario de Salamanca), Spain*
[2] *Department of Hematology, Hospital Santa Creu i Sant Pau, Barcelona, Spain*
[3] *Department of Hematology, Hospital Gregorio Marañon, Madrid, Spain*
[4] *Department of Hematology, Hospital La Fe, Valencia, Spain*
[5] *Department of Hematology, Hospital Ramón y Cajal, Madrid, Spain*
[6] *Department of Hematology, Hospital 12 de Octubre, Madrid, Spain*
[7] *Department of Hematology, Hospital Morales Messeguer, Murcia, Spain*
[8] *Department of Hematology, Hospital La Princesa, Madrid, Spain*
[9] *Department of Hematology, Hospital Central de Asturias, Oviedo, Spain*
[10] *Department of Hematology, Hospital Marqués de Valdecilla, Santander, Spain*

Article history:
Received 3 May 2016
Accepted 5 October 2016

Key Words:
Allogeneic transplantation
Reduced-intensity conditioning
Radioimmunotherapy
B cell lymphoma
Clinical trial

A B S T R A C T

We designed a phase II clinical trial including Y-90 ibritumomab-tiuxetan as part of a reduced-intensity conditioning (RIC) allogeneic stem cell transplantation (AlloSCT) in high-risk non-Hodgkin lymphoma (Clinical Trials Identifier: NCT00644371). Eligible patients had high-risk relapsed/refractory aggressive lymphoma. The conditioning regimen consisted of rituximab 250 mg (days –21 and –14), Y-90 ibritumomab IV (.4 m Ci/kg, day –14), fludarabine 30 mg/m² i.v. (days –3 and –2) plus melphalan 70 mg/m² i.v. (days –3 and –2) or 1 dose of melphalan and thiotepa 5 mg/kg (day –8). Donors were related. Eighteen patients were evaluable. At the time of transplantation, responses were complete remission (CR) (n = 7, 39%), partial remission (n = 6, 33%) or refractory disease (n = 4, 28%). Y-90-ibritumomab infusions were well tolerated, with no adverse reactions. Nonrelapse mortality at 1 year was 28%. Median follow-up was 46 (range, 39 to 55) months. Estimated 1-year progression-free survival (PFS) was 50%, and 4-year overall survival (OS) and PFS were both 44.4%. CR at the moment of AlloSCT had significant impact on PFS (71% versus 27%, $P = .046$) and OS (71% versus 27%, $P = .047$). Our results show that Y-90-ibritumomab-tiuxetan as a component of RIC for AlloSCT is feasible in patients with high-risk B cell lymphoma. Development of phase III clinical trials is needed to clarify the contribution of radioimmunotherapy to RIC AlloSCT.

INTRODUCTION

Allogeneic stem cell transplantation (AlloSCT) is a potentially curative option for patients with non-Hodgkin lymphomas (NHLs), even those for whom salvage chemotherapy or autologous stem cell transplantation (ASCT) have failed, based on the addition of an immune graft-versus-lymphoma (GVL) effect to cytotoxic treatment [1-3]. However, post-AlloSCT relapse continues to be a major cause of failure with this procedure [4], especially in chemorefractory or higher-risk patients [5]. The conditioning regimen may play an important role in early disease control until an effective GVL effect appears, but candidates for AlloSCT are usually heavily pretreated patients, have undergone a previous ASCT, or are too old and, therefore, cannot receive a conventional myeloablative conditioning regimen. Under these circumstances, nonmyeloablative AlloSCT is an alternative; however, the relapse rate is higher with reduced-intensity conditioning (RIC) [6], and so new drugs are needed to improve results.

