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Scientific Article

^{90}Y-ibritumomab Tiuxetan in B-cell Non-Hodgkin Lymphomas: Real-world Data From the United Arab Emirates

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Abstract

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

Methods and Materials: We conducted this study based on data from the United Arab Emirates lymphoma registry. All patients with NHL subjected to ^{90}YIT were eligible for inclusion. The country of research lacked a national autologous stem cell transplantation (ASCT) center, but many ASCT-eligible patients received ^{90}YIT. We investigated overall survival (OS) and event-free survival (EFS), as well as safety outcomes.

Results: Between 2004 and 2008, 54 of 111 patients with B-cell NHL received radioimmunotherapy. The therapy was applied as first-line treatment in 18 cases (33.3%) and second- or later-line treatment in 36 cases (66.7%). All patients were evaluable for response. The first-line group consisted mainly of follicular lymphoma cases, and 3 of 18 patients died (16.7%) during the 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 range, 30.5-44 months]). The second- or later-line group consisted mainly of diffuse large B-cell lymphoma cases, and 3 of 36 patients died (8.3%) during the 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 range, 30.5-44 months]). ^{90}YIT had acceptable short- and long-term safety profiles.

Conclusions: The findings suggest that patients with NHL may benefit from ^{90}YIT as salvage treatment if ASCT is not available; however, this should be validated in randomized studies.

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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

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World Health Organization distinguishes, among others, mature B-cell neoplasms,[1] which account for the vast majority of non-Hodgkin lymphomas (NHLs).[2] Based on data from the Surveillance, Epidemiology, and End Results program, the age-adjusted incidence of NHL was 18.6 per 100,000 persons with a death rate of 5.3 per 100,000 persons in the United States in 2017, and NHLs were estimated to be responsible for 4.3% of all cancer cases and 3.3% of cancer-related deaths in 2020. Although the 5-year survival has prolonged to 72.7% (2010-2016), one-third of patients are diagnosed at an advanced stage (https://seer.cancer.gov/).[3]

Among NHLs, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) are the 2 most common subtypes, representing approximately 30% and 20% of cases, respectively.[2] In the native Arab population, data from the United Arab Emirates lymphoma registry showed that 59% and 7% of cases were DLBCL and FL, respectively.[4] In the United States, DLBCL has an expected 5-year survival rate of 63.8%, and the rate of FL is 89.0% (https://seer.cancer.gov/).

In B-cell NHLs, conventional chemotherapy combined with rituximab (a monoclonal antibody targeting cluster of differentiation 20 [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 chemoimmunotherapy, 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-labeled ibritumomab tiuxetan (^{90}YIT) 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% to 99% of B-cell NHLs,[7] minimizing the drug's uptake on normal tissues.[8]

In 2002, the results of a randomized controlled trial (RCT) were released, showing that ^{90}YIT 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, ^{90}YIT became the first RIT modality approved by the U.S. Food and Drug Administration (FDA) in the United States.[10] According to the drug label, ^{90}YIT is indicated "for the treatment of relapsed or refractory, low-grade, or follicular B-cell NHLs" and "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 have proven that ^{90}YIT is effective as consolidation after induction of remission[12,13] and as pretreatment before ASCT in patients with NHLs.[14]

The current guidelines of the European Society for Medical Oncology (ESMO) do not mention RIT as a therapeutic option for DLBCL[15] and marginal zone lymphoma,[16] and do not recommend RIT as stand-alone therapy for induction (stage IIIB). The guidelines do propose RIT as a potential therapeutic option in patients after multiple relapses in the elderly (>65 years) in mantle cell lymphoma.[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 (stage IIIC), and may be considered for consolidation as an alternative for rituximab (stage IIB). In relapsing/progressing FL, RIT may be an option for patients with comorbidities who are not eligible for chemotherapy (stage IVB).[18]

In this study, we aimed to examine the efficacy and safety of ^{90}YIT in a unique hospital setting using data from the United Arab Emirates lymphoma registry, where the indication of RIT was far broader than that approved by the FDA or the ESMO guidelines.

Methods and Materials

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 of data on consecutive patients from regional hospitals in the United Arab Emirates lymphoma registry. Patients diagnosed between 2004 and 2008 were identified based on International Classification of Diseases 10th Revision codes in the United Arab Emirates registry.

