

Safety and Efficacy of Radioimmunotherapy with ⁹⁰Yttrium-rituximab in Patients with Relapsed CD20+ B cell Lymphoma: A Feasibility Study

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Abstract

Purpose: Both anti-CD20 antibodies (ibritumomab; ZEVALIN[®] and tositumomab; BEXXAR[®]) currently used for radioimmunotherapy of B cell non-Hodgkin's lymphoma are murine immunoglobulins. The aim of this feasibility study was to evaluate the safety and efficacy of radioimmunotherapy with a human chimeric anti-CD20 antibody labelled with Yttrium-90 (⁹⁰Y-rituximab) in patients with B cell lymphoma.

Methods: Patients with CD20+ B-cell lymphoma in partial remission or with progressive disease after at least one line of therapy were included. ⁹⁰Y-rituximab was administered according to a similar schedule as currently approved by the European Medicines Agency for the treatment with ⁹⁰Y-ibritumomab tiuxetan (ZEVALIN[®]): a first infusion of rituximab 250 mg/m² is repeated one week later and directly followed by the injection of ⁹⁰Y-rituximab (14.8 MBq/kg). ¹⁸F-DG-PET/CT was performed before treatment and repeated 3 months after for response assessment.

Results: Twenty-six patients were treated with ⁹⁰Y-rituximab. Disease histologies included mainly follicular lymphomas (53%). Toxicity was primarily haematological. The incidence of grade 3-4 neutropenia, thrombocytopenia and anemia were 34%, 38%, and 8% respectively, with spontaneous recovery in all but one patient that needed autologous stem cell transplant for refractory thrombocytopenia. Among the relevant long-term side effects, one patient developed secondary myelodysplasia 2 years after the treatment. The overall response rate was 88% (95% CI: 70%-98%), including 65% complete metabolic responses and 23% partial metabolic responses. After a median follow-up of 29.6 months, the Kaplan-Meier estimated median progression-free survival was 9.1 months (95% CI 6.1-17.9). Median time to next treatment was 24 months (95% CI: 12.8-28).

Conclusion: Radioimmunotherapy with ⁹⁰Y-rituximab in patients with relapsed CD20+ B-cell lymphomas is safe, well tolerated and effective when the ZEVALIN[®] treatment schedule is used.

Keywords: CD20+; Radioimmunotherapy; Non Hodgkin's Lymphoma; Rituximab Yttrium-90; Monoclonal antibody

Abbreviations: RIT: Radioimmunotherapy; NHL: Non-Hodgkin's Lymphoma; ANC: Absolute Neutrophil Count; HAMA: Human Antimurine Antibodies; HACA: Human Anti-Chimeric Antibodies; ORR: Overall Response Rate; PFS: Progression-Free Survival; DR: Duration of Response; OS: Overall Survival; CR: Complete Response; PR: Partial Response; TTNT: Time to Next Treatment; MDS: Myelodysplastic Syndromes; AML: Acute Myeloid Leukemia; EBRT: External Beam Radiation Therapy; NPLHL: Nodular Lymphocyte Predominant Hodgkin's Lymphoma; DLBCL: Diffuse Large B Cell Lymphoma; FLIPI: Follicular Lymphoma International Prognostic Index; ASCT: Autologous Stem Cell Transplant

Introduction

Radioimmunotherapy (RIT) is a targeted molecular radiotherapy in which radiation from radionuclides is delivered selectively to tumours by using monoclonal antibodies directed to tumour-associated antigens. The most widely studied radioimmunoconjugates for treatment of B cell Non-Hodgkin's Lymphoma (NHL) are murine anti-CD20 monoclonal antibodies radiolabelled with Yttrium-90 (⁹⁰Y-ibritumomab tiuxetan; ZEVALIN[®]) or Iodine-131 (¹³¹I-tositumomab; BEXXAR[®]). Several

studies have shown the efficacy of these radioimmunoconjugates in patients with B cell NHL, as a single agent in indolent lymphoma and in combination with chemotherapy in both indolent and aggressive lymphoma [1-6]. In Europe, only ⁹⁰Y-ibritumomab tiuxetan (ZEVALIN[®]) has been approved, and this radioimmuno conjugate is used in combination with unlabeled rituximab.

