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ORIGINAL ARTICLE

Radioimmunotherapy-augmented BEAM chemotherapy vs BEAM alone as the high-dose regimen for autologous stem cell transplantation (ASCT) in relapsed follicular lymphoma (FL): a retrospective study of the EBMT Lymphoma Working Party

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Relapse remains the most common cause of treatment failure in patients receiving autologous stem cell transplantation (ASCT) for follicular lymphoma (FL). The aim of this study was to evaluate the effect of adding radioimmunotherapy or rituximab (R) to BEAM (carmustine, etoposide, ara-c, melphalan) high-dose therapy for ASCT in patients with relapsed FL. Using the European Society for Blood and Marrow Transplantation registry, we conducted a cohort comparison of BEAM ($n = 1973$), Zevalin-BEAM (Z-BEAM) ($n = 207$) and R-BEAM ($n = 179$) and also a matched-cohort analysis of BEAM vs Z-BEAM including 282 and 154 patients, respectively. BEAM, Z-BEAM and R-BEAM groups were well balanced for age, time from diagnosis to ASCT and disease status at ASCT. The cumulative incidences of relapse (IR) at 2 years were 34, 34 and 32% for Z-BEAM, R-BEAM and BEAM, respectively. By multivariate analysis, there were no significant differences with Z-BEAM or R-BEAM compared with BEAM for IR, non-relapse mortality, event-free survival or overall survival. With the caveat that the limitations of registry analyses have to be taken into account, this study does not support adding radioimmunotherapy or R to BEAM in ASCT for relapsed FL. However, we cannot rule out the existence a particular subset of patients who could benefit from Z-BEAM conditioning that cannot be identified in our series, and this should be tested in a randomized trial.

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INTRODUCTION

High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) is considered to be a standard treatment for eligible patients with relapsed chemosensitive follicular lymphoma (FL).[1] However, disease recurrence remains the most common cause of treatment failure after ASCT. As FL is highly sensitive to radiotherapy, TBI has been traditionally used as part of high-dose regimens for ASCT and has been associated with lower relapse rates,[2,3] although this has been outweighed in some studies by a higher long-term toxicity.[3,4] Other strategies have been used to reduce relapse rates, including the use of post-transplant immunotherapy with rituximab (R).[5]

Radioimmunotherapy (RIT) has been explored as a means of harnessing the antitumour effects of radiation while potentially reducing toxicity compared with fractionated TBI. It combines the potency of radiotherapy with the targeting capability and immunological potency of cell-type-specific monoclonal antibodies. The use of targeted antibodies to deliver radiation directly to the tumour and its microenvironment is intended to spare critical organs, thereby allowing treatment of older and more heavily pretreated patients. Hence, there is a strong rationale for using RIT as part of the conditioning treatment for ASCT. Two different radiolabelled anti-CD20 antibodies have been used in this setting to treat B-cell lymphomas: iodine-131 (I131)-tositumomab (Bexxar)[6,7] and yttrium-90 (Y90)-ibritumomab tiuxetan (Zevalin).[8]

Augmenting the high-dose regimen for ASCT with RIT has been evaluated in patients with B-cell non-Hodgkin lymphoma (NHL) in several studies.[9–12] Although RIT is approved for treatment of FL,

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Table 1. Patient characteristics by HDT regimen (BEAM vs Z-BEAM vs R-BEAM)

	BEAM (1973)	*Z-BEAM (207)*	*R-BEAM (179)*	P
Age at ASCT, years (median, range)	56 (19–77)	55 (25–70)	55 (25–72)	NS
Age ⩾65 years	4%	2%	5%	NS
Male gender	56%	67%	60%	0.007
Good performance status (ECOG: 0–1)	88%	84%	96%	0.004
Year of ASCT				
2004–2006	16%	8%	14%	0.003
2007–2009	37%	60%	36%	
2010–2012	46%	31%	50%	
Time from diagnosis to ASCT, months (median, range)	41 (2–336)	35 (4–204)	37 (5–229)	NS
Sensitive disease at ASCT	98%	95%	88%	NS
Follow-up, months (median, interquartile range)	16 (4–40)	22 (4–42)	14 (4–36)	NS