Financial disclosure: See Acknowledgments on page 59.
All the hospitals and authors are members of Grupo GELTAMO.
* Correspondence and reprint requests: Alejandro Martin, MD, Hematology Department, Hospital Universitario de Salamanca/IBSAL, Paseo de San Vicente 54-182, 37007 Salamanca, Spain.
E-mail address: amartingar@usal.es (A. Martin).

http://dx.doi.org/10.1016/j.bbmt.2016.10.003
1083-8791/

Radioimmunotherapy (RIT) with yttrium-90 ibritumomab tiuxetan (Y-90-IB) is a promising approach for treating CD20-positive tumors, based on the binding of the radioisotope yttrium 90 to a murine antibody that targets CD20 (ibritumomab). This drug has been used to treat relapse/refractory NHL, in which it gave an 80% overall response rate (ORR) and 20% complete remission (CR) in the first phase III clinical trial [7]. It has also been included in ASCT conditioning regimens [8,9]. However, none of these approaches is a curative treatment for indolent lymphomas and they seem to be insufficient for treating many aggressive lymphomas. To manage relapse after conventional chemotherapy or ASCT, RIT has been proposed as part of RIC AlloSCT. Our hypothesis is that this strategy can enhance the initial cytotoxic effect of the conditioning regimen to allow the GVL effect to subsequently control the disease in higher-risk relapse patients. To explore the effect, in terms of survival and toxicity, of Y-90-IB added to a nonmyeloablative conditioning regimen with fludarabine and melphalan in AlloSCT, the GELTAMO group designed a phase II multicenter clinical trial. Here, we report the long-term follow-up results of the study with a median 4-years of follow-up.

PATIENTS AND METHODS

Study Design and Aims

This is a phase II multicenter clinical trial designed to analyze the efficacy and toxicity of Y-90-IB in the context of AlloSCT in CD20-positive NHL patients. The study was registered at www.clinicaltrials.gov as NCT 00644371. The clinical trial was conducted under the Ethical Principles for Medical Research Involving Human Subjects included in the World Medical Association Declaration of Helsinki. All the local ethics committee of the participating centers approved the trial. Written informed consent was obtained from all patients for the study following Good Clinical Practice rules.

The primary endpoint was to evaluate progression-free survival (PFS). The secondary endpoints were to analyze toxicity, overall survival (OS), relapse rate, and the incidence of acute and chronic graft-versus-host disease (GVHD).

Adverse events (AE) were notified by the official form of "serious and unexpected adverse reaction occurred in Spain" (RD 223/204), and were recorded in the protocol case record form, in accordance with World Health Organization criteria.

Patient Selection

Eligible patients were between 18 and 65 years of age and diagnosed with relapsed or refractory CD20-positive aggressive lymphoma, including diffuse large B cell lymphoma (DLBCL), follicular lymphoma grade 3B (FL), Burkitt lymphoma (BL), and mantle cell lymphoma (MCL), with 1 of the following criteria: (1) achievement of less than a partial response (PR) after 2 lines of therapy, (2) relapse after an ASCT, (3) positive positron emission tomography (PET) before or after ASCT, or (4) failure to mobilize stem cells for ASCT. Other inclusion criteria were Eastern Cooperative Oncology Group performance status ≤2 and no major organ dysfunction (bilirubin <2 mg/dL transaminases, gamma-glutamyl transferase and alcaline phosphatase <2 times upper limit of normal, ejection fraction >40%, and creatinine <2 mg/dL). Exclusion criteria included progressive disease at the time of transplantation, prior RIT, human immunodeficiency virus–associated lymphoma, pregnancy or breastfeeding, severe comorbidities, and allergy to murine antibodies or Y-90.

Statistical Analysis

Data were analyzed using SAS software (SAS Institute, v9.1.3, Cary, NC) and SPSS v.20 (IBM, Endicott, NY). *PFS* was defined as the time from AlloSCT to progression, relapse, or death from any cause. *OS* was defined as the time from the moment of AlloSCT to death from any cause. PFS and OS curves were estimated by the nonparametric Kaplan-Meier method, and the log-rank test was used to establish the statistical significance of every variable to survival. Patients were censored at day +100 for acute GVHD (aGVHD) and, when considering chronic GVHD (cGVHD) for any survival analysis, we conducted a landmark analysis [10] on day +100. A multivariate analysis was not performed because the limited number of patients. Cumulative incidence was calculated for the relapse rate and GVHD considering death from any other cause as a competitive risk [11]. Differences were considered statistically significant for values of $P < .05$.