Rituximab (RITUXAN[®] or MABTHERA[®]), a chimeric IgG1 Kappa monoclonal antibody, targets the same epitope on the CD20 antigen

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as its murine counterpart, ibritumomab. Rituximab has delivered an increased survival both in low grade and aggressive lymphoma's and is currently part of the standard of care in NHL, mostly in combination with chemotherapy regimens [7-10]. Using antibody structures with human characteristics may potentially increase immune-based anti-tumour activity, improve pharmacokinetics and reduce immunogenicity. RIT with iodine-131 (^{131}I)-labelled rituximab has been evaluated in patients with relapsed or refractory indolent NHL, revealing an acceptable toxicity profile and efficacy [11]. Yttrium-90 (^{90}Y) is a pure β -emitting isotope with the potential to emit particles that deliver 5 times more energy to the tumour site than ^{131}I (2.3 MeV versus 0.6 MeV β energy), with a longer path length (5.3 mm versus 0.8 mm) and a shorter half-life (2.7 days versus 8 days) [12,13]. Its longer path length may provide an advantage, particularly for bulkier tumours or those with poor antibody penetration. As ^{90}Y has no coexisting gamma radiation (in contrast to ^{131}I), radiation safety precautions are minimal and RIT may be delivered on an outpatient basis [12,13].

Study Objectives

The primary objective of the study was to assess the safety of radioimmunotherapy with ^{90}Y -rituximab in patients with CD20+ B cell lymphoma in partial remission or relapse. Secondary endpoints included the Overall Response Rate (ORR), Progression-Free Survival (PFS), Duration of Response (DR) and Overall Survival (OS). Additional efficacy endpoints were Complete Response (CR) rate, Partial Response (PR) Rate and Time to Next Treatment (TTNT). To our knowledge, this is the first report of treatment with ^{90}Y -rituximab.

Methods

Patient selection

In this prospective, single-center feasibility study, 26 patients were enrolled between June 2007 and December 2011. Eligible patients had histologically confirmed CD20+ B-cell lymphomas (according to the World Health Organization classification) in progressive disease or partial remission after at least one line of treatment. Patients had to be at least 18 years old, have lesions measurable on ^{18}F FDG-PET/CT, World Health Organization performance status ≤ 2 , absolute neutrophil count (ANC) $\geq 1500/\mu\text{L}$, platelet count $\geq 100.000/\mu\text{L}$ and a life expectancy of at least 6 months.

Patients were excluded if the serum creatinin level or the total bilirubin level was more than two times normal, the ALT level more than 3 times normal or if they had a history of Human Antimurine Antibodies (HAMA) or Human Anti-Chimeric Antibodies (HACA). Patients with known HIV infection, HCV positivity or Hbs antigen positivity, any other uncontrolled malignancy and any other active infection uncontrolled by treatment were not eligible. Pregnant or lactating women, patients of reproductive potential without accepted birth control method, patients who received investigational drugs less than 4 weeks before entry in this study, who underwent surgery within 4 weeks of entering the study, and patients with a history of psychological illness or condition which could interfere with their ability to understand the requirements of the study were excluded.

The study was approved by the institutional ethical committee and all patients signed a written informed consent prior to their study inclusion.

Baseline evaluations were performed within 28 days prior to the inclusion of the patient in the study and included demographic data,

medical history, physical examination, electrocardiogram, and ^{18}F FDG-PET/CT. Laboratory studies included complete blood count (differential and platelet count), serum chemistry, serum immunoglobulins, thyroid function and pregnancy test for women of childbearing potential. For all patients, a bone marrow or peripheral blood stem cell harvest was mandatory to rescue unexpected marrow toxicity from the procedure.

