



Treatment with Yttrium-90 (⁹⁰Y)-Ibritumomab Tiuxetan (Zevalin[®]) in Diffuse Large B-Cell Lymphoma: A Meta-Analysis

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The ORR and CRR were 74.8% ($n=374$) and 67.4% ($n=365$), respectively. Outcomes were superior when Zevalin is used in consolidation after immunochemotherapy induction at first line of treatment. OS2y and PFS2y were 87.5% and 82.8%, respectively. The primary toxicity was neutropenia (49.9%).

CONCLUSION: The use of Zevalin in patients with DLBCL is safe and effective.

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Key words: Diffuse Large B cell lymphoma; 90Y-ibritumomab tiuxetan; Zevalin[®]; Radioimmunotherapy

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ABSTRACT

BACKGROUND: Diffuse large B-cell lymphoma (DLBCL) is the most frequently diagnosed non-Hodgkin's lymphoma (NHL). Current treatment paradigm in first line, is based on immunochemotherapy and, in case of relapse or refractory, on a salvage therapy with high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). Yttrium-90 (90Y)-ibritumomab tiuxetan (Zevalin[®]), off label, offers a new therapeutic approach for DLBCL, both as first-line induction or consolidation and in relapsed or refractory disease. Data on this subject is increasingly being reported as well in consolidation as alone, in first line or after. To assess efficacy and find the best place of Zevalin in DLBCL, we conducted a literature review and meta-analysis of randomized clinical trials and observational studies on the effect of Zevalin treatment in this setting, except in ASCT.

MATERIALS AND METHODS: The primary goal was to assess the effect of Zevalin on overall response rate (ORR) and complete response rate (CRR) then assess the 2-year overall survival (OS2y) and 2-year progression-free survival rates (PFS2y).

RESULTS: Sixteen studies were identified (399 patients) with DLBCL receiving Zevalin as consolidation or as treatment alone.

IMPLICATIONS FOR PRACTICE

Diffuse large B cell lymphoma (DLBCL) is currently treated by 8 cycles of immune-chemotherapy in first line and in case of relapse followed by autologous bone marrow transplantation. These treatments give often toxicity and are not feasible in elderly or frail patients. In order to reduce toxicity, we can reduce chemotherapy. Zevalin[®] is a radio-immunotherapy, offering a new therapeutic approach for DLBCL, both as first-line (induction or as consolidation) or in relapsed or refractory disease.

Zevalin is commonly used in follicular lymphoma and, several studies have evaluated the use of Zevalin in DCLBL, but it is not yet uniformly accepted as a treatment in this setting. A trial is ongoing in elderly patients.

This meta-analysis aims to give a first assessment of efficacy and safety of use Zevalin[®] in DCLBL treatment, and could allow change the actual practice in reducing cycles of chemotherapy.

INTRODUCTION

The current treatment paradigm for Diffuse large B-cell lymphoma (DLBCL) in first line is based on immunochemotherapy and, in case of relapse or refractory, on a salvage therapy with high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). Use of involved field radiation is common in case of advanced systemic disease or bulky disease. However, many patients, particularly the elderly, are not suitable candidates for these treatments. The principle of radio-immunotherapy offers a new therapeutic approach for DLBCL, both as first-line (induction or as consolidation) and also in relapsed or refractory disease.

The use of ⁹⁰Y-ibritumomab tiuxetan (Zevalin) in indolent lymphomas has been established as an effective treatment option^[1]. In DLBCL, several studies have evaluated the use of Zevalin, but it is not yet uniformly accepted as a treatment in this setting. To date, only one study with a randomized patient population has been reported^[2] and the majority of studies have enrolled patients with a mix of lymphoma subtypes. One phase 2 study of note was designed to assess efficacy and safety of Zevalin in consolidation in patients with DCLBL after chemotherapy induction^[3]. In the initial phase 1/2 study in relapsed or refractory patients with intermediate grade disease^[4], objective response rates were 43% with 29% of patients achieving complete response (CR). In a multicenter phase 2 trial in relapsed/refractory DLBCL, the overall response rate (ORR) was 53% in patients pretreated with chemotherapy while ORR was 19% in patients pretreated with chemotherapy + Rituximab^[5].

It remains important to determine whether Zevalin is an effective treatment option for DLBCL patients. To provide further evidence, we performed the first non-comparative meta-analysis of randomized trials, prospective and observational studies on the effect of Zevalin in patients with DLBCL.

MATERIALS AND METHODS

Data Sources and Searches

Overall methods were adapted from MOOS and PRISMA guidelines for meta-analyses^[6,7]. A literature search was conducted to identify randomized controlled trials and observational studies of Zevalin in adult patients with DLBCL. On June 30, 2013, a systematic literature search was performed on the following databases: the National Library of Medicine PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>), the American Society of Hematology (<http://www.hematologylibrary.org/>), the European Haematology Association (<http://www.haematologica.org/>), and the American Society of Clinical Oncology (<http://meetinglibrary.asco.org/abstracts>). The search terms were B cell lymphoma [MeSh] and ZEVALIN[®] or yttrium-90 (⁹⁰Y)-ibritumomab tiuxetan. The results were limited to studies in adult humans that were reported in the English or French language.