A target sample size of 30 patients was calculated by the Fleming method for phase II clinical trials assuming a 80% power (beta is 20%) for detecting a significant improvement over 25% and a .05 alpha significance level (1-sided), a 65% target 1-year PFS and a 20% dropout rate. However, because of slow recruitment, the study was closed after including 20 patients.

TREATMENT PROTOCOL

Patients received rituximab 250 mg/m^2 on days –21 and –14, and .4 mCi/kg of Y-90-IB after the last rituximab dose (Zevalin, Spectrum Pharmaceutical, Henderson, NV); they also received fludarabine 30 mg/m^2 on days –7 to –3, and melphalan 70 mg/m^2 on days –3 and –2. Patients relapsing after a melphalan-containing high-dose therapy and ASCT within the last 6 months received only 1 dose of melphalan and thiotepa 5 mg/kg was added on day –8 (Figure 1).

GVHD prophylaxis consisted of cyclosporine A (CSPA) and methotrexate. Intravenous CSPA was given at a dose of .25 mg/kg from days –7 to –2, 1.5 mg/kg from day –1 to +1, and adjusted to blood levels afterwards. CSPA levels in peripheral blood were determined twice a week. After discharge, patients received CSPA per oral (p.o.) twice a day, which was tapered on day +56 in the absence of GVHD. Methotrexate followed by folic acid was administered intravenously at a dose of 15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6, and +11. Antimicrobial prophylaxis and supportive treatment were administered according to the standard of care of each center.

Patients were evaluated for response on days +100 and +180, +1 year after AlloSCT, and every 6 months for up to 2 years. Responses were scored using standard criteria [12] based on PET/computed tomography or computed tomography scan (in patients from center were PET where not available), as at the time of trial design, PET was not standardized in all centers of our group.

RESULTS

Patient Characteristics

Twenty patients were enrolled in the clinical trial in 10 referral centers for AlloSCT in Spain between June 2008 and April 2010. Two patients could not be evaluated because of screening failure, 1 of them because of disease progression before AlloSCT (the patient received the same conditioning regimen with Y-90-IB off protocol), and the other because of renal failure (the patient did not receive the drug). Thus, 18 patients were ultimately considered evaluable. The main characteristics of patients are listed in Table 1. The median age was 50 (range, 32 to 63) years and 44% of patients were older than 55 years. Diagnoses were of DLBCL (n = 6), MCL (n = 5), grade 3B FL (n = 4), transformed FL (n = 2), and BL (n = 1).

Patients had received a median of 3 lines of chemotherapy (range, 2 to 5 lines) and 45% of them had received at least 4 treatments. Ten patients (56%) had undergone a previous ASCT and relapsed, 7 patients were refractory to first-line chemotherapy, and 1 patient failed mobilizing autologous stem cells for an ASCT. Eleven patients (61%) had active disease at the time of the AlloSCT; of these, 6 (33%) were in PR, and 5 (28%) had stable disease. The other 7 patients (39%) were in CR at the time of the AlloSCT, 1 in first CR and 6 in second or subsequent CR. Regarding the 10 patients who received a prior ASCT; all of them had a CR after ASCT and subsequently relapsed. After different salvage therapy, only 2 of them achieved a CR before AlloSCT. Thiotepa was added to the conditioning regimen in 4 patients (2 PR and 2 stable disease [SD]).

Donor and Stem Cell Source

Donors were HLA-matched siblings in all patients. Granulocyte colony–stimulating factor–mobilized peripheral blood