Conjugate production, quality controls, and administration

Production of ^{90}Y -rituximab was performed in a Good Manufacturing Practice (GMP) compliant way in a dedicated facility with manufacturing license at the VU University Medical Center (Tracer Center Amsterdam, The Netherlands), essentially as described by Perk et al. [14]. In short, the buffer in which Rituximab (MABTHERA[®], Roche, Basel, Switzerland) is delivered, was changed to 0.1M NaHCO_3 pH 9 by use of a pyrogen-free PD-10 column. Then rituximab was modified by coupling of p-SCN-Bz-DOTA (Macrocyclics, Dallas, USA) at 45°C, at pH 9 and the modified protein was purified on a pyrogen-free PD-10 column and eluted in ammonium acetate buffer with ascorbic acid of pH 5.5. This modified rituximab was used for labeling with ^{90}Y . For labeling, to the solution of rituximab-DOTA 0.1 ml ^{90}Y (Perkin Elmer, Boston, USA) in 0.05 M HCl was added and reacted for 30 min at 45°C. ^{90}Y -rituximab was purified on a pyrogen-free PD-10 column. The end stage was final sterile filtration of the product. The total production cost of the radioconjugate ^{90}Y -rituximab was ± 3300 €/patient, covering the ^{90}Y (60%), rituximab (10%) and laboratory/labeling costs (30%).

Quality controls were performed as described previously by Perk et al. [15]. The radiochemical purity as assessed by instant thin-layer chromatography was always $>98\%$ (mean $99.4 \pm 0.4\%$). In vitro binding characteristic of ^{90}Y -rituximab were determined in an immune reactivity assay, using Ramos cells fixed with 2% paraformaldehyde. By doing so, the mean immune reactive fraction was $83.6 \pm 4.7\%$. The labeling procedure always resulted in a sterile product with endotoxin levels <2.5 EU/mL.

Drug administration followed the treatment schedule approved by the European Medicines Agency for the treatment with ^{90}Y -ibritumomab tiuxetan. Patients received rituximab 250 mg/m² IV on day 1 (after premedication with paracetamol, cetirizine and corticosteroids). The same infusion of rituximab was repeated on day 8 immediately followed by a 10-minute infusion of ^{90}Y -rituximab (11.1 MBq/kg if platelet count was between 100.000 and 150.000/ μL and 14.8 MBq/kg if platelet count was higher than 150.000/ μL). No hospitalization, patient isolation or shielding was required.

Evaluation of response

^{18}F FDG-PET/CT was performed for response assessment 3 months after the treatment or when progressive disease was clinically suspected, using the International Workshop Response Criteria for malignant lymphoma [16]. During follow-up, ^{18}F FDG-PET/CT was repeated (until disease progression) every 3 months during the first year and every 6 months during the second year or when progressive disease was suspected.

Evaluation of toxicity

For the purpose of collecting safety data, the treatment period was defined as the time from registration to 14 weeks afterwards. The basic follow-up period within the study started after the treatment period until disease progression or up to 2 years after registration. After this follow-up period within the study, a further follow-up based on clinical

reports provides additional information about late toxicity, PFS, TTNT and OS.

All adverse events from study during the treatment period were reported according to the Common Toxicity Criteria of the National Cancer Institute, version 3.0. Adverse events after this period, which were considered to be possibly or probably related with study drug, were also recorded. Laboratory assessments included complete blood count (differential and platelet count) and serum chemistry and were performed weekly during the treatment period and every 3 months during the follow up period.

Statistical methods

Statistical analysis includes descriptive analysis of baseline characteristics, response to treatment, safety variables (median and range for continuous variables, frequency tabulations for categorical variables). Time-to event distributions were estimated using the Kaplan-Meier method. Median follow-up was estimated using the reverse Kaplan-Meier method (i.e. considering as censored a patient who died). Overall survival was measured from treatment administration (⁹⁰Y-rituximab infusion) until death, any cause. Progression free survival was defined as the time interval between treatment administration and documented progression or death. For time to next treatment, death or initiation of a new treatment were considered as events. Duration of response was considered only for responding patients and was defined as the time elapsed between date of response assessment and progression or death. Logistic regressions models have been used to assess the impact of baseline characteristics on response or on toxicity. For the toxicity, the modelled probability is the occurrence of grade III-IV event. A P value of <0.05 was considered statistically significant. All statistical analyses were performed by using the software SAS 9.2.