Study Selection

The publication searches, study selection, and data extraction were carried out independently by two investigators (SA, PQ); discrepancies were solved by discussion between authors until consensus. Studies were included in the meta-analysis if they matched all pre-specified eligibility criteria. Studies were excluded for the following reasons: (1) patients had mantle cell lymphoma, Richter lymphoma, or indolent lymphoma (except for transformed follicular lymphoma); (2) patients were <18 years of age; (3) patients had consolidation with Z-BEAM regimen; and (4) patients had

allogeneic stem cell transplantation. Studies with patient populations of mixed lymphomas were included if the required data for patients with DLBCL were extractable from the reports. Studies enrolling fewer than 5 patients were not included due to risk of extreme bias. Review articles and registers were not included. There was no restriction in study design and reports in abstract form were allowed. When duplicate publications were found, only the most complete or most recent version was retained. For the first screening, titles and abstracts were reviewed for relevancy. Then, the full-text of each retained article was scrutinized for whether it met the pre-specified inclusion and exclusion criteria.

Data Extraction and Quality Assessment

From eligible studies, two investigators independently extracted data using selected forms. Between-study variables included information on study characteristics [author(s), publication year, journal, study design, follow-up duration], sample characteristics [Ann Arbor stage, International Prognostic Index (IPI), first-line status, number of prior treatments, use of rituximab in prior therapy, sample size], type of treatment before Zevalin (drug and administration route) and outcome definition. For each study, baseline demographics (mean age, gender), response data [ORR, CR, overall survival (OS), and progression-free survival (PFS)], and toxicity data (incidence of grade 3/4 hematological and non-hematological adverse events after 90Y-ibritumomab tiuxetan) were extracted if available. Individual data were used where possible. Classical tools [ie, Newcastle-Ottawa Scale (NOS) or Jadad scale] to assess study quality were not utilized in all included studies; therefore, the investigators chose a quality assessment score on compounded items extracted from classical quality assessment scales (study design, randomization, and individual data). This quality assessment is detailed in appendix table I (available online as a supplementary file). Both reviewers independently assessed study quality in a blinded manner.

Data Synthesis and Analysis

The primary assessment for this study was ORR and complete response rate (CRR). The definition of ORR was based on international criteria. Secondary assessments included OS, PFS, and grade 3/4 toxicities. For PFS and OS, the mean values were estimated by including censored data. The mean duration of platelets <50×10⁹ per liter was also assessed.

We defined the effect of Zevalin treatment as a weighted median proportion (event rate). To account for expected heterogeneity, a mixed effects analysis (random effects model) is used to combine studies within each subgroup. The study-to-study variance (tau-squared) is assumed to be the same for all subgroups - this value is computed within subgroups and then pooled across subgroups. Summary estimates of event rates were obtained using the fixed effects model method when heterogeneity was not significant. The percentage of variability beyond chance was estimated using the I² statistic^[8,9]. An I² statistic for which values are over 50% (*p*-value<0.1) may indicate substantial heterogeneity. To explain heterogeneity, the effects of quantitative covariates on study event rates were investigated using mixed-effects meta-regression (Method of Moments). Qualitative covariates were investigated using mixed effects analysis. Results of fixed effects analysis (pwithin) is given as an indication.

The risk of publication bias was assessed using the one-tailed Egger's test^[10] and graphically by the funnel plot, which plots the natural logit of even rate versus their standard error. Additionally, Duval and Tweedie's trim-and-fill method was used^[11]. A *p*-value

< 0.05 was considered statistically significant in all analyses. In sensitivity analyses, the impact of study selection was addressed by a “one-study removed” meta-analysis approach.

Secondary analyses included estimation of ORR and CRR in treatment-naïve patients (at first line), in rituximab-naïve patients, according to use of chemotherapy associated to Zevalin, according to number of cycle of chemotherapy induction if it's used (performed for PFS and OS too), and according to the design of study.

All analyses were performed using Comprehensive Meta-analysis [Comprehensive Meta-analysis Version 2.2.048 November 7, 2008. Biostat, 14 North Dean Street, Englewood, NJ 07631, USA] and STATA (Stata/SE 12.1 for Windows Revision 09 Jul 2013 Copyright 1985-2011 StataCorp LP 4905 Lakeway Drive College Station, TX 77845 USA).

RESULTS

Study Selection and Description

A flow diagram of the search results is presented in Figure 1.