Population and exposure

All patients with CD20 positive, B-cell NHLs were screened to identify those who received ^{90}YIT. In all cases, the diagnoses were made based on histopathology test results from lymph node or other tissue biopsy samples. All histologic samples were reported by 2 hematopathologists (cosigned), and all diagnoses were based on the 3rd (2001) and 4th (2008) editions of the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues.[19,20] Staging was performed per the Ann-Arbor classification.[21]

The indications of ^{90}YIT were far broader than those approved by the FDA, because the country of research 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 these facts, the United Arab Emirates provided full support and all ^{90}YIT expenses were generously sponsored.

RIT-eligible patients included patients with early-stage (I-II), nonbulky, indolent B-cell NHL in whom limited field radiation therapy or rituximab monotherapy was planned (most patients refused external beam radiation therapy); patients who had relapsed FL after rituximab-containing systemic chemoimmunotherapy or had a transformation from FL to an aggressive B-cell NHL (with nonbulky disease and absence of significant bone marrow involvement); and patients with primary DLBCL who relapsed after induction treatment with rituximab-based chemoimmunotherapy 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)[22] and revised Cheson criteria (2007).[23] First, ^{90}YIT-treated patients were 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 reduced dose (11.1 MBq/kg; 9 patients, because of advanced age, hypocellular bone marrow, >3 lines of previous chemotherapy, and poor performance status) of ^{90}YIT 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 time of ^{90}YIT treatment). Response to treatment was assessed according to the Cheson criteria (2007),[23] and determined based on all available clinical (physical examination, vital signs, laboratory test results, quality of life assessment, and Eastern Cooperative Oncology Group score) and radiology follow-ups. The evaluation of ^{90}YIT's efficacy was done by computed tomography scan every 3 months for the first 2 years, then every 6 months until 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. A rebiopsy was performed in all cases of relapse or progression. Safety outcomes included hematologic toxicity and secondary neoplasms.

Patients were followed up with regularly at the outpatient clinic while residing in the United Arab Emirates or, if returned to their home countries, contacted by email or phone.

Statistical analysis

We calculated proportions (% 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 the OS of patients receiving RIT in second or later lines. All calculations were carried out with R statistical language (version 4.1.1), and the "survminer" and "survival" packages were used to generate the Kaplan-Meier curve.

Results

Characteristics of patients included

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

Effectiveness

All patients had data that were evaluable for response (Table 1, Table E1). In patients who received RIT as first-line therapy, the length of follow-up ranged between 22 and 67 months from the time of diagnosis. Altogether, 3 of 18 patients died (16.7%), and the 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 who received RIT as second- or later-line therapy, the length of follow-up ranged between 4 and 68 months from the time of diagnosis. Altogether, 3 of 36 patients died (8.3%), and the median OS was not reached (Fig. 1). One case did not respond to treatment at all, and the patient died 7 days later. There was no case of progression otherwise (median EFS, 33 months [Q_1-Q_3, 30.5-44 months]).

Safety

Grade 3 to 4 hematologic toxicities occurred in 7 patients (13.0% of total; all after 14.8 MBq/kg dose of ^{90}YIT), and 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 to 5 sessions of platelet transfusions with an

Table 1 Characteristics of patients who received ^{90}Y-labeled ibritumomab tiuxetan treatment

	First-line treatment (n = 18)	Second- or later-line treatment (n = 36)
Age at time of diagnosis, mo, median (Q1-Q3)	45.5 (43.3-59.8)	53.5 (45.8-62.8)
Male, n (% of total)	10 (55.6)	23 (63.9)
Diagnostic period, y		
2004-2006	16 (88.9)	26 (72.2)
2007-2008	12 (11.1)	10 (27.8)
Ethnicity, n (% of total)		
African-Arab	17 (94.4)	29 (80.6)
Asian	1 (5.6)	7 (19.4)
Disease type, n		
Diffuse large B-cell lymphoma	3*	32†
Mantle cell lymphoma	1*	0
Follicular lymphoma	14	0
Marginal zone lymphoma	0	4
Time between diagnosis and progression to first-line treatment, mo, median (Q1-Q3)	15 (13-18)	15 (14-18)
Eastern Cooperative Oncology Group performance status score, n (%)		
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)

* One case had central nervous system involvement.
† Two cases had central nervous system involvement.

average of 2 units of pooled platelet transfusion per session. None of these cases had clinically significant bleeding. Two of these 7 cases also received a packed red blood cell transfusion on a single occasion. One serious adverse event occurred when a patient developed febrile neutropenia. We did not identify any secondary neoplasms or transformation to aggressive disease in our cohort of patients, except for 1 patient with DLBCL developing acute myeloid leukemia, which resulted in a fatal outcome 22 months after ^{90}YIT treatment.

