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PII: S2452-1094(21)00240-2
DOI: https://doi.org/10.1016/j.adro.2021.100882
Reference: ADRO 100882

To appear in: *Advances in Radiation Oncology*

Received date: 7 July 2021
Accepted date: 15 December 2021

Please cite this article as: Zsolt Szakács , Amar Lal , Jorgen Kristensen , Nelli Farkas , Zsombor Ritter , Szabolcs Kiss , Anett Balikó , Hussain Alizadeh , ^{90}Y-ibritumomab tiuxetan in B-cell non-Hodgkin lymphomas: Real-world data from the United Arab Emirates, *Advances in Radiation Oncology* (2021), doi: https://doi.org/10.1016/j.adro.2021.100882

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Running title: Radioimmunotherapy in non-Hodgkin lymphomas

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Conflict of Interest: None.

Funding: None.

Data Availability Statement: All data are available within the supplementary material.

Acknowledgement: Khaled Qawasmeh of the Department of Nursing, Tawam Hospital—Johns Hopkins Medicine Affiliate, is acknowledged for his technical help with data collection.

TITLE: 90Y-ibritumomab tiuxetan in B-cell non-Hodgkin lymphomas: Real-world data from "Anonymized for Review"

RUNNING TITLE: Radioimmunotherapy in non-Hodgkin lymphomas

ABSTRACT

Introduction: B-cell non-Hodgkin lymphomas (NHL) are significant contributors to cancer-related mortality. In this single-arm, retrospective cohort study, we aimed to examine the outcomes of a radioimmunotherapeutic modality, 90Y-labelled ibritumomab tiuxetan (90YIT) in B-cell NHLs.

Methods: We conducted this study based on the data of the lymphoma registry of the "Anonymized for Review". All NHL patients subjected to 90YIT were eligible for inclusion. As the country lacked a national autologous stem cell transplantation (ASCT) center, many ASCT-eligible patients received 90YIT. We investigated overall (OS) and event-free survival (EFS) and safety outcomes.

Results: Between 2004 and 2008, 54 of 111 B-cell NHL patients received RIT. The therapy was applied as first-line treatment in 18 cases (33.3%) and as second- or later-line treatment in 36 cases (66.7%). All patients were evaluable for response (Table 1, Supplementary Table 1). In the first-line group consisting mainly follicular lymphoma cases, three of 18 cases died (16.7%) during follow-up (range: 22-67 months); median OS was not reached. No progression occurred after treatment (median EFS: 36.5 months [Q_1-Q_3: 30.5-44 months]). In the second- or later-line group consisting mainly diffuse large B-cell lymphoma cases, three of 36 cases died (8.3%) during follow-up (range: 4-68 months), median OS was not reached. One case of progression was registered (median EFS: 33 months [Q_1-Q_3: 30.5-44 months]). 90YIT had an acceptable short- and long-term safety profile.

Conclusion: The findings implicate that NHL patients may benefit from 90YIT as salvage treatment if ASCT is not available; however, this should be validated in randomized studies.

INTRODUCTION

Lymphoma encompasses an array of heterogeneous neoplasms that originate in lymphoid tissues but may arise in almost any tissue. The 2016 classification of the World Health Organization distinguishes, among others, mature B-cell neoplasms [1], which account for the vast majority of non-Hodgkin lymphomas (NHL) [2]. Based on data from the Surveillance, Epidemiology, and End Results Program (SEER), NHLs' age-adjusted incidence was 18.6/100,000 persons with a death rate of 5.3/100,000 persons in the United States in 2017, and NHLs are estimated to be responsible for 4.3% of all cancer cases and 3.3% of cancer-related deaths by 2020. Although 5-year survival has prolonged to 72.7% (2010–2016), one-third of the patients are diagnosed in an advanced stage [3].

Among NHLs, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) are the two most common subtypes, representing about 30 and 20% of the cases, respectively [2]. In the native Arab population, "Anonymized for Review", 59 and 7% of the cases had DLBCL and FL, respectively [4]. DLBCL has an expected 5-year survival of 63.8%, whereas that of FL is 89.0% in the United States [3].

In B-cell NHLs, conventional chemotherapy combined with rituximab, a monoclonal antibody targeting CD20 molecules on the cell surface, radiation therapy, high-dose chemotherapy with autologous stem cell transplantation (ASCT), and other target therapies offer a wide range of therapeutic options [2,5]. Despite the inherent sensitivity of most NHLs to initial chemo-immunotherapy, a high percentage of cases eventually relapse, and patients die of their disease [6]. In many cases, radioimmunotherapy (RIT) is a promising therapeutic option. The most commonly used ^{90}Y-labelled ibritumomab tiuxetan (90YIT) consists of an anti-CD20 murine monoclonal antibody conjugated with a radioactive isotope (^{90}yttrium) purely emitting beta particle (2.293 MeV, 2.6 days isotope half-life). The molecule specifically binds to CD20 positive cells, expressed in 98–99% of B-cell NHLs [7], minimizing the drug's uptake on normal tissues [8].