A total of 221 records were identified through electronic databases. Removing search overlap and irrelevant studies based on title and abstract review reduced the results to 36 records. After full-text analysis, 16 studies were selected for inclusion in the meta-analysis (10 Abstracts, 6 Articles). Study types included 1 randomized trial^[2] 1 prospective phase I/II trial^[4], 10 phase II trials^[3,5,12-20], 1 observational study^[21], and 2 prospective studies^[22,23].

Study characteristics, including design, populations, and outcome are provided in Table 1.

Across the 16 studies, 399 patients with DLBCL received Zevalin alone or associated with chemotherapy. The dose was administered by intravenous injection at 0.3 or 0.4 mCi/Kg according to platelet count. In 10 studies, patients were treatment-naïve. In 5 studies, patients received only Zevalin in the actual line of treatment without induction therapy. In 8 studies, patients received prior rituximab. The median follow-up was 31.1 months (range, 13.9-51.6). Two publications represented the same study but provided complementary data^[13,14] and were thus included together. Strategies were used to check for possible confounding bias (appendix Table I). The studies were classified according to their design.

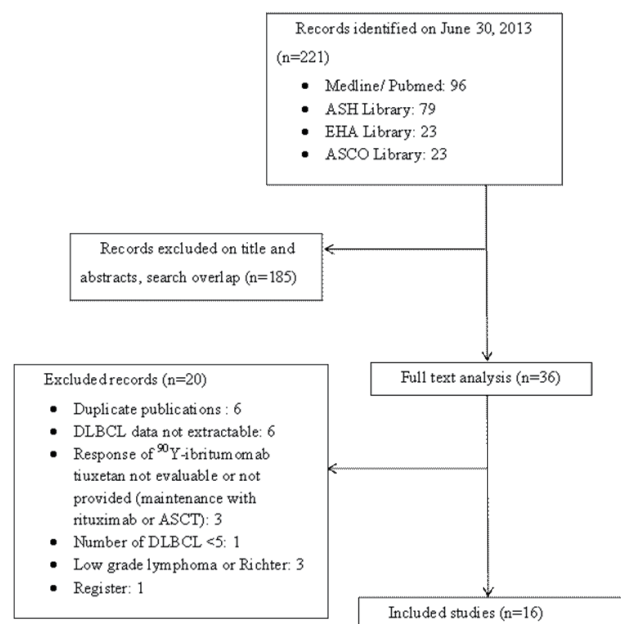


Figure 1 Flow diagram of the trial selection process.

Table 1 Study characteristics.

Study	Article type	Prospective design	N	Median age (years)	Female (%)	1st-line only	CITX induction	Type of chemotherapy	Rituximab induction	ORR (%)	CRR (%)	2-year OS	2-year PFS	Thrombocytopenia (%)	Neutropenia (%)
Peyrade (2012)	Abstract	Y	25	72.6	50	Y	Y	3 RCHOP14	Y	100	100	90	4	45	
Rohn (2007)	Abstract	Y	11	69	N	N	N	---	N	36	27	90	76.9		
Issaragrisil (2010)	Abstract	Y	13	38	Y	Y	Y	6 CHOP	N	92.3	92.3	92.3			
Montes-Limon (2012)	Article	Y	9	53	26.4	N	Y	Not done	Y	66.6	55.5			31.5	
Karmali (2010)	Abstract	Y	16	60	60	Y	Y	6 RCHOP14	Y	100	90			12.5	50
Botto (2007)	Abstract	Y	9	53	N	N	N	---	Y	46	22				
Witzig (2012)	Abstract	Y	48	68	40	Y	Y	2-6 RCHOP	Y	90	89	98	90		
Zinzani (2008)	Article	Y	20	68	40	Y	Y	6 CHOP	N	100	95	95	75	37	58
Zinzani (2010)	Article	Y	48	70	53	Y	Y	4 RCHOP	Y	91.6	83.3	86	85	39.5	48
Morschhauser (2007)	Article	Y	102	48	48	N	N	CHOP/RCHOP	Y/N	52	27.4	80	75	35	60
Yang (2012)	Article	Y	20	42	33.3	Y	Y	6 RCHOP	Y	89.9	76.2	80	75		
Witzig (2002)	Article	Y	9		N	N	N	---	N	56					
Witzig (1999)	Article	Y	14		N	N	N	---	N	43	29				
Hamlin (2010)	Abstract	Y	44	75	65	Y	Y	6 RCHOP	Y	100	86	84	81.5		
Cho (2009)	Abstract	Y	11	54		Y	Y	6-8 RCHOP	Y	45.5	45.5				

Overall Response Rate

The ORR was 74.8% (95% CI, 59.7-85.5) for 374 DCLBL patients after Zevalin (Figure 2). Heterogeneity was high ($I^2>50\%$, $p<0.001$).

