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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*

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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.

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* 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).

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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

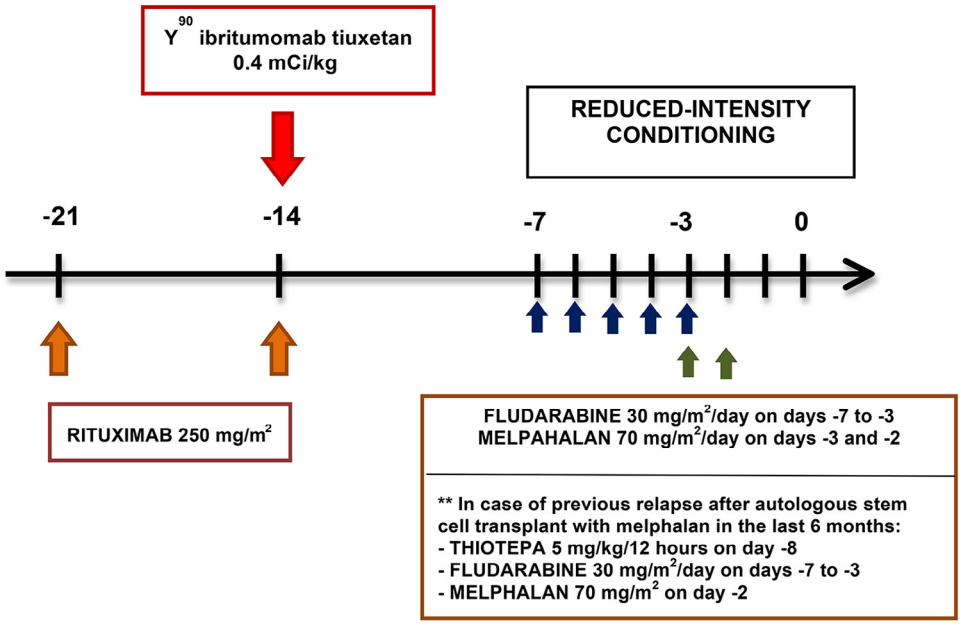

Figure 1. Treatment schema.

(n = 17) and bone marrow (n = 1) hematopoietic stem cells without any manipulation were infused on day 0.

Engraftment and Immune Reconstitution

The median times to attain more than 500×10^9/L granulocytes and more than 20×10^9/L platelets were 15 (range, 12 to 24) and 12 (range, 2 to 19) days, respectively. All patients engrafted and no cases of secondary graft failure were documented. At the last follow-up, 100% of living patients had achieved a CD4 cell count above 400/μL.

Table 1
Patient Characteristics

Characteristic	Value
Median age (range), yr	50 (32-63)
Sex	
Female	3 (17%)
Male	15 (83%)
Diagnosis	
Grade 3B FL	4 (22%)
Transformed FL	2 (11%)
DLBCL	6 (33%)
MCL	5 (28%)
BL	1 (6%)
IPI score	
II	3 (16)
III	5 (28)
IV	10 (56)
Previous lines of therapy	
2	3 (17%)
3	7 (39%)
4	5 (28%)
5	3 (17%)
Previous ASCT	10 (56%)
Related donor	18 (100%)
Disease status at AlloSCT	
CR	7 (39%)
PR	6 (33%)
SD	5 (28%)

Data presented are n (%) unless otherwise indicated.
IPI indicates International Prognostic Index.

GVHD

Thirteen patients (72.3%) developed aGVHD, with a median onset of 34 (range 12 to 82) days. The incidence of grades 2 to 4 aGVHD was 50%; 4 patients (22%) had grade 3 to 4 aGVHD.

cGVHD was present in 7 of the 12 evaluable patients (59%) and the median day of cGVHD appearance was 343 (range, 122 to 626); 3 patients (25%) developed limited cGVHD and 4 (33%) developed an extensive cGVHD. In 2 patients, cGVHD appeared after withdrawal of immunosuppression or donor lymphocyte infusions after disease relapse or progression.

At last follow-up, 6 of 8 (75%) living patients had discontinued immunosuppression and did not present signs of active cGVHD.