In 2002, a randomized controlled trial (RCT) was released, in which 90YIT proved to be superior over rituximab regarding overall response rate and complete response in relapsed or refractory low-grade, follicular, or transformed CD20 positive NHLs [9]. That year, 90YIT became the first RIT modality approved by the Food and Drug Administration (FDA) in the US [10]. According to the drug label, 90YIT is indicated (1) 'for the treatment of relapsed or refractory, low-grade or follicular B-cell NHLs'; and (2) 'for the treatment of previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy.' [11]. Since then, RCTs proved that 90YIT is effective as consolidation after

induction of remission [12,13] and as pre-treatment before ASCT in NHLs [14]. The current guidelines of the European Society for Medical Oncology (ESMO) do not mention RIT as a therapeutic option regarding DLBCL [15] and MZL [16], and do not recommend RIT as stand-alone therapy for induction (III, B) but propose it as a potential therapeutic option in patients after multiple relapses in the elderly (>65 years) in MCL [17]. In FL, ESMO preserves RIT mainly for selected, advanced (stage III-IV) cases. As a first-line therapy, RIT can be given for induction in low-risk FL if conventional chemotherapy is contraindicated (III, C), and may be considered for consolidation as an alternative for rituximab (II, B). In relapsing/progressing FL, RIT may be an option for those patients with comorbidities not eligible for chemotherapy (IV, B) [20].

In this study, we aimed to examine the efficacy and safety of 90YIT in a unique hospital setting in “Anonymized for Review”, where the indication of RIT was far broader than that approved by the FDA or the ESMO guidelines.

MATERIALS AND METHODS

The study was carried out in accordance with the Declaration of Helsinki (last amended in Fortaleza, Brazil, 2013).

Study design and data sources

This study is a single-arm, retrospective cohort study collecting data about consecutive patients referred from the regional hospitals to the "Anonymized for Review". Patients diagnosed between 2004 and 2008 were identified based on the International Classification of Diseases (ICD) 10 codes from the "Anonymized for Review".

Population and exposure

All patients with CD20 positive, B-cell NHLs were screened to identify those who received 90YIT. In all cases, the diagnoses were made based on histopathology from a lymph node or other tissue biopsy samples. All the histological samples were reported by two hematopathologists (co-signed), and all diagnoses were based on the third (2001) and fourth (2008) editions of the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues [21,22]. Staging was performed as per the Ann-Arbor classification [23].

The indications of 90YIT were far broader than those approved by the FDA because the country lacks a national center for ASCT (available only at remote centers). At the same time, most of our patients were expatriates with difficult financial conditions. Considering the facts mentioned above, the "Anonymized for Review" received full support from the "Anonymized for Review", by which all the expenses of 90YIT were generously sponsored. RIT-eligible patients included (1) patients with early-stage (I-II), non-bulky indolent B-cell NHL in whom limited field radiation therapy or rituximab monotherapy was planned (most of these patients refused to receive external beam radiation therapy); (2) patients who had relapsed FL after rituximab-containing systemic chemo-immunotherapy or had a transformation from FL to an aggressive B-cell NHL (with non-bulky disease and absence of significant bone marrow involvement); and (3) patients with primary DLBCL who relapsed after induction treatment with rituximab-based chemo-immunotherapy and those whose disease relapsed in extranodal sites with less than 25% involvement of bone marrow.

Assessment of remission status before treatments was based on the Cheson (1999) [24] and the revised Cheson criteria (2007) [25].

90YIT-treated patients were first preloaded with unlabeled rituximab as an infusion of 250 mg/m^2 on days 1 and 8. Then, on day 8, a therapeutic dose (14.8 MBq/kg, 45 patients) or a reduced dose (11.1 MBq/kg, nine patients, because of advanced age, hypocellular bone

marrow, more than three lines of previous chemotherapy, and poor performance status) of 90YIT was administered as an intravenous push over 10 minutes. The dose was given at least 4 weeks after the last treatment taken by each patient.