In patients receiving chemotherapy and Zevalin ($n=209$), ORR was 90.7% (95% CI, 85.2-94.4). In patients receiving Zevalin alone ($n=147$), ORR was 49.7% (95% CI, 41.7-57.8) (Appendix Figure 1A). There was high heterogeneity between the 2 groups ($p_{\text{between}}<0.001$, $p_{\text{within}}=0.64$). ORRs were superior in patients receiving <6 cycles of chemotherapy [90.8% (95% CI, 64.4-98.2) vs ≥ 6 cycles 83.5% (95% CI, 63.6-93.7)] without heterogeneity between groups ($p_{\text{between}}=0.51$, $p_{\text{within}}=0.64$).

In patients receiving Zevalin (alone or with chemotherapy) at first line ($n=322$), ORR was 85.9% (95% CI, 71.4-93.7) vs 49.2% (95% CI, 24.1-74.8) in 52 at second line and plus treated patients (Appendix Figure 1B). Heterogeneity between the 2 groups was high ($p_{\text{between}}=0.012$, $p_{\text{within}}<0.001$).

The ORR was higher for 213 patients having previously received rituximab [80.7% (95% CI, 57.4-92.9)] than for the 143 rituximab-naïve patients [65.2% (95% CI, 35.7-86.4)], without significant heterogeneity between the groups ($p_{\text{between}}=0.34$, $p_{\text{within}}<0.001$) (Appendix Figure 1C).

In the sub-analysis by study design, ORR was higher at 80.7% (95% CI, 65.1-90.3) in phase II and phase III trials ($n=345$ patients) than in retrospective studies [$n=29$ patients; ORR=49.3% (95% CI, 18.2-80.9)] with heterogeneity between the 2 groups ($p_{\text{between}}=0.09$, $p_{\text{within}}<0.001$).

Complete Response Rate

The CRR was 67.4% (95% CI, 47-82.8) for 365 patients with DLBCL (Figure 3), with high heterogeneity ($I^2>50\%$, $p<0.001$).

For 138 patients receiving Zevalin alone, CRR was 29.1% (95% CI, 22.1-37.3) vs 85.9% (95% CI, 80.3-90.1) for 209 patients receiving associated chemotherapy (Appendix Figure 2A). Heterogeneity between both groups was high ($p_{\text{between}}<0.001$,

$p_{\text{within}}=0.78$). CR rates were better in patients receiving <6 cycles of chemotherapy [86.4% (95% CI, 44.6-98)] compared to those receiving ≥ 6 cycles [76.8% (95% CI, 50.5-91.4)], without significant heterogeneity between groups ($p_{\text{between}}=0.59$, $p_{\text{within}}<0.001$).

In patients receiving Zevalin (alone or with chemotherapy) at first line ($n=322$), the CRR was 79.4% (95% CI, 58.6-91.3) while in patients who were at second line and plus treated ($n=43$), the CRR was lower at 32.6% (95% CI, 9.5-69) (Appendix Figure 2B). Heterogeneity between both groups was high ($p_{\text{between}}=0.03$, $p_{\text{within}}<0.001$).

The CRR was higher for 213 patients having previously received rituximab [72.4% (95% CI, 48.9-87.9)] than for the 134 rituximab-naïve patients [56.9% (95% CI, 27.5-82.4)], without significant heterogeneity between the groups ($p_{\text{between}}=0.40$, $p_{\text{within}}<0.001$) (Appendix Figure 2C).

In the sub-analysis according to study design, the CRR was higher at 75.5% (95% CI, 53.9-89) in phase II and phase III trials ($n=336$) compared with other studies ($n=29$; 34% (95% CI, 8-75.8) with heterogeneity between groups ($p_{\text{between}}=0.09$, $p_{\text{within}}<0.001$).

2-Year Overall Survival and 2-Year Progression-Free Survival

For 218 assessable patients, 2-year OS after Zevalin was 87.5% (95% CI, 81.6-91.7) with moderate heterogeneity ($I^2<50\%$, $p=0.22$) (Figure 4).

Two-year PFS was 82.8% (95% CI, 77-87.3) with nonsignificant heterogeneity ($I^2=0\%$, $p=0.57$) (Figure 5).

For patients receiving <6 cycles vs. ≥ 6 cycles of chemotherapy, 2-year OS and 2-year PFS were 92.36% (95% CI, 81.5-97.3) and 87.8% (95% CI, 80.6-92.6) vs 86.5% (95% CI, 73.7-93.6) and 77.9% (95% CI, 68.5-85.1), respectively. Heterogeneity between the 2 groups was moderate for OS ($p_{\text{between}}=0.32$, $p_{\text{within}}=0.20$) and high for PFS ($p_{\text{between}}=0.05$, $p_{\text{within}}=0.95$).

The percentage of relapse for 356 assessable patients was 24.3% (95% CI, 12-43.1) with high heterogeneity ($I^2>50\%$, $p<0.001$).