Abbreviations: ASCT = autologous stem cell transplantation; BEAM = carmustine, etoposide, ara-c, melphalan; ECOG = Eastern Cooperative Oncology Group; HDT = high-dose therapy; NS = not significant; R = rituximab; Z = Y90-ibritumomab tiuxetan.

however, there are no studies analysing the role of RIT-ASCT specifically in patients with FL. Here we report a registry analysis of the effect of adding Y90-ibritumomab tiuxetan (Z) or R to BEAM (carmustine, etoposide, ara-c, melphalan) HDT for ASCT in patients with relapsed FL.

PATIENTS AND METHODS

Data source

The European Society for Blood and Marrow Transplantation (EBMT) is a voluntary organization consisting of >600 transplant centres mainly from Europe. Accreditation as a member centre requires submission of minimal essential data (MED-A form) from all consecutive patients to a central registry in which patients may be identified by the diagnosis of underlying disease and type of transplantation. MED-A data are updated annually. Informed consent for transplantation and data collection was obtained locally according to regulations applicable at the time of transplantation. Since 1 January 2003, all transplant centres have been required to obtain written informed consent before data registration with the EBMT following the Helsinki Declaration 1975.

Patient eligibility

Eligible for this registry study were patients with FL aged ⩾18 years who underwent a first ASCT after BEAM HDT with or without Z (Z-BEAM) or R (R-BEAM) from 2004 to 2012 and were registered with the EBMT with a full data set as required for this analysis. Patients who had received other drugs in addition to BEAM were not eligible. Patients with histological transformation, those undergoing a second transplant and patients in first CR or PR were excluded.

Disease status categorization

For the purposes of this analysis, any CR or PR were considered as sensitive disease, while primary refractory disease, chemoresistant and untreated relapse, stable disease and progressive disease were grouped together as active disease.

Outcome measures

Overall survival (OS) was defined as the time from ASCT to death from any cause, and surviving patients were censored at last follow-up. Event-free survival (EFS) was defined as time from ASCT to recurrence, progressive disease or death from any cause. Non-relapse mortality (NRM) was defined as death from any cause without progression. Incidence of relapse (IR) was defined as the time from ASCT to relapse or progression (taking into account NRM as competing risk).

Statistical analysis

Patient characteristics were compared with *t*-test for continuous variables and χ^2 or Fisher's exact test for categorical variables. The primary end point was IR and secondary end points included OS, EFS, NRM and time to engraftment. OS and EFS were determined using the Kaplan–Meier method, and curves were compared by log-rank test. IR and NRM were calculated by cumulative incidence curves to account for competing risks and compared by Gray's test. For analysing the effect of Z and R, respectively, as supplement to BEAM, multivariate comparisons adjusting for potential confounders were performed with the whole patient sample. Multivariate analyses of OS and EFS were carried out using Cox regression modelling stratified for variables not respecting the proportional hazard assumption. Multivariate analyses of IR and NRM were carried out using Fine and Gray regression models. Variables included in multivariate models were significant at the 0.2 level in univariate or unbalanced between the groups under study or known to have an impact on outcome studied.

In addition, a matched-cohort comparison of BEAM vs Z-BEAM (2:1 ratio) was performed. In situations where more than two BEAM patients were identified as potential matches for a Z-BEAM patient, the best-matched patients were selected. The variables used for matching were age, time from diagnosis to transplant, gender, performance status, year of transplant and disease status at ASCT. In the matched sample, outcome in BEAM vs Z-BEAM cohorts were compared using a Cox model stratified on matched pairs.