Results

Patient's characteristics

A total of 26 patients were included in the study between June 2007 and December 2011. Patient demographics and baseline characteristics are listed in table 1. Median age was 61 years old (range 29-73) and main disease histology included follicular lymphomas (53%). Ninety-two percent of patients were in progressive disease and 62% of patients had a disease stage III/IV at study entry. Patients were treated previously with a median of 2 therapy regimens (range 1-7), with 97% of patients previously treated with rituximab. Seven patients (27%) had prior autologous stem cell transplant and 4 patients had bone marrow infiltration.

Safety

All patients had baseline platelets >150.000/μl and were to be administered the standard dose (14.8 MBq/kg) of ⁹⁰Y-rituximab. Toxicity was primarily hematologic, with grade 3 anemia, thrombocytopenia and neutropenia respectively in 8%, 23% and 15% of patients. Grade 4 thrombocytopenia and neutropenia occurred in 15% and 19% of patients respectively. No grade 4 anemia occurred. Fourteen patients (54%) experienced at least one grade 3/4 hematotoxicity. Median hematologic nadir values were as follows: ANC 1090/μl; platelets 62.500/μl; and hemoglobin, 12.1 g/dl. Median time to nadir and median time to recover 50.000 platelets/μl and 1000 neutrophils/μl are presented in table 2.

Variable		Number	%
Age	Median (range)	61 (29-73)	
Sex	Male	18	69
	Female	8	31
Histology	Follicular	14	53
	Transformed follicular	2	8
	NLPHL ^a	3	12
	Marginal zone lymphoma	2	8
	Mantle cell lymphoma	2	8
	DLBCL ^b	2	8
Disease Stage at study entry	Small lymphocytic	1	3
	I/II	10	38
Disease Status at study entry	III/IV	16	62
	Partial remission	2	8
Follicular lymphoma (n=14)	Progressive disease	24	92
	FLIPI ^c low (0-1)	9	64
	FLIPI intermediate (2)	2	14
Prior therapies	FLIPI high (>2)	3	22
	Median (range)	2 (1-7)	
	1-2	16	62
Prior rituximab therapy	>2	10	38
Prior ASCT ^d		24	92
Bone marrow infiltration		7	27
		4	15

^aNLPHL: Nodular Lymphocyte Predominant Hodgkin's Lymphoma

^bDLBCL: Diffuse Large B Cell Lymphoma

^cFLIPI: Follicular Lymphoma International Prognostic Index

^dASCT: Autologous Stem Cell Transplant

Table 1: Characteristics of all patients (n=26).

One patient experienced grade 4 pancytopenia, with severe thrombocytopenia (platelets <5000/μl) and neutropenia (ANC <500/μl) refractory to platelet transfusions and growth factors respectively. A rescue autologous stem cell transplant was administered 52 days after the treatment with ⁹⁰Y-rituximab. The patient recovered a platelet count >20.000/μl and an ANC >1000/μl respectively 21 days and 12 days after stem cell rescue. However, bone marrow reserve remained poor requiring intermittent injections of Granulocyte-Colony Stimulating Factor (G-CSF) and with platelet counts varying from 35.000 to 100.000/μl. Despite a prolonged pancytopenia, no infectious episode or severe bleeding occurred. Aside from this patient, hematologic toxicity was transient and reversible in all patients, with one patient requiring 3 units of red blood cell transfusions and another patient requiring one platelet administration. There occurred no major bleeding event and no febrile neutropenia. One patient with chronic bronchial infections developed fever and sputum the day before ⁹⁰Y-rituximab administration and was treated with amoxicillin-clavulanate for one week.