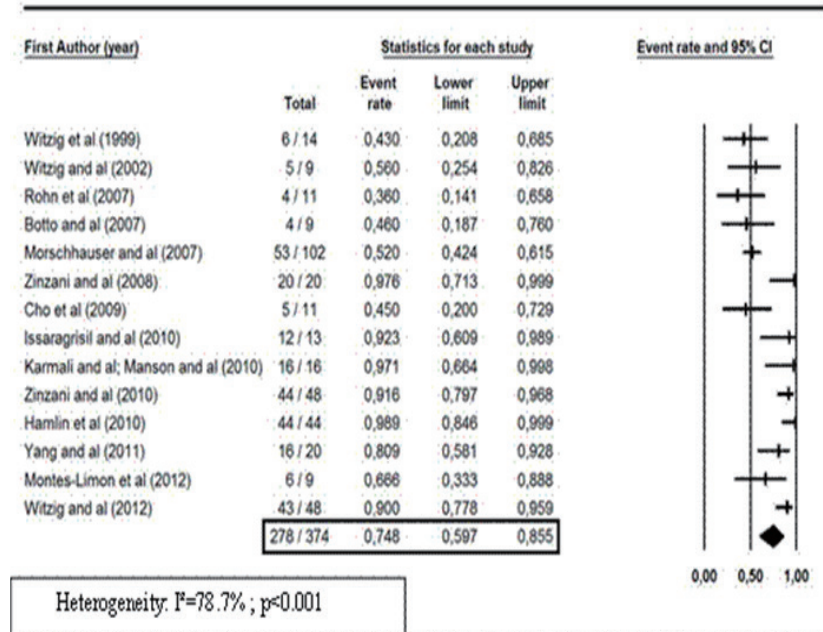


Figure 2 Forest plot of ORR after 90Y-ibritumomab tiuxetan. Heterogeneity was estimated with the I^2 statistic according to Higgins et al, (2003) and Higgins and Thompson (2002).

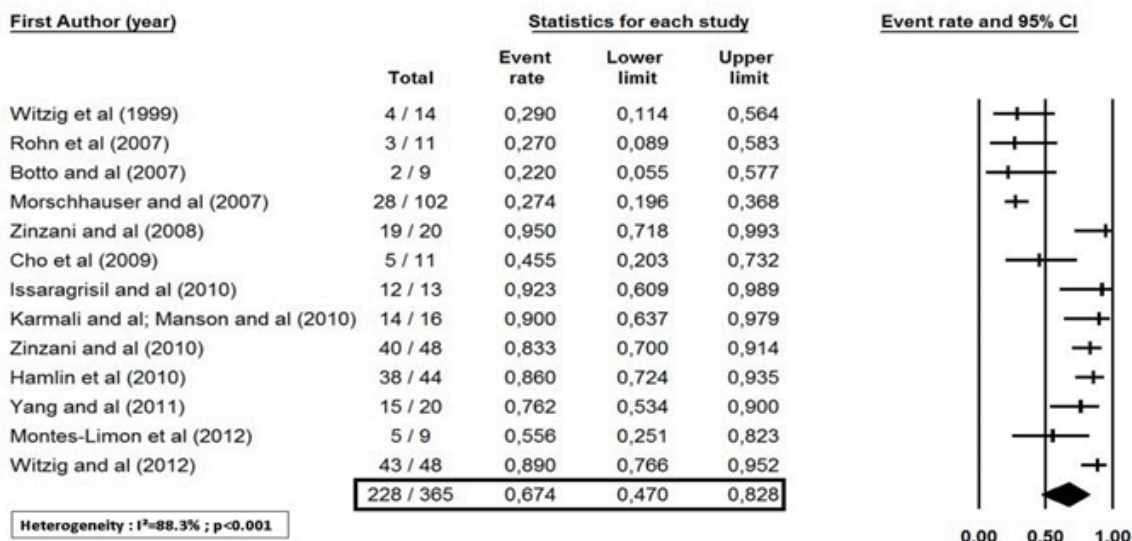


Figure 3 Forrest plot of CR after 90Y-Ibritumomab tiuxetan. Heterogeneity was estimated with the I^2 statistic according to Higgins et al, (2003) and Higgins and Thompson (2002).