All *P*-values <0.05 were considered significant. All statistical analyses were carried out using R 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

RESULTS

BEAM vs Z-BEAM vs R-BEAM comparison

Altogether, 2359 patients who received either BEAM ($n=1973$), Z-BEAM ($n=207$) or R-BEAM (R-BEAM, $n=179$) were eligible, see Supplementary Table S1. Patient characteristics were well balanced among the three groups except that Z-BEAM patients tended to contain more male patients, a higher proportion of patients with a reduced performance score and to be preferentially transplanted between 2007 and 2009, Table 1.

The cumulative IR at 2 years for the whole series was 32% with no differences according to high-dose regimen ($P=$NS, univariate with 32% for the BEAM group, 32% for the R-BEAM group and 34% for the Z-BEAM group). With similar 12-month NRM figures of 3% in each of the three groups, 2-year EFS and OS after BEAM vs Z-BEAM vs R-BEAM were 63% vs 62% vs 63% ($P=0.978$) and 82% vs 86% vs 88% ($P=0.463$), respectively (Figure 1). By multivariate analysis, there were no significant differences in NRM in the Z-BEAM group (hazard ratio (HR): 0.88 (95% confidence interval (CI): 0.4–1.94); $P=0.74$) and in the R-BEAM cohort (HR: 1.24 (95% CI: 0.57–2.72); $P=0.59$) compared with BEAM. The same accounted for IR, with an HR = 1.02 ((95% CI: 0.78–1.33); $P=0.89$) for patients treated with Z-BEAM and HR = 0.92 ((95% CI: 0.68–1.23); $P=0.58$) for patients who received R-BEAM. Similarly, no significant differences between the BEAM and the Z-BEAM or R-BEAM cohorts were found for OS (HR = 0.93 (95% CI: 0.64–1.35);

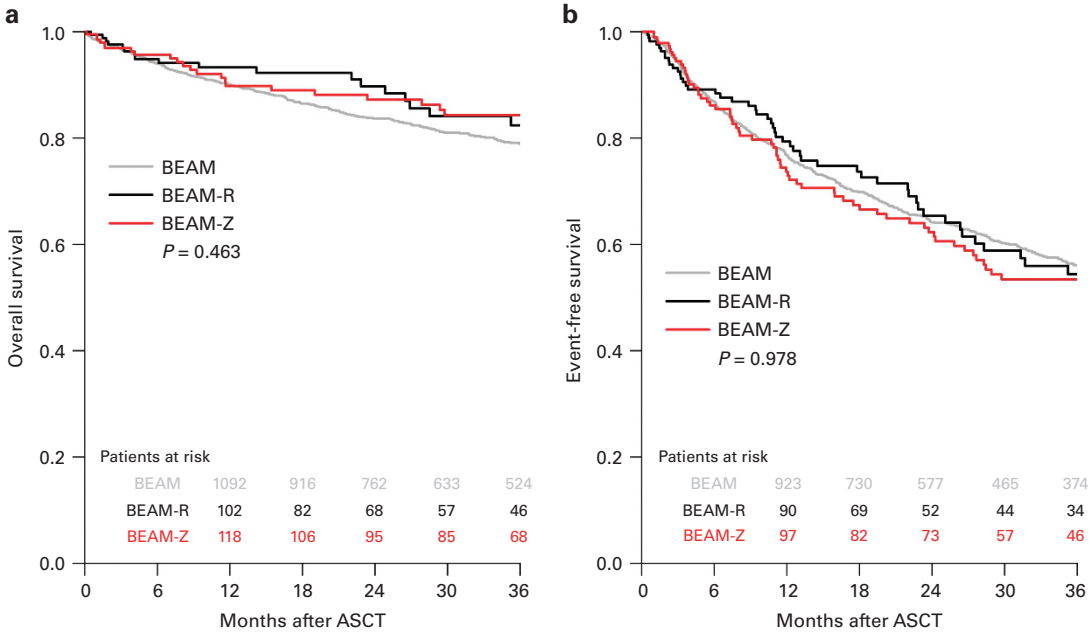

Figure 1. Survival analysis in total cohort. (**a**) OS; (**b**) EFS.