Response

On day +100, the ORR in 10 out of 14 evaluable patients was 71.5% response, with CR in 9 and PR in 1 of them. Four patients were not evaluated because of early mortality before day +100 (fungal infectious disease in 2 patients, septic shock in 1, and aGVHD in 1); all of them had refractory disease before AlloSCT. Of those patients with active disease (PR or SD) before AlloSCT (n = 11), the ORR was 36% (27% with CR) at day +100. Regarding different diagnosis, the CR rate was 75% for FL, 60% for MCL, and 50% for DLBCL. No CR was documented in the BL and transformed FL patient group. Table 2 shows the progress of response during follow-up.

Four patients had disease progression documented at day +100, resulting in an estimated cumulative incidence of relapse or progression of 26% at 4 years (Figure 2A); all relapses and progressions were documented early after transplantation, with a median of 3 (range, 1 to 3) months after AlloSCT. Among these relapsing and progressing patients, disease status at the moment of the AlloSCT was CR in 1, PR in 1, and SD in 2 cases.

Considering the causes of death, 4 patients (22%) died from disease progression and 5 died from infections (in 3 of whom infection occurred in the early post-AlloSCT period, 2

Table 2
Disease Response

Status at AlloSCT	Response at Day +100	Status at Last Follow-Up	Cause of Death
CR, n = 7	CR, n = 6	Alive in CR, n = 5	
		Death while in CR, n = 1	Viral encephalitis
	Relapse, n = 1	Death	Relapse of lymphoma
PR, n = 6	CR, n = 2	Alive in CR, n = 2	
	PR, n = 1	Death while in PR	Pneumonia (*Pseudomonas*)
	Progression, n = 1	Death	Progression of lymphoma
	Not evaluable, n = 2	Death before +100	Aspergillosis
SD, n = 5	CR, n = 1	Alive in CR	
	Progression, n = 2	Death	Progression of lymphoma
	Not evaluable, n = 2	Death before +100	Septic shock
			aGVHD

aspergillosis and 1 septic shock). The 2 remaining cases of fatal infections were 1 of pneumonia in a patient with refractory disease at day +100 and the other of a viral meningitis 1 year after AlloSCT. aGVHD was the cause of death in 1 of them. The mortality rate was higher among patients with poorer prognosis based on disease status (80% for PR/SD versus 29% for CR at the time of AlloSCT, $P = .067$).

PFS and OS

With a median follow up of 46 (range, 39 to 55) months, 8 patients (44.4%) were alive and disease-free at last follow-up. The estimated 1-year PFS (the primary objective of the trial) was 50%. The 4-year OS and PFS estimated by the Kaplan-Meier were both 44.4% (Figure 2B and 2C). Patients in CR at the time of transplantation had significantly better 4-year PFS (71% versus 27%; $P = .046$) and OS (71% versus 27%; $P = .047$), as shown in Figure 3A. Development of aGVHD was also associated with poorer 4-year OS (67% for grade 1 versus 22% for patients with grades 2 to 4 aGVHD), although the difference was not statistically significant ($P = .077$) (Figure 3B). Age, diagnosis, number of previous treatments, or receiving a prior ASCT were also included in the univariate analyses and had no significant impact on PFS or OS. In the particular case of previous ASCT, 4-year OS was 40 versus 50% for those