Outcomes

We analyzed overall survival (OS, calculated from the time of diagnosis) and event-free survival (EFS, calculated from the time of 90YIT treatment). Response to treatment was assessed according to the Cheson criteria (2007) [25] and determined based on all available clinical (physical examination, vital signs, laboratory tests, quality of life assessment, and the Eastern Cooperative Oncology Group [ECOG] score) and radiology follow-ups. The evaluation of 90YIT's efficacy was done by computed tomography scan every 3 months for the first 2 years, then every 6 months till present, unless there was clinical indication for earlier imaging study. Ancillary imaging (magnetic resonance imaging or positron emission tomography) was performed based on clinical indication. Re-biopsy was performed in all cases of relapse or progression. Safety outcomes included hematological toxicity and secondary neoplasms.

Patients were followed up regularly in the outpatient clinic while they were residing in UEA or, if they returned to their home countries, they were contacted by email or phone.

Statistical analysis

We calculated proportions (given in % of total) for categorical variables and central tendencies with the measure of dispersion (median with 25–75% quartiles [Q_1–Q_3]) after the assessment of the distribution with Q–Q plots, for continuous variables. We constructed a Kaplan-Meier curve for OS of patients receiving RIT in second or later lines. All calculations were carried out with R statistical language (version 4.1.1), the ‘survminer’ and ‘survival’ packages were used to generate the Kaplan-Meier curve.

RESULTS

Characteristics of the patients included

A total of 111 NHL patients were identified, of which 54 (48.6%) received 90YIT. Of these cases, 18 (33.3%) received RIT as first-line, whereas the other 36 (66.7%) patients received RIT as second- or later-line therapy. Characteristics of the patients are summarized in Table 1. In the 90YIT group, 27 patients (50.0%) had stage IV disease, only 4 with stage I; 10 and 13 patients were classified as stages II and III, respectively. The average number of previous treatment regimens before RIT was 3 (range of 1 to 5). After induction, 24 cases (44.4%) were in complete remission; the rest were in partial remission.

Effectiveness

All patients were evaluable for response (Table 1, Supplementary Table 1).

In patients received RIT as first-line therapy, the length of follow-up ranged between 22 and 67 months from diagnosis. Altogether, three of 18 cases died (16.7%); median OS was not reached. No progression occurred after RIT treatment during follow-up (median EFS: 36.5 months [Q_1-Q_3: 30.5–44 months]).

In patients received RIT as second- or later-line therapy, the length of follow-up ranged between 4 and 68 months from diagnosis. Altogether, three of 36 cases died (8.3%); median OS was not reached (Figure 1). One case did not respond to treatment at all and died seven days after; there was no case of progression otherwise (median EFS: 33 months [Q_1-Q_3: 30.5-44 months]).

Safety

Grade 3–4 hematologic toxicities occurred in seven patients (13.0% of total, all following 14.8 MBq/kg dose of 90YIT); all were reversible with supportive therapies. Six patients (11.1% of total) had prolonged severe thrombocytopenia (platelet count <10 G/L). These patients received 1–5 sessions of platelet transfusions with an average of 2 units of pooled platelet transfusion per session. None of these cases had clinically significant bleeding. Two out of these seven cases also received packed red blood cell transfusion on one single occasion. One serious adverse event occurred: a patient developed febrile neutropenia. We did not identify any secondary neoplasms or transformation to aggressive disease in our cohort of patients, except for one DLBCL case developing acute myeloid leukemia, which resulted in a fatal outcome 22 months after 90YIT treatment.

DISCUSSION

This study aimed to examine B-cell NHL patients' outcomes, who were treated with 90YIT. The unique setting of our study is ensured by the facts (1) that ASCT was not available in our center, (2) that many patients did not afford to move to remote centers for ASCT treatment, (3) that 90YIT-eligible patients were offered to receive the treatment in the first line, and (4) that 90YIT was well-funded, so that is available for all eligible patients. Consequently, the indication of 90YIT was far broader than that described in the drug's labels and extended the application of this treatment modality beyond the guidelines. In our study population comprising indolent and aggressive B-cell NHL cases, patients treated with 90YIT showed good EFS both in first and later lines, while the safety profile of the therapy was acceptable.