Table 2. Patient characteristics of the matched cohorts

	BEAM	*Z-BEAM*	P
N	282	154	
Age at ASCT, years (median, range)	55 (31–69)	55 (31–69)	0.72
Gender (M/F)	206 (73%)/ 76 (27%)	112 (73%)/ 42 (27%)	0.99
Good performance status (ECOG: 0–1)	96%	94%	0.67
Year of transplant			
2004–2006	16 (6%)	11 (7%)	
2007–2009	169 (60%)	89 (58%)	0.60
2010–2012	97 (34%)	54 (35%)	
Time from diagnosis to ASCT, months (median, range)	39 (2–134)	40 (5–136)	0.60
Disease status at ASCT			
Sensitive disease	278 (99%)	151 (98%)	0.25
Active disease	4 (1%)	3 (2%)	

Abbreviations: ASCT = autologous stem cell transplantation; BEAM = carmustine, etoposide, ara-c, melphalan; ECOG = Eastern Cooperative Oncology Group; F = female; M = male; Z = Y90-ibritumomab tiuxetan.

$P = 0.71$ and HR = 0.78 (95% CI: 0.51–1.2); $P = 0.26$) and for EFS (HR = 0.93 (95% CI: 0.71–1.23); $P = 0.63$ and HR = 1.1 (95% CI: 0.84–1.41); $P = 0.51$). In contrast, a long interval between diagnosis and ASCT (⩾2 years) and sensitive disease status at ASCT predicted both favourable IR (HR = 0.67 (95% CI: 0.57–0.79); $P < 0.0001$ and HR = 0.38 (95% CI: 0.31–0.48); $P < 0.0001$) and OS (HR = 0.76 (95% CI: 0.61–0.95); $P = 0.016$ and HR = 0.41 (95% CI: 0.31–0.55); $P < 0.0001$) but had no significant impact on NRM (HR = 1.1 (95% CI: 0.62–1.79); $P = 0.84$ and HR = 1.18 (95% CI: 0.47–2.95); $P = 0.73$). In addition, the Eastern Cooperative Oncology Group performance status was an independent variable of OS (HR = 0.4 (95% CI: 0.27–0.7); $P = 0.006$).

Matched cohort comparison

Altogether, there were 154 Z-BEAM patients who could be matched with 2 ($n = 128$) or 1 ($n = 26$) BEAM recipients, resulting in a total sample size of 436 patients (282 patients treated with BEAM and 154 patients who received Z-BEAM). Their characteristics are described in Table 2.

Ninety-seven percent and 98% of the BEAM and Z-BEAM patients respectively engrafted. The median time to engraftment was similar in both groups (11 days (range: 5–29) in patients treated with BEAM and 11 days (range: 7–47) in the Z-BEAM group). NRM in the BEAM and Z-BEAM cohorts was 2% and 0.7% on day +100, 2.4% and 0.7% at 1 year and 9% and 8% at 5 years, respectively (HR: 0.5 (95% CI: 0.13–1.93); $P = 0.3$; Figure 2). Similarly, there were no significant differences in the risk of secondary malignancies for both groups, including AML/myelodysplastic syndrome (MDS), NHL and solid tumours. Seven patients (2.5%) in the BEAM group and 4 (2.5%) in the Z-BEAM group developed secondary malignancies.

With a median follow-up of 19 months for survivors (range: 1–86), 25% of patients in the BEAM group relapsed, in comparison to 34% in the Z-BEAM cohort. This translated into an increased IR after Z-BEAM compared with BEAM that was, however, not statistically significant (HR = 1.55 (95% CI: 0.96–2.51); $P = 0.07$). Similarly, no significant differences between the BEAM and Z-BEAM groups were found in EFS (HR = 1.34 (95% CI: 0.86–2.08); $P = 0.2$) nor in OS (HR = 0.77 (95% CI: 0.41–1.46); $P = 0.43$) (Figure 2). We analysed the subgroup of patients who were in PR at the time of ASCT to assess whether Z-BEAM would result in a greater benefit in this subgroup. Patients who received BEAM had a significantly higher NRM ($P = 0.02$), but there were no differences in any of the other outcomes (Figures 3 and 4).