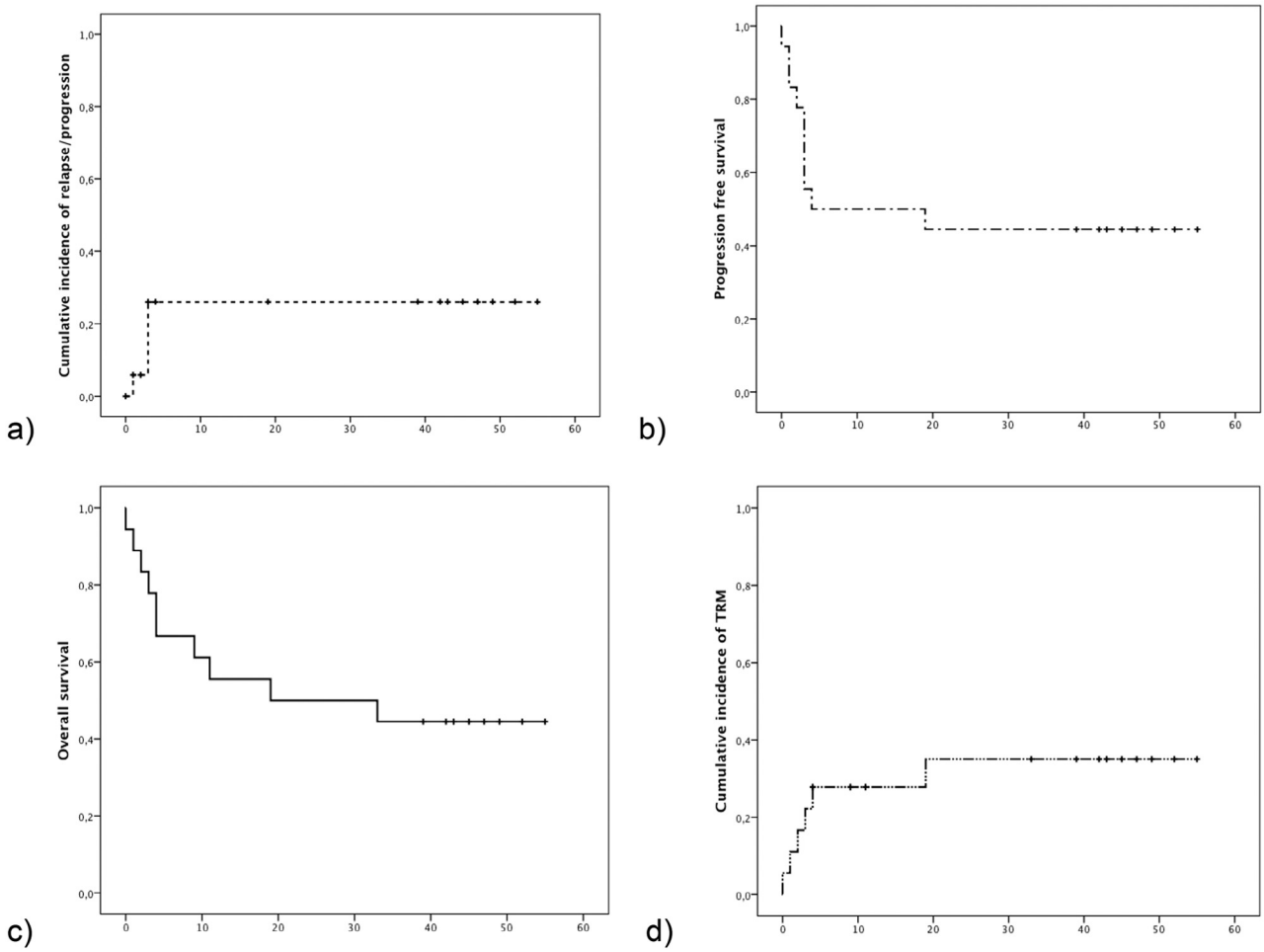

Figure 2. (A) Cumulative incidence of relapse/progression, (B) progression-free survival, (C) overall survival, and (D) transplantation-related mortality (TRM).