Logistic regression analysis demonstrated that baseline absolute neutrophil count was significantly associated to the occurrence of grade 3-4 neutropenia (OR=0.38 (95% CI: 0.15-0.85) for an increase of baseline neutrophils of 1000 cells/μl; P=0.02). In contrast, baseline platelet count was not predictive for grade 3-4 thrombopenia and

	Baseline ^a	Nadir ^a	Time to nadir ^a (weeks)	Time to recovery ^a (weeks)
Hemoglobin (g/dl)	13.5 (9.7-15.8)	12.1 (7.2-14.2)	7.5 (1-13)	
Platelets (cells/ μ l)	249.000 (150.000-405.000)	63.000 (3000-206.000)	6 (4-9)	2 (1-7)
ANC(cells/ μ l)	3260 (1240-5520)	1090 (90-2760)	7 (4-12)	1 (1-4)

^aAll values are expressed in median (range)

Table 2: Hematologic toxicity.

	All lymphoma's (N=26)		Follicular lymphoma's (N=14)	
	N	%	N	%
Overall response	23	88%	14	100%
Complete response	17	65%	11	79%
Partial response	6	23%	3	21%
Stable disease	1	4%		
Progressive disease	2	8%		

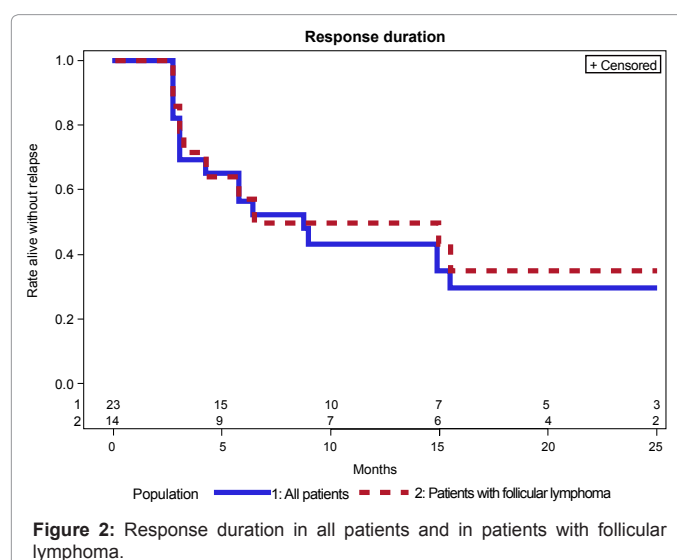
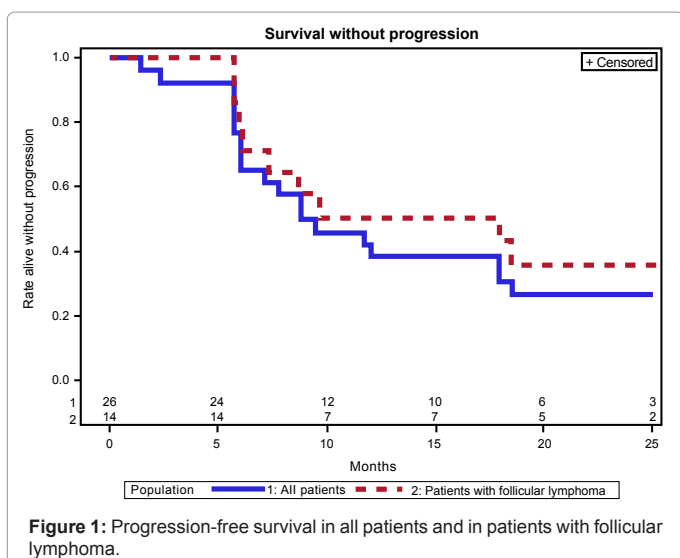
Table 3: Response rates.

there were not enough anemia events to allow the analysis of baseline hemoglobin and anaemia occurrence. No other factor were found to significantly affect the occurrence of grade 3-4 hematologic toxicity. The following factors were assessed: age, sex, disease stage, number of prior regimens (1 versus >1), bone marrow infiltration, prior external beam radiation therapy, prior autologous stem cell transplant.