Discussion

This study aimed to examine the outcomes of patients with B-cell NHL who were treated with ^{90}YIT. The unique setting of our study is ensured by the facts that ASCT was not available at our center, many patients could not afford to move to remote centers for ASCT treatment, ^{90}YIT-eligible patients were offered treatment in the first line, and ^{90}YIT treatment was well-funded and available for all eligible patients. Consequently, the indication of ^{90}YIT 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 comprised of indolent and aggressive B-cell NHL cases, patients treated with ^{90}YIT showed good EFS, both in first and later lines, and the safety profile of the therapy was acceptable.

The efficacy of RIT has been investigated by many studies in the rituximab era.[24] As first-line monotherapy, ^{90}YIT was proven effective in a phase 2 trial in FL (overall response rate: 87% in patients age >50 years with stage II-IV disease),[25] as well as in bulky, advanced FL.[26] According to recent, long-term, follow-up data from the international RIT Network, patients receiving ^{90}YIT in first line had a higher 8-year OS and progression-free survival (PFS) compared with those treated with the drug after relapse (78.1 vs 54.5% and 53.6 vs 29.6%, respectively).[27] In refractory or relapsing FL cases, ^{90}YIT proved to be effective in the long term (≥5 years of follow-up; mean estimated OS, 82.3 months) with an acceptable health-related quality of life.[28]

In our study, the length of follow-up was a median 3 years for the ^{90}YIT group (median OS and EFS were not reached), but no FL cases treated with ^{90}YIT relapsed during follow-up. In this regard, PFS may be more informative