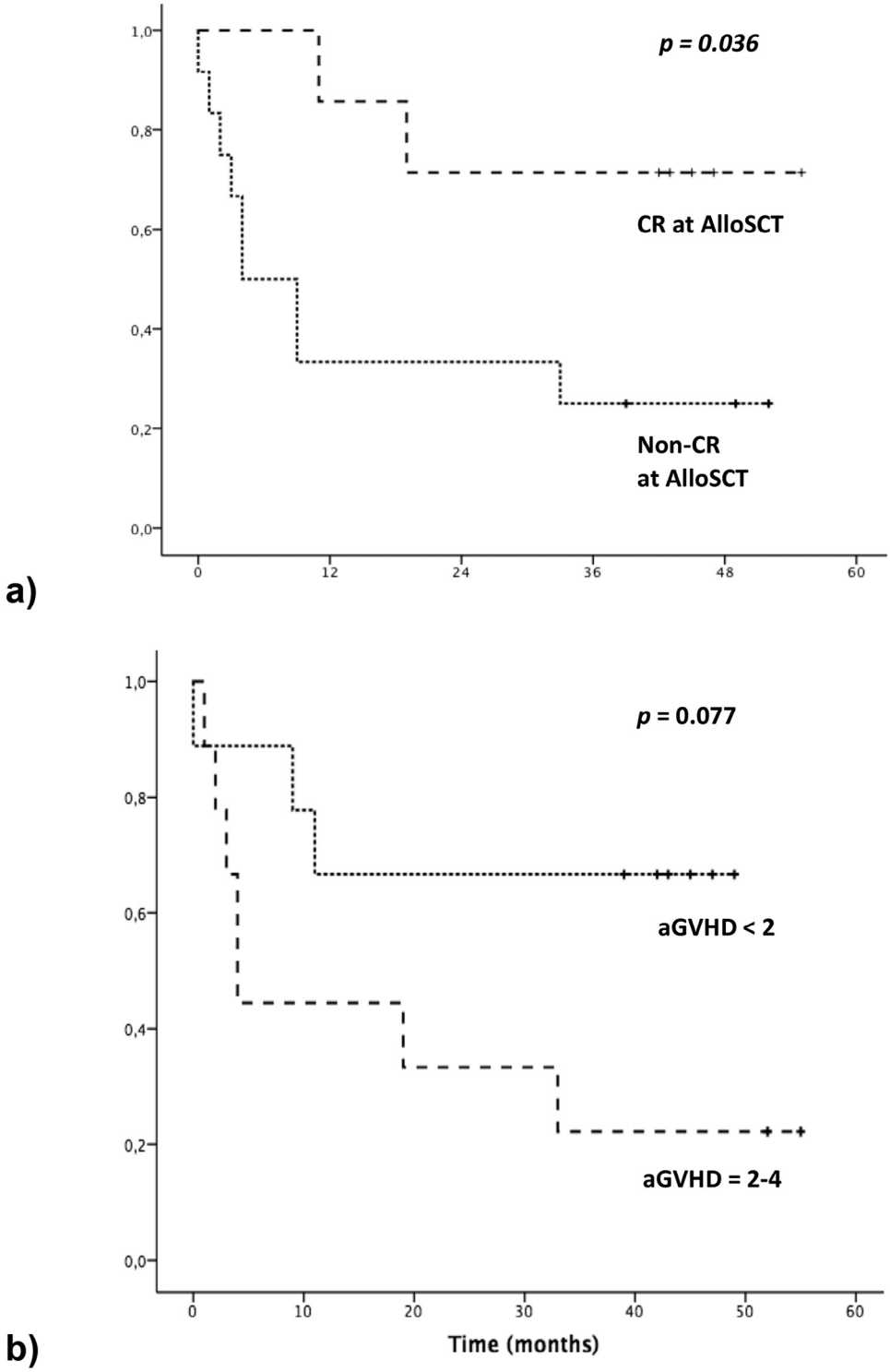

Figure 3. Overall survival depending on (A) status at AlloSCT, CR versus non-CR; $P = .036$. (B) Acute graft-versus-host disease (aGVHD).

receiving a previous ASCT or not ($P = .68$); PFS was also 40 versus 50% at 4 years ($P = .49$).

Early post-AlloSCT response was also an important variable affecting both OS and PFS in a landmark analysis at day +100. Patients achieving CR at day +100 had a markedly better prognosis in terms of 4-year OS (89% versus 20%; $P < .001$) and PFS (89% versus 0%; $P < .001$).