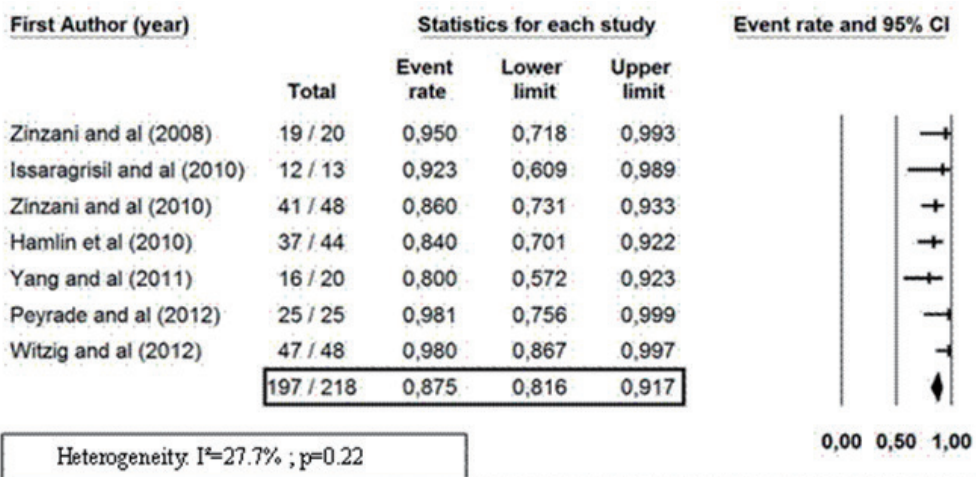


Figure 4 Forrest plot of 2-Year Overall Survival. Heterogeneity was estimated with the I^2 statistic according to Higgins and al (2003) and Higgins and Thompson (2002).

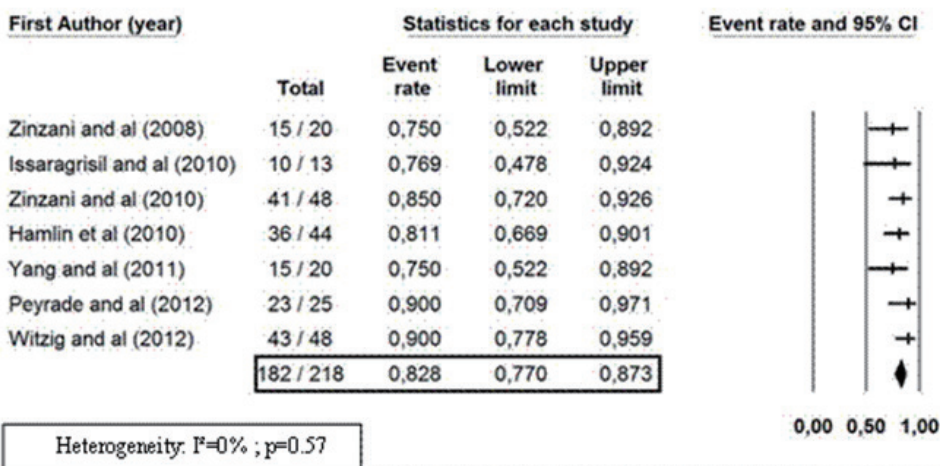


Figure 5 Forrest plot of 2-Year Progression-Free Survival. Heterogeneity was estimated with the I^2 statistic according to Higgins and al (2003) and Higgins and Thompson (2002).

Toxicity

Grade 3/4 non-hematologic toxicities were estimated at 11.3% (95% CI, 6.4-19.2): thrombocytopenia at 27.1% (95% CI, 16.5-41.3), and neutropenia at 50.8% (95% CI, 41.5-58.2). A total of 12.3% (95% CI, 5.8-24.1) of 224 patients received a transfusion. In patients receiving <6 cycles of chemotherapy, 1% (95% CI, 1-14.3) experienced grade 3/4 non-hematologic toxicity, 21.3% (95% CI, 5.8-54.5) had grade 3/4 thrombocytopenia, 47% (95% CI, 35.9-58.4) had grade 3/4 neutropenia, and 6.9% (95% CI, 2.1-20.7) received a transfusion.

Investigating heterogeneity

In a univariate mixed-effects meta-regression analysis [evaluating age, sex, proportion of Ann Arbor stage III/IV, proportion of IPI >2, publication year, and sample size (Table 2A and B)], ORR and CRR were both significantly correlated with publication year with superior responses observed in more recent publications ($p=0.01$ for both, tau squared=0.74 for ORR and 1.09 for CRR). There was a trend for correlation between ORR and proportion of patients with Ann Arbor stage III/IV ($p=0.12$) but the slope was very low (0.01).

There were no significant correlation between trial quality (prospective, retrospective, reported as an abstract or an article, etc.) and ORR or CRR using univariate mixed effects meta-regression analysis. A “one study removed” approach did not substantially modify results for these parameters (Figure 6).

Publication bias

Results of an Egger’s test showed significant evidence of publication bias on ORR ($p=0.02$). This is consistent with an asymmetrical shape of the funnel plot shown in Figure 7A. There were three missing studies for ORR. Adding three studies using a trim-and-fill method reduced ORR (67.2%; 95% CI, 50.7-80.3) (Figures 7A and 7B).