DISCUSSION

Despite the increasing efficacy of first-line treatment in FL and the advent of targeted drugs for the salvage setting, ASCT remains a standard treatment option for the relapse setting, in particular in patients with short-lived remissions.[1,13] Although a substantial proportion of patients might enjoy remissions lasting ⩾10 years after ASCT,[2–5] relapse represents the main cause of treatment failure. To this end, the radio-sensitivity of FL makes the use of RIT as part of the high-dose regimen for ASCT a very attractive option to increase disease control while avoiding the potential long-term complications of TBI. Apart from Zevalin, other RIT,

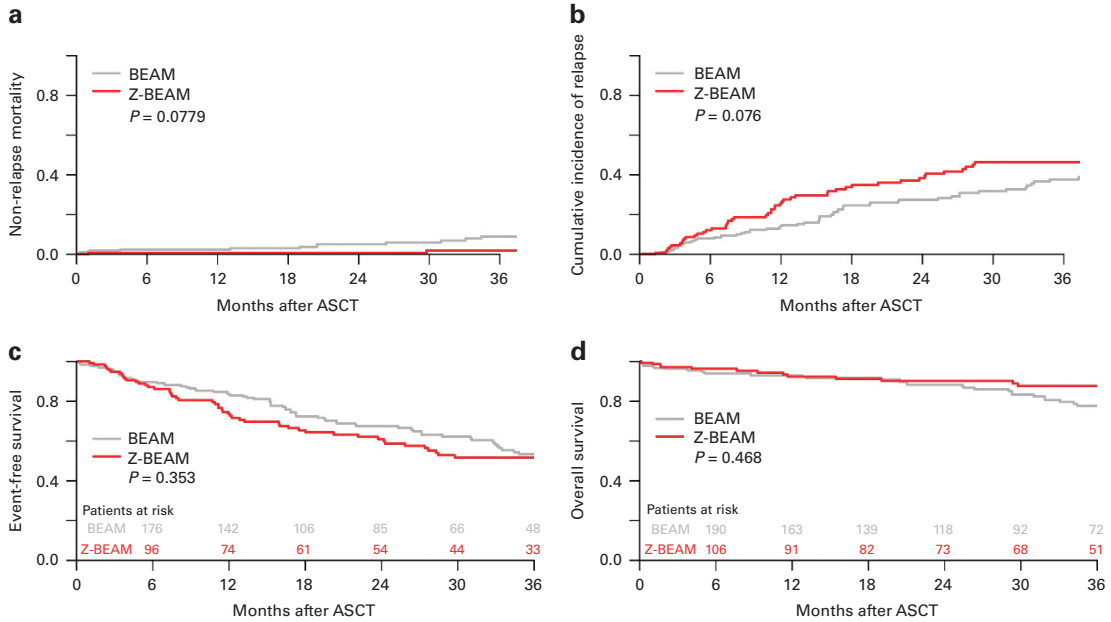

Figure 2. Survival analysis in the matched cohorts. (**a**) NRM; (**b**) cumulative incidence of relapse; (**c**) EFS; (**d**) OS.