Nonrelapse Mortality

Nonrelapse mortality (NRM) at day +100 and 1 year after AlloSCT were 22% and 28%, respectively, with an overall NRM of 33% (n = 6) after 4 years of follow-up (Figure 2D). Age was the main prognostic factor for NRM: patients older than 55 years had significantly higher NRM at day +100 ($P = .039$). Presence of grades 2 to 4 aGVHD (44% versus 11%, $P = .074$)

Table 3
Published AlloSCT Series Including RIT in Conditioning Regimen

Study	n	Comments	Response to Transplantation	Median FU	OS/PFS	aGVHD	cGVHD	NRM
Shimoni et al. (2008)[15]	12	All with active disease before AlloSCT	CR + PR 83%	21 months	2 years: 33%/33%	Gr. II-IV: 67% Gr. III-IV: 50%	57%	42%
Bethge et al. (2010) [16]	40	DLBCLs and transformed lymphomas not included	CR 62% PR 32%	672 days	2 years: 51%/43%	Gr. II-IV: 43%	53%	45%
Abou-Nassar et al. (2010) [17]	12	10 FLs and 2 transformed FLs	CR 67%	31 months	2 years: 83%/74%	25%	63%	18%
Gopal et al. (2011) [14]	40	Includes 14 DLBCLs	CR 35% PR 25%	1.7 years	30 months: 54%/31%	Gr. I-III: 78% Gr. III: 10% No grade IV	20%	16%
Bethge et al. (2012) [18]	20	All with aggressive lymphomas	CR 45% PR 5%	1115 days	3 years: 20%/20%	Gr. II-IV: 45%	70%	30%
Khouri et al. (2012) [19]	26	All with FLs, 60% in CR/PR	CR 96%	33 months	3 years: 88%/85%	Gr. II-IV: 23%	39%	8%
Bouabdallah et al. (2015) [20]	31	Includes 14 DLBCLs and 5 transformed FLs. All in CR/PR	—	32 months	2 years: 80%/80%	Gr. II-IV: 27%		13%
GELTAMO series (present)	18	Includes high-grade NHLs	ORR 71.5% CR 64%	46 months	4 years: 44.5%	Gr. II-IV: 50% Gr. III-IV: 22%	59%	28%

FU indicates follow-up; GR, grade.

and non-CR at the time of the AlloSCT (37% versus 0%, $P = .136$) were also associated with higher NRM at day +100, although the differences were not statistically significant. Prior ASCT had no impact on NRM.

Conditioning Toxicity

All patients received the scheduled doses of treatment included in the conditioning regimen, with no dose reductions either in Y-90-IB or in the conventional drugs. Y-90-IB infusions were well tolerated, with no immediate adverse reactions reported. Eleven grade 3 or 4 AEs were reported during the trial. Grade 3 toxicities comprised diarrhea, cytomegalovirus enteritis, chronic renal failure exacerbation, congestive heart failure (2 cases), pleural effusion, and gland infection. The grades 4 AEs were 2 cases each of pneumonia and septic shock. Because these AEs are commonly observed in the context of AlloSCT, we cannot clearly relate them with Y-90-IB.

DISCUSSION

We present a multicenter phase II clinical trial in which Y-90-IB was included as part of a RIC regimen with melphalan and fludarabine for high-risk relapsed or refractory aggressive NHL, with the goals of increasing the antitumor effect and controlling disease early after AlloSCT without significantly increasing toxicity. The results of this study support the feasibility and safety of the approach, with a favorable toxicity profile with respect to adverse events. On the other hand, our main limitation is the small number of patients because of a slow recruitment.

In addition, our conditioning regimen was effective, resulting in a 4-year PFS of 44% after a very long median follow-up (46 months). Although the number of patients is small, these results are promising, considering the very poor prognosis of the study population: 61% of patients had active disease before AlloSCT, including around 30% of patients who did not even achieve PR with the last chemotherapy course before AlloSCT, and 56% of them had relapsed after a previous ASCT. However, although PFS was acceptable in this context, it did not achieved our assumed threshold of 65% at 1 year, probably because the consideration to calculate sample size was too optimistic considering the risk of patients included in the trial. At day +100 after Allo-SCT, 71.4% of the patients were in CR. This ORR was 36% among patients who underwent AlloSCT with active disease (PR or less than PR), which could be related to an enhanced antitumor effect due to the incorporation of Y-90-IB in the RIC regimen. According to our data, disease status at AlloSCT affects survival, but early disease control after the AlloSCT is also essential, since all patients who achieved CR at day +100 were disease-free at last follow-up. Although there was a small number of patients, we can assume that some intensification in the conditioning regimen, as RIT, could improve post-AlloSCT response in refractory NHL. In addition, similar results from other studies had been reported: chemosensitive patients have a better outcome after AlloSCT, especially for histologies that are less sensitive to the GVL effect [3,5,13], but the impact of day +100 response, supports the role of RIT in early disease control, which may subsequently be completed by long-term immune-mediated effect, as reported by Gopal et al. [14].