There were no grade 3-4 non hematologic adverse events reported, in particular no infusion-related adverse events. Asthenia was the most common type of grade 1-2 non hematologic adverse events. No clinically significant chemistry abnormalities were associated with the treatment. None of the patients had significant reductions in immunoglobulin levels following treatment. Among the relevant long-term side effects, one patient previously treated with 2 prior treatment regimens (including alkylating agents, Total Body Irradiation, and autologous stem cell transplant) developed secondary myelodysplasia 27 months after the treatment and subsequently died.

Response-efficacy

An ORR of 88% (95% CI: 70%-98%) was achieved based on



International Workshop Criteria. A CR was achieved in 65% of patients (95% CI: 44%-83%) and PR in 23% patients. Patients with follicular histology (n=14) had an ORR of 100% with 79% of CR (Table 3).

Progression-free survival (PFS) was estimated by Kaplan-Meier analysis: the median PFS was 9.1 months (95% CI: 6.1-17.9) after a median follow up of 29.6 months (Figure 1). The estimated rate of patients without progression at 2 years is 26%. Responders had an estimated median response duration of 8.7 months (95% CI: 3.1-15.5) for all patients and of 10.6 months among patients with follicular lymphoma (Figure 2). Median time to next treatment (TTNT) was 24 months (95% CI: 12.2-28) with 43% of patients without a treatment at 2 years of follow-up. Median OS was not reached (Figure 3).

Logistic regression analysis did not identify any prognostic factor for ORR. The following factors were assessed: age, sex, disease stage, disease histology, number of prior regimens, medullary infiltration, prior external beam radiation therapy, prior autologous stem cell transplant.

Among the 23 responding patients, response duration lasted for

12 months or more in 10 patients (43%). Characteristics of responders according to their response duration are detailed in table 4.

Discussion

Our study showed that RIT with ⁹⁰Y-rituximab is safe and effective for treating patients with CD20+ B cell lymphoma using the ⁹⁰Y-ibritumomab tiuxetan treatment schedule. The primary and dose-limiting side effect from RIT is hematologic toxicity. In our study, all patients received the standard dose (14.8 MBq/kg) of ⁹⁰Y-rituximab and grade 4 neutropenia, thrombocytopenia and anemia occurred in 19%, 15% and 0% of patients; grade 3 toxicities in 15%, 23% and 8% respectively. Median time to recover from neutropenia and thrombopenia was 1 and 2 weeks respectively and recovery was not due to heavy use of hematopoietic growth factors as only one patient was treated with growth factors during the study. Those results are comparable with toxicities observed with ⁹⁰Y-ibritumomab tiuxetan, as evaluated in an integrated safety analysis of data from five clinical trials with ⁹⁰Y-ibritumomab tiuxetan: toxicity observed was primarily hematologic and lasting approximately 1 to 4 weeks [17]. Grade 4 neutropenia, thrombocytopenia, and anemia occurred in 30%, 10%, and 3% of patients respectively, and these grade 3 toxicities occurred in 30%, 53% and 13% respectively [17].

One of our patients developed grade 4 pancytopenia refractory to platelet transfusions and growth factors, requiring an autologous stem cell transplant 52 days after the treatment with ⁹⁰Y-rituximab. She had been treated with 2 prior chemotherapy regimens (EBVP-epirubicine, bleomycine, vinblastine, prednisone- and BEACOPP) and an autologous stem cell transplant 5 months before RIT. Anti-platelet antibodies and several anti-HLA class I antibodies were identified, accounting for refractoriness to platelet transfusions. Stem cell collection before RIT revealed poor culture with 5 CFU-GM (Colony Forming Unit-Granulocyte, Monocyte) and 0 BFU-E (Burst Forming Unit-Erythroid) for 2 × 10⁵ cells, reflecting a poor bone marrow reserve before RIT treatment [18,19].