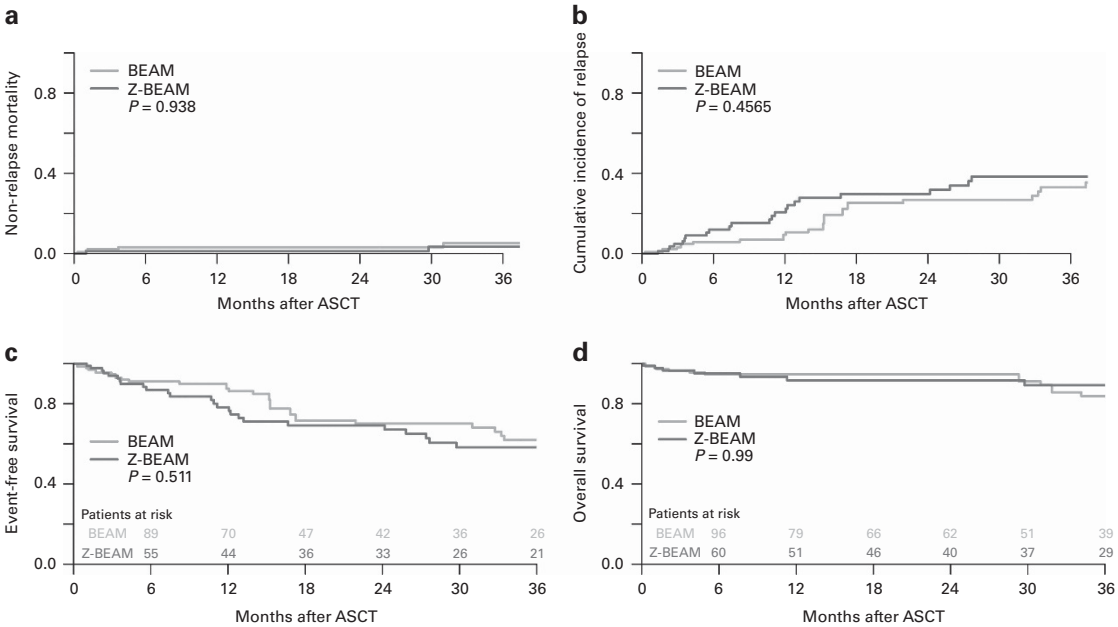

Figure 3. Survival of patients in CR prior to ASCT in the matched cohort. (**a**) NRM; (**b**) cumulative incidence of relapse; (**c**) EFS; (**d**) OS. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

such as ^{90}Y-labelled anti-CD22 (epratuzumab) combined with a humanized antibody anti-CD20 (veltuzumab), could be used as a part of HDT.[14] The feasibility of combining RIT with BEAM or other chemotherapy-based conditioning regimens has been explored in a number of phase I–II studies in patients with NHL, demonstrating its safety[8,15–17] and efficacy.[16,17] These studies, mostly in patients with aggressive lymphoma or with a mixture of different histological subtypes were limited by small patient numbers and lack of comparators.[8,15] A small randomized trial compared the outcomes of ASCT for relapsed/refractory aggressive B-cell lymphoma with or without Z as an adjunct to BEAM.[18] However, there have been no randomized studies analysing the role of RIT-BEAM specifically in patients with relapsed FL. The present study is the largest study comparing BEAM vs RIT-BEAM and the first one specifically in FL.

The hypothesis that Z-BEAM would result in better disease control reducing the relapse rate was not confirmed. As R-based chemoimmunotherapy has represented the standard for first-line treatment for FL since the early 2000s[19] and many of the patients in need for ASCT will have received R maintenance as well,[20] one explanation for the lack of effect of CD20-based (radio-) immunotherapy as adjunct to HDT as observed here might be that patients with relapsed/refractory FL proceeding to ASCT are very likely to be heavily preexposed to CD20-directed treatment. Another explanation for the lack of efficacy could be the hypothetical use of standard doses of Zevalin instead of a dose