The efficacy of radioimmunotherapy was investigated by many studies in the rituximab era [26]. 90YIT, as first-line monotherapy, was proven effective in a phase II trial in FL (overall response rate was 87%; in patients aged >50 years with stage II–IV disease) [27] as well as in bulky, advanced FL [28]. According to recent, long-term follow-up data from the international RIT Network, patients receiving 90YIT in first line had a higher 8-year OS and PFS compared to those treated with the drug after relapse (78.1 vs. 54.5% and 53.6 vs. 29.6%, respectively) [29]. In refractory or relapsing FL cases, 90YIT proved to be effective on the long-term (≥5 years of follow-up with mean estimated OS of 82.3 months), with acceptable health-related quality of life [30]. In our study, the length of follow-up was a median 3 years for the 90YIT group (median OS and PFS were not being reached) but no FL cases treated with 90YIT relapsed during follow-up. With this regard, PFS may be more informative about the efficacy of the treatment than OS due to the crossover and sequential treatments after relapse [31]. Our results on efficacy of treatment are comparable to that observed in the literature. Note that we did not use the treatment in bulky cases (as per the drug's label), and most patients refused to receive external beam radiotherapy. Besides, the proportion of patients receiving 90YIT in first-line (33%) was higher than that observed in the literature (19%) [29], which is probably the consequence of our unique setting (easy-to-access RIT vs. difficult-to-access ASCT, Fig. 1).

In DLBCL, 90YIT proved to be effective as first-line treatment, following R-CHOP, in patients >60 years of age (estimated 2-year PFS was 75%) [32], in high-risk elderly patients on the short-term (estimated 2-year PFS was 85%) [33] as well as on the long-term (estimated 7-year PFS and OS were 36.1 and 38.9%, respectively) [34]. These studies included exclusively (or dominantly) ASCT-ineligible DLBCL cases. In our study involving patients treated with

90YIT both in the first and later lines, OS and EFS were comparable to that reported in the literature.

While being effective, 90YIT treatment has an acceptable short-term safety profile [35]. The most informative controlled study is a phase III RCT comparing 90YIT to no treatment as consolidation therapy in 409 FL cases. In this study, grade 3 or 4 non-hematological toxicities affected only 5.4% of the treated cases (of which infections accounted for 1%), compared to 5.9% in the no-treatment arm [13]. In general, thrombocytopenia (<25–50 G/L) is expected to develop 4–6 weeks after treatment, whereas less apparent decline in hemoglobin level (15–25% compared to baseline) is expected a few weeks later [27,32,33]. Another minor concern is the deteriorating quality of life with 90YIT [30]; however, in a study, the treated elderly NHL patients (in an FL-dominant population) scored similarly for global health and social functioning compared to that in the healthy population [36]. Long-term follow-up data of 90YIT-treated cases are scarce. In the report of the RIT Network (285 FL cases), secondary neoplasms developed in 12.5% (22 solid and 13 hematological neoplasms, most commonly acute myeloid leukemia and myelodysplastic syndrome), and histological transformation occurred in 5.7% of the cases with a median follow-up of 8.2 years [29]. In our study, the treatment's short-term safety profile was similar to that reported earlier: 13.0% of the cases developed grade 3 or 4 hematological toxicity, of which none urged therapy cessation. Although we had one case of acute myeloid leukemia, the follow-up length does not allow us to draw firm conclusions about long-term safety (the carcinogenic effects of radiation may manifest 5–10 years later than the exposure).

Our study has several strengths and limitations. The main strength of our study is its unique setting: many ASCT-eligible patients were treated with 90YIT due to the unavailability and unaffordability of ASCT. Our study's major limitation is the single-arm design and the retrospective nature, with their inherent limitations (vulnerability to selection and information bias). Besides, the median length of follow-up was shorter than that required to analyze the treatment's long-term safety. Finally, we did not investigate cost-effectiveness of 90YIT [37].

CONCLUSION

Our results imply that B-cell NHL patients treated with 90YIT experience OS and EFS, while the safety profile of RIT is acceptable. Based on these, B-cell NHL patients, particularly those with DLBCL, may benefit from 90YIT as adjunctive therapy if ASCT is not available. However, due to our study's limitations, these findings should be used for hypothesis-generating purpose for RCTs validating the associations.

AUTHORS' CONTRIBUTIONS

"Anonymized for Review"

ETHICS APPROVAL

This study was approved by "Anonymized for Review"; the need for written informed consent was waived.

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Figure legends

Fig 1. Overall survival of relapsing patients treated with 90Y-ibritumomab tiuxetan.