Despite 34% of grade 3-4 neutropenia and no prophylactic use of antibiotics, no serious infections were observed. This is probably due to non disruption of gastrointestinal mucosal barriers, the fact that T-cells are unaffected by rituximab and maintained serum immunoglobulin

		DR ≥ 12 months	DR<12 months
Responding patients (n=23)		N=10 (43%)	N=13 (57%)
Histology	Follicular	7	7
	Other	3	6
Prior treatment lines	1	6	1
	>1	4	12
DR of last treatment	<1 an	4	8
	≥ 1 an	6	5
Response status	CR	9	8
	PR	1	5

Table 4: Characteristics of patients according to their duration of response (DR).

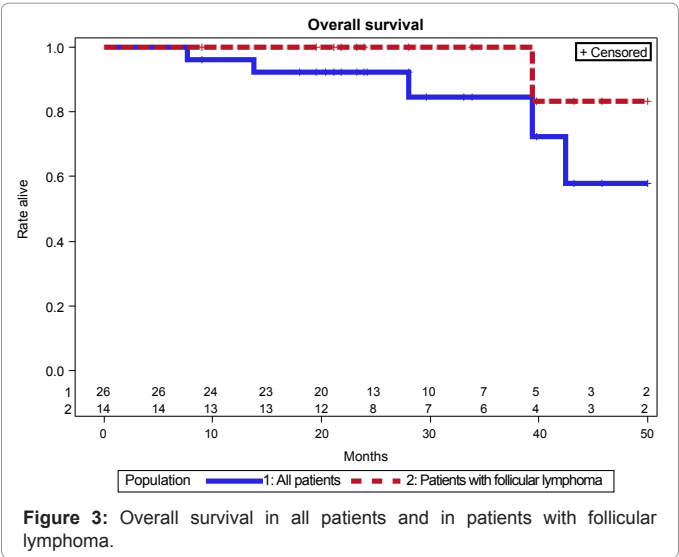
concentrations, despite B-cell depletion. Other side effects reported with ⁹⁰Y-ibritumomab tiuxetan are flu-like symptoms, including chills, fever, abdominal pain, and allergic reactions. Those were most linked to rituximab preload [17]. No infusion reaction has been observed in our study, probably due to the fact that premedication was administered before rituximab and infusion was performed during 4 hours.

The development of treatment-related myelodysplasic syndromes (MDS) and acute myeloid leukemia (AML) is a potential concern for patients receiving radioimmunotherapy. An extensive analysis of 746 patients who had received ⁹⁰Y-ibritumomab tiuxetan demonstrates that there does not seem to be an increased incidence of secondary MDS or AML: 2.5% MDS/AML occurred, 1.9 year after RIT, which is expected for this heavily pre-treated patient population [20]. In our study, one patient developed MDS (4%) 2 years after the treatment, but he had prior Total Body Irradiation for autologous stem cell transplant and chemotherapy with alkylating agents, which is known to be a risk factor for MDS [21].

The safety of the ⁹⁰Y-ibritumomab tiuxetan treatment schedule in NHL has been proven in various studies, with myelosuppression being the most important observed toxicity [1,17,22]. Radioimmunotherapy with rituximab labelled with Iodine-131 have also been well tolerated in a phase II study [11]. The available safety data for ⁹⁰Y-ibritumomab tiuxetan on one hand and the safety data of ¹³¹I-rituximab on the other hand justify performing no dose-escalating study, particularly in patients with a majority of low grade lymphomas in their early course of disease.

Both ⁹⁰Y-ibritumomab tiuxetan and ¹³¹I-tositumomab are contraindicated in following conditions: bone marrow involvement of more than 25%, external beam radiation therapy (EBRT) of >25% of active marrow, prior autologous stem cell transplant. In our study, those patients were not excluded, because of the availability of stem cells collection for rescue transplant in case of severe or prolonged toxicity. No significant increase in toxicity was observed in the 7 patients with prior autologuous stem cell transplant or in the 4 patients with bone marrow infiltration, neither in the patients with prior EBRT. However 3 of the 4 patients with bone marrow infiltration experienced reversible grade 4 neutropenia and thrombopenia, so the absence of significant differences could be attributable to the small number of patients.