DISCUSSION

The goal of our meta-analysis was to evaluate the role of Zevalin, associated or not with chemotherapy, in DLBCL patients. This report is unique in that it is the first, to our knowledge, to show in a large sample of patients, the clinical outcomes of Zevalin in this setting. Use of 90Y- ibritumomab tixetan in DLBCL resulted in an ORR of 74.8% and a CRR of 67.4%. In all sub-analyses, the ORR and CRR varied according to treatment status and chemotherapy induction. Use of Zevalin alone provided poor outcomes. As expected, response was higher when patients received first-line Zevalin after chemotherapy induction. Surprisingly, patients who received fewer than 6 cycles of chemotherapy had superior outcomes compared to those who

received 6 or more cycles. This could be due to less toxicity or an expected better prognosis in these patients. At 2 years, OS and PFS were 87.5% and 82.8%, respectively.

Current first-line treatment for DLBCL consists of immunochemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab (R-CHOP) or R-CHOP-like therapy for 6 to 8 cycles every 14 days or 21 days. Coiffier et al report that 6 cycles regimen has resulted in 2- and 5-year PFS and OS rates of 57% and 54% and 70% and 58%, respectively, but was associated with significant toxicities, particularly in frail patients^[24,25]. More recently, an attenuated dose of R-CHOP was proposed in an attempt to maintain efficacy and improve safety in elderly patients. Use of R-miniCHOP resulted in 2-year PFS and OS rates of 47% and 59%, respectively^[26]. In this study^[26], the three last cycles of R-CHOP were primarily responsible for improved CRR. As shown in our sub-analysis, <6 cycles of chemotherapy followed by Zevalin resulted in a CRR equal to or better than 6 cycles with superior 2-year PFS and OS. In comparison, maintenance therapy with 4 cycles of weekly rituximab, every 6 months during a 2-year span leads to 2-year OS and 2-year PFS of 72% and 71%, respectively; this was lower than results observed in our study^[27].

Relapsed or refractory patients with DLBCL may benefit from high-dose therapy followed by ASCT if they are still responding to salvage therapy^[28]. However, some patients are not candidates for ASCT due to age and comorbidity and a regimen that is easily tolerated yet provides a reasonable response rate may be an attractive alternative to more toxic regimens. Even if treatment with Zevalin alone showed inferior results, it could be a good option for very frail patients, in whom an anthracycline-based chemotherapy regimen is not feasible.

Primary toxicities were neutropenia (49.9%) and thrombocytopenia (31.6%) which were higher than what was observed with attenuated R-CHOP^[26]. However, toxicities decreased when patients received <4 cycles of chemotherapy induction.

We caution that the results of our analysis are to be interpreted as descriptive and not comparative. Use of abstracts and no available of individual data were some limits of this work. Moreover, ideally, formal meta-analyses should solely include RCTs. While there is a lack of RCTs on the use of Zevalin in the DLBCL setting, 14 of the 16 included studies were prospective in nature, including 10 phase II trial, which we believe strengthens our findings. No study had a particular impact, as shown by the ‘one study removed’ approach. Analysis of publication bias revealed no evidence of bias for CRR but indicated a lack of 3 studies for ORR. Therefore, ORR was corrected by adding 3 studies via the trim-and-fill method giving a

Table 2A Results of mixed effects meta-regression on ORR using method of moments.

ORR	Study N	Slope	Slope 95% CI	p-value	Tau-Squared	% residual variation due to heterogeneity
Age	8	0.06	-0.05, 0.17	0.31	2.28	79.1%
Sex (female %)	8	0.06	-0.03, 0.17	0.21	2.29	85.1%
Stage III/IV	7	0.01	-0.002, 0.02	0.12	0	0%
IPI > 2	9	0.02	-0.04, 0.07	0.54	1.8	83.6%
Publication Year	14	0.2	0.04, 0.35	0.01	0.74	69.6%
Sample Size	14	0.006	-0.02, 0.03	0.66	1.7	79.2%

Table 2B Results of mixed effects meta-regression on CRR using method of moments.

CR rate	Study N	Slope	Slope 95% CI	p-value	Tau-Squared	% residual variation due to heterogeneity
Age	8	0.02	-0.004, .01	0.50	0.98	73.3%
Sex (female %)	9	0.02	-0.07, 0.11	0.66	2.55	91.6%
Stage III/IV	8	0.0008	-0.008, 0.01	0.86	0	0%
IPI > 2	9	0.01	-0.04, 0.06	0.72	2.04	89.6%
Publication Year	13	0.25	0.05, 0.45	0.01	1.09	80.2%
Sample Size	13	-0.02	-0.03, 0.03	0.89	2	86%