Although the greatest proportion of patients with PR before their transplantation failed to achieve remission, suggesting that the GVL effect had no impact on early post-AlloSCT response in patients with active disease, our results suggest a probable GVL effect in long-term responses, given that a previous high-dose regimen and ASCT had failed in many of our patients. Our 46-month median follow-up of our series is, to our knowledge, the longest reported in a clinical trial of Y-90-IB–containing RIC regimen for aggressive B cell lymphomas. At the time of the last analysis, no late relapses had been documented, which implies the role of a GVL effect in previously chemorefractory NHL.

We observed an estimated NRM in our series of 28% at 1 year after AlloSCT. This is not surprising considering the substantial proportion of high-risk patients in the study, since NRM was lower for young and good-prognosis patients (0% for young patients who underwent AlloSCT in CR). Regarding GVHD, we found a cumulative incidence of 50% grades 2 to 4 aGVHD and 59% for cGVHD. Although the fatal GVHD rate was low (6%), this group of patients tends to have a higher NRM, probably related to GVHD-associated comorbidity. With respect to cGVHD, 75% of patients had discontinued immunosuppressive therapy and were free of cGVHD signs or symptoms at last follow-up. It is difficult to compare these NRM and GVHD data with those of other series of RIT-based Allo-SCT (Table 3) because of the heterogeneity of the

patients, who had different types of indolent and aggressive lymphomas, pre-AlloSCT status, and GVHD prophylaxis. Series that included aggressive lymphomas or chemorefractory patients, in whom the GVL effect was forced with an early immunosuppression therapy withdrawal, showed similar results to our series [15,16,18]. On the other hand, the inclusion of indolent lymphomas, lower-risk patients, or the addition of antithymocyte immunoglobulin in GVHD prophylaxis seems to reduce both aGVHD and NRM in some series [17,19,20]. In the most recent reports by Khouri et al. [19], which differs from ours by the inclusion criteria (it included 26 FLs), and Bouabdallah et al. [20], which did not include refractory patients, the cumulative incidences of grades 2 to 4 aGVHD were 23% and 27%, respectively. Therefore, it seems that the addition of Y-90-IB by itself is not associated with a higher GVHD but the management of high risk of relapse patients is. Nonetheless, the first clinical trial published by Shimoni et al. [15], in which all the patients had persistent disease at the time of AlloSCT, had a cumulative incidence of aGVHD of up to 62% (Table 3).

Y-90-IB has also been employed as part of the conditioning regimen of ASCT. Our previous report of the efficacy of Zevalin, Bendamustine, Etoposide, Cytarabine, Melphalan and ASCT in chemorefractory patients, with 70% of CR at day +100 and an estimated OS and PFS of 63% and 61%, respectively [8], shows that RIT is highly efficient in the relapse/refractory aggressive lymphoma setting, although the only reported phase III trial with RIT (Bexxar-Bendamustine, Etoposide, Cytarabine, Melphalan) on ASCT has not shown it to be superior to Rituximab, Bendamustine, Etoposide, Cytarabine, Melphalan conditioning schema [21]. Given these controversial results and considering that no results from a phase III trial on AlloSCT have been published, the benefit of RIT in addition to a conventional conditioning regimen remains to be established. Therefore, a randomized phase III trial should be carried out so that the optimal role for RIT in AlloSCT can be clearly determined.

Our results show that the combination of Y-90-IB with fludarabine and melphalan as nonmyeloablative regimen is safe and well tolerated. However, the small number of patients included in the trial makes difficult to establish the exact role of Y-90-IB in this context. This question can only be answered by the design of randomized trials that allow us to optimize AlloSCT conditioning regimens in high-risk lymphoma patients.

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