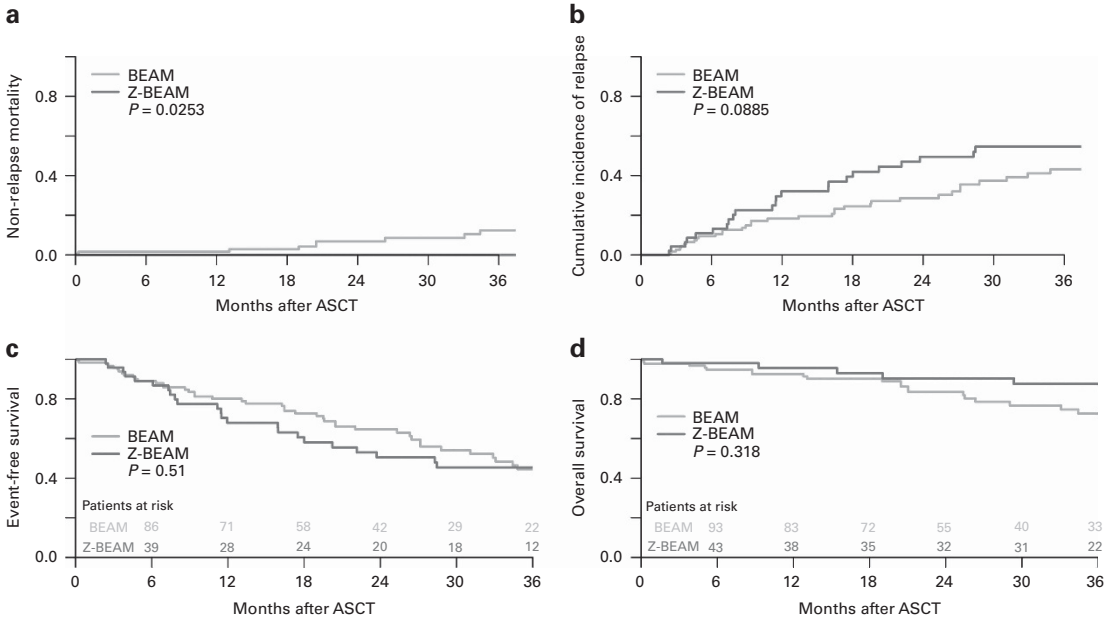

Figure 4. Survival of patients in PR prior to ASCT in the matched cohort. (**a**) NRM; (**b**) cumulative incidence of relapse; (**c**) EFS; (**d**) OS. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

escalation for the conditioning regimen. Unfortunately, we do not have the doses of Zevalin administered to confirm or refute this hypothesis. Notwithstanding the fact that even in R-naive patients *in vivo* purging with R prior to ASCT had no significant effect on disease control in a large randomized trial in relapsed FL.[5]

Similarly, no significant differences were found in NRM. The increased use of RIT in the management of patients with indolent lymphomas raised concerns about the risks associated with this therapy, including the risk of developing MDS/AML.[21,22] Z-BEAM has been demonstrated to be well tolerated in the initial phase I/II studies.[11,15] A randomized study in aggressive lymphoma confirmed the previously reported observations that the addition of Z to high-dose BEAM is safe and not associated with excess toxicity. Although there was a trend for more mucositis and more serious infections in the Z-BEAM arm, all the toxicities were reversible with no early deaths.[18] Also, median engraftment times in the initial trials are similar to conventional high-dose regimens as it has been confirmed in our study. The risk of AML/MDS after RIT was reported to be low[21] and no cytogenetic abnormalities after RIT and ASCT were reported.[23] In our series, there were no differences in the risk of secondary malignancies (including AML/MDS, NHL and solid tumours), although the follow-up of the series is not long enough to draw any conclusions in this regard.

However, this study has some limitations that are inherent to a registry study. For instance, there are some missing data with potential prognostic importance, such as the number of treatment lines, the fraction of patients with R-refractory disease pre-ASCT or the indication for using RIT-BEAM by the treating physician. The number of treatment lines was not mandatory in the MED-A forms until recently so the time from diagnosis to transplant was used as a surrogate for the matched analysis. Whereas it is clear that they are not equivalent, the fact that patients in first response were excluded from the study suggests that a short time from diagnosis to transplant is a poor risk factor. Thus, with these caveats in mind, our study demonstrates that Z-BEAM is a safe regimen, but we have not been able to demonstrate that it is more efficacious than BEAM.

In conclusion, although it is not excluded that Z-BEAM might be superior to BEAM despite the results presented here, this study is clearly not an argument in favour of pursuing this approach. Instead, further improvement of ASCT outcome in FL may be achieved by CD20 antibody maintenance, as recently shown in a large randomized trial,[5] or by other post-transplant interventions, which could also include RIT.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on Bone Marrow Transplantation website (http://www.nature.com/bmt)