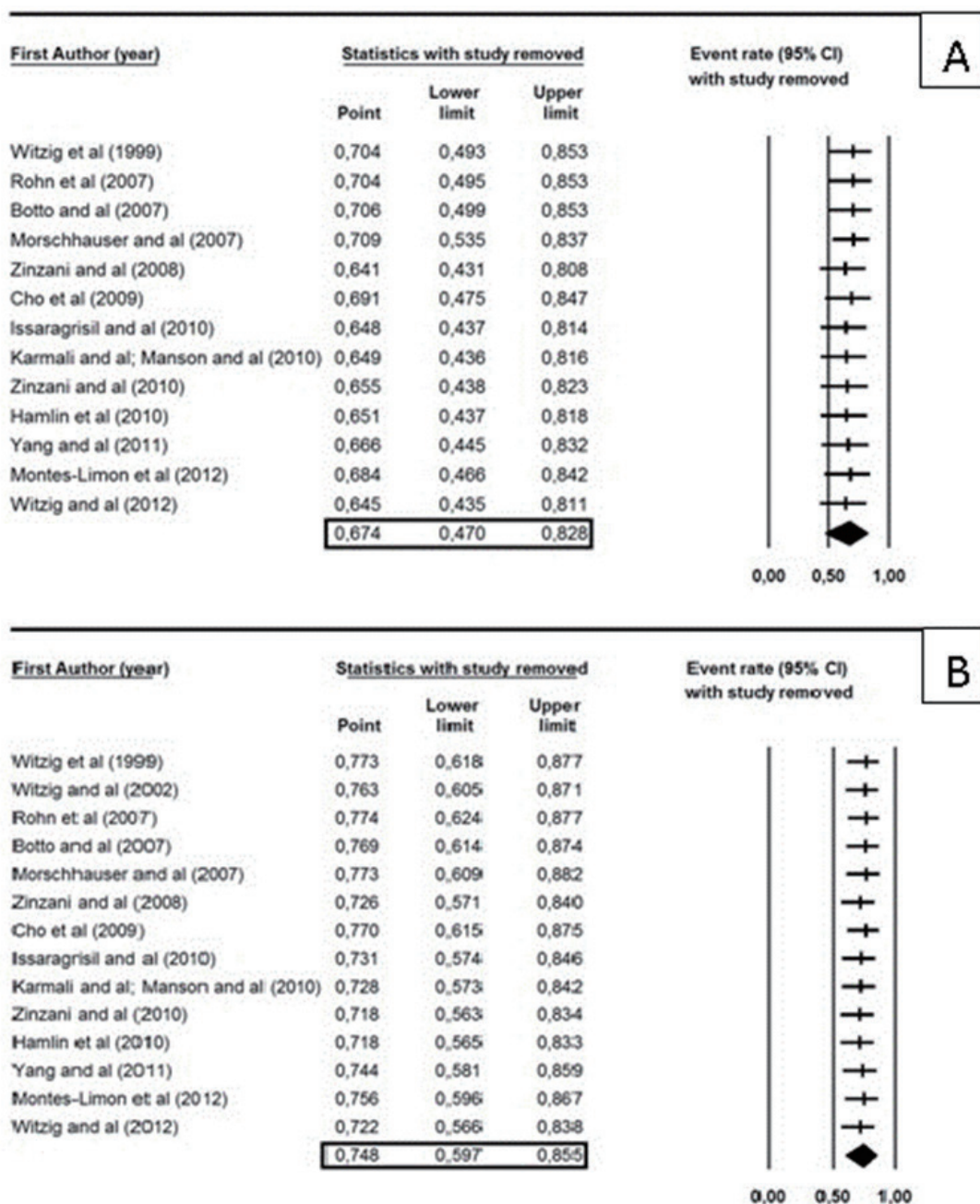


Figure 6 One study removed analysis on CRR after Zevalin(A) and ORR after Zevalin with random method.

corrected ORR of approximately 67%. In comparison, in one study that utilized attenuated R-CHOP^[26], the ORR was 87.5% with 62% achieving CR and 2-year OS at 59%. Our results showed a lower ORR but better CRR and patients had an improved 2-year OS.

Despite the use of a random model, the heterogeneity in the design of the studies may be a limitation to this analysis. The ORR and CRR were found to be higher in the RCT and prospective studies. The heterogeneity of the studies was principally related to the type of patients and induction chemotherapy. The best results for ORR and CRR were obtained in patients at first line when Zevalin is associated to induction chemotherapy. Use of Rituximab in induction improved ORR and CRR but did not adequately explain heterogeneity. Patients were also heterogeneous in terms of age, sex, previous treatment, and year of publication. We could not explore the previous treatment effect because data were not always reported. Using univariate meta-regression analysis for year of publication, ORR and CRR were

better in recent publications. One study gives leverage for ORR and CRR^[4]. This could be explained by improving effectiveness of induction chemotherapy but more likely because in recent studies patients were in first line. Surprisingly, there was no effect on stage or IPI.

CONCLUSIONS

Until the ongoing RCTs that compare Zevalin to other consolidation or nothing are published, this meta-analysis provides valuable information due to a large sampling of patients and may provide support for the modification of current management practices in DCLBL. Place of Zevalin could be at first-line treatment after induction immunochemotherapy. In frail patients, it could allow decrease or replace chemotherapy to decrease toxicities and spare the quality of life.