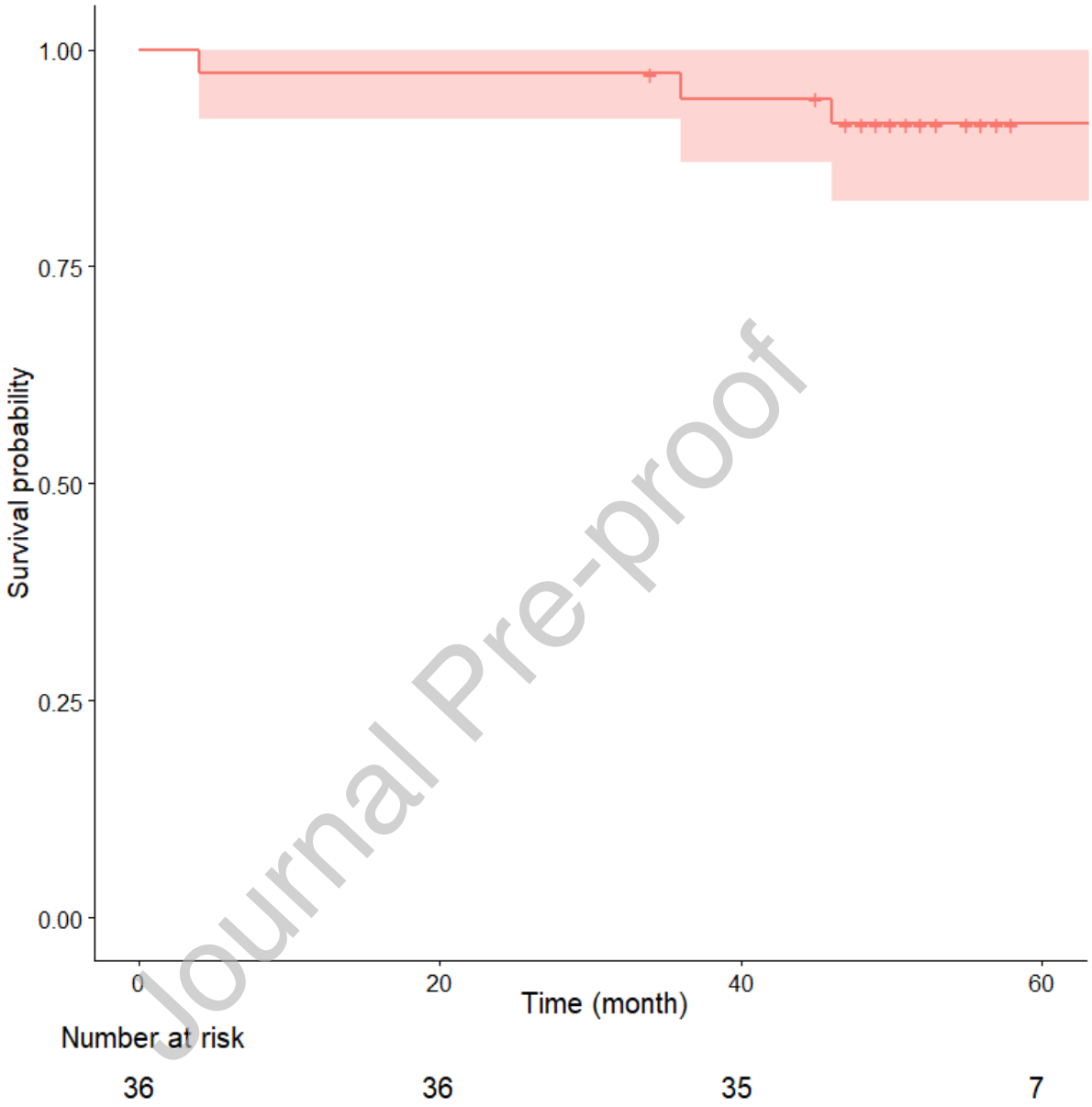

Table 1. Characteristics of patients received ^{90}Y-labelled ibritumomab tiuxetan treatment

	First-line treatment (n=18)	Second- or later line treatment (n=36)
Age at diagnosis (median [Q1–Q3] in months)	45.5 (43.3–59.8)	53.5 (45.8–62.8)
Males (n, [% of total])	10 (55.6)	23 (63.9)
Diagnostic period (years)		
2004–2006	16 (88.9)	26 (72.2)
2007–2008	12 (11.1)	10 (27.8)
Ethnicity		
African-Arab (n, [% of total])	17 (94.4)	29 (80.6)
Asian (n, [% of total])	1 (5.6)	7 (19.4)
Disease type		
Diffuse large B-cell lymphoma	3[a]	32[b]
Mantle cell lymphoma	1[a]	0
Follicular lymphoma	14	0
Marginal zone lymphoma	0	4
Time between diagnosis and progression to first-line treatment (median [Q1–Q3] in months)	15 (13–18)	15 (14–18)
Eastern Cooperative Oncology Group Performance Status		
0	0 (0.0)	3 (8.3)
1	5 (27.8)	12 (33.3)
2	11 (61.1)	18 (50.0)
3	2 (11.1)	3 (8.3)
4	0 (0.0)	0 (0.0)

[a]one case had central nervous system involvement. [b]two cases had central nervous system involvement.