In contrast, our study revealed that lower baseline neutrophil count significantly augments the risk of developing grade 3-4 neutropenia. Indeed some patients had already grade 1-2 neutropenia at baseline. These results suggest that baseline neutrophil count, as a surrogate of the bone marrow reserve, could be a predictive factor of toxicity complementary to bone marrow infiltration. No correlation was found



between baseline platelet count and thrombopenia as all patients had baseline platelets >150.000/μl.

Hematological toxicity not only depends on bone marrow reserve and infiltration degree, but also on bone marrow absorbed dose and subsequently on radiotracer's biodistribution. Inter-patient variabilities of radiotracer's biodistribution can vary with the spleen size, the amount of circulating B cells and the tumour load. Performing imaging with monoclonal antibody labelled with a positron emitting isotope such as Zirconium-89 in combination with PET scanning could be useful to visualize individual radiotracer's biodistribution and eventually define patients at high risk for toxicity [23,24].

Using the treatment schedule of ⁹⁰Y-ibritumomab tiuxetan for ⁹⁰Y-rituximab administration, we obtained an ORR of 88% with 65% of CR, assessed by ¹⁸FDG-PET/CT 3 months after treatment. For note, in the different trials using ⁹⁰Y-ibritumomab tiuxetan in NHL, ORR ranged from 67% to 80% with CR rates from 15% to 30% [1,22,25]. For ¹³¹I-rituximab, ORR of 76% with 53% of CR was obtained in 91 patients with relapsed or refractory indolent NHL [11]. However, no comparison can be made between trials with different treatment schedules, patient selection, radiotracers and imaging techniques used for response assessment. In our study response assessment was performed by ¹⁸FDG-PET/CT at 3 months in comparison to CT scan at 1 month in the ⁹⁰Y-ibritumomab tiuxetan trials and at 3 months in the ¹³¹I-rituximab trial.

No clinical factor was found to be significantly correlated with the response rate, but the small number of patients and the high response rate limit the analysis. Although, clinical efficacy was particularly prominent in the subgroup of patients with follicular histology (ORR of 100% with 79% of CR), a small number of patients with other histologies, like nodular lymphocyte predominant Hodgkin's lymphoma, mantle cell lymphoma or diffuse large B cell lymphoma did respond well, showing the interest to further explore RIT in those diseases.

For a median follow up of 29.6 months, the median PFS in our study was 9.1 months and median DR in responders was 8.7 months. No comparison can be done with ⁹⁰Y-ibritumomab tiuxetan trials or ¹³¹I-rituximab trials as progression was assessed on ¹⁸FDG-PET/CT in our study and not by CTscan. Median time to next treatment was 24 months, which is a better surrogate of the clinical efficacy of ⁹⁰Y-rituximab, particularly in follicular lymphomas, as small and asymptomatic lesions detected on periodically PET/CT wouldn't be diagnosed with a standard clinical follow up.

As there is no universally accepted definition of what constitutes a long-term durable response, we have defined as long-term responders the patients with duration of response of 12 months or more. As a reminder, duration of response was defined as the time elapsed between date of response assessment (3 months after treatment administration) and progression or death. Forty-three percent of the responding patients experienced durable response and their disease histology was mainly follicular lymphomas (70%), with two NLPHL and one transformed follicular lymphoma. All but one patient who had a PR relapsed within 12 months, confirming that induction of a CR is key to achieve a long-term durable response. This has been observed with ⁹⁰Y-ibritumomab tiuxetan [26] and ¹³¹I-rituximab [27]. ⁹⁰Y-ibritumomab tiuxetan has also been shown to be more effective when administered early in the course of disease [28]. In our study the proportion of patients with only

one prior treatment was higher in the long-term responders than in the short-term responders. Among long-term responders, 40% responded less than 12 months to their most recent therapy.

Conclusion

In conclusion, this prospective trial revealed that radioimmunotherapy with ⁹⁰Y-rituximab in patients with relapsed CD20+ B-cell lymphoma is safe, well tolerated and effective when the ⁹⁰Y-ibritumomab tiuxetan treatment schedule is used, while preserving quality of life.

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