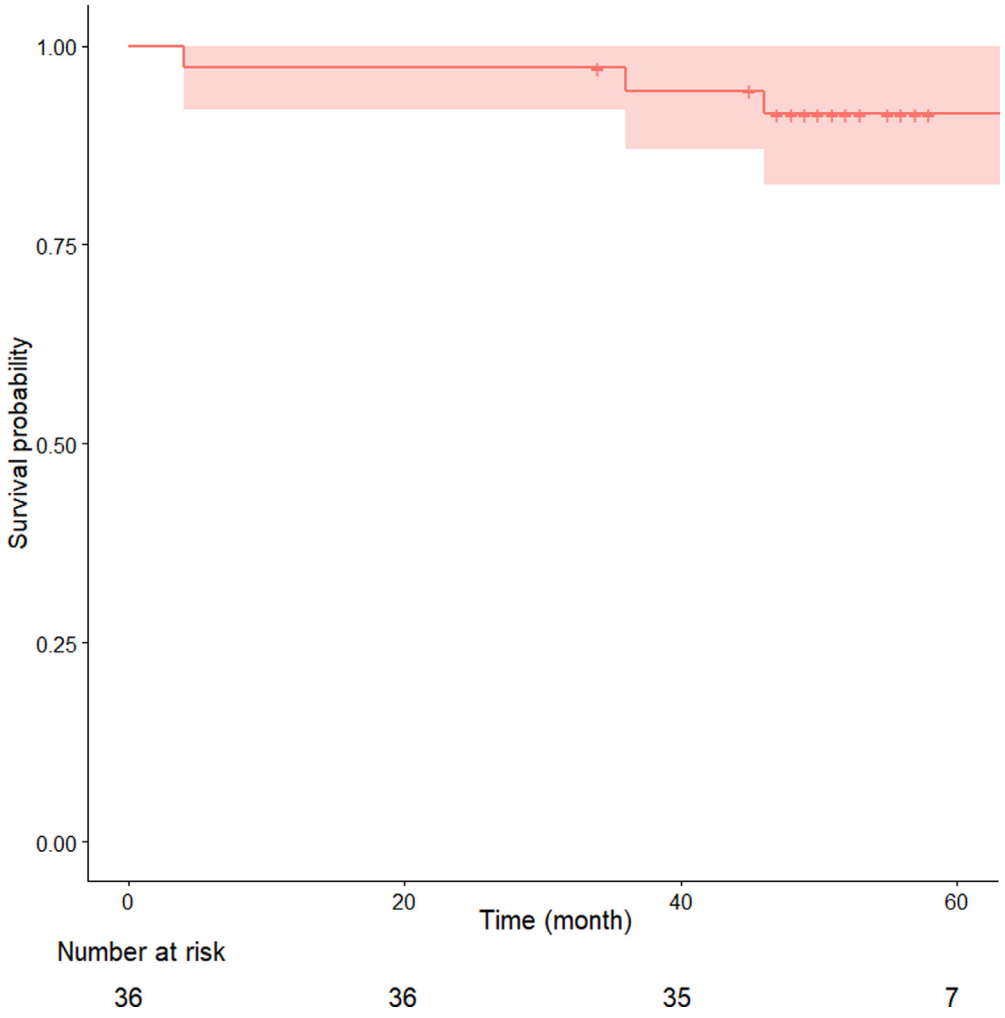

Fig. 1 Overall survival of relapsing patients treated with ^{90}Y-ibritumomab tiuxetan. Crosses indicate censoring, the red area refers to 95% confidence interval.

about the efficacy of the treatment than OS due to the crossover and sequential treatments after relapse.[29] Our results on efficacy of the treatment are comparable with those observed in the literature. Of note, we did not use the treatment in bulky cases (per the drug's label), and most patients refused external beam radiation therapy. Besides, the proportion of patients receiving ^{90}YIT in first line (33%) was higher than that observed in the literature (19%),[27] which is probably the consequence of our unique setting (easy-to-access RIT vs difficult-to-access ASCT; Fig. 1).

In DLBCL, ^{90}YIT proved to be effective as first-line treatment after R-CHOP in patients age >60 years (estimated 2-year PFS: 75%),[30] short term in high-risk elderly patients (estimated 2-year PFS: 85%),[31] as well as long term (estimated 7-year PFS and OS: 36.1% and 38.9%, respectively).[32] These studies included exclusively (or dominantly) ASCT-ineligible DLBCL cases. In our study of patients treated with ^{90}YIT both in the first and later lines, OS and EFS were comparable with those reported in the literature.

Although effective, ^{90}YIT treatment has an acceptable short-term safety profile.[33] The most informative controlled study is a phase 3 RCT comparing ^{90}YIT to no treatment as consolidation therapy in 409 FL cases. In this study, grade 3 or 4 nonhematologic toxicities affected only 5.4% of the treated cases (of which infections accounted for 1%) compared with 5.9% in the no-treatment arm.[13] In general, thrombocytopenia (<25-50 G/L) is expected to develop 4 to 6 weeks after treatment, but a less apparent decline in hemoglobin level (15%-25% compared with baseline) is expected a few weeks later.[25,30,31]

Another minor concern is the deteriorating quality of life with ^{90}YIT[28]; however, in another study, treated elderly patients with NHL (in an FL-dominant population) scored similarly for global health and social functioning compared with that in the healthy population.[34] Long-term follow-up data of ^{90}YIT-treated cases are scarce. In the report of the RIT Network (285 FL cases), secondary neoplasms developed in 12.5% (22 solid and 13 hematologic neoplasms, most commonly acute myeloid

leukemia and myelodysplastic syndrome), and histologic transformation occurred in 5.7% of cases with a median follow-up of 8.2 years.[27] In our study, the treatment's short-term safety profile was similar to that reported earlier, with 13.0% of cases developing grade 3 or 4 hematologic toxicity of which none urged therapy cessation. Although we had 1 case of acute myeloid leukemia, the follow-up length did not allow us to draw firm conclusions about long-term safety (carcinogenic effects of radiation may manifest 5-10 years later than 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 ^{90}YIT due to the unavailability and unaffordability of ASCT. Our study's major limitation is the single-arm design and 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 the cost effectiveness of ^{90}YIT.[35]

Conclusions

Our results suggest that patients with B-cell NHL treated with ^{90}YIT experience satisfactory OS andEFS with acceptable safety profile. Based on this, patients with B-cell NHL, and particularly those with DLBCL, may benefit from ^{90}YIT 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.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.adro.2021.100882.

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