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The Potency of Radiolabelled Monoclonal Antibody Anti-CD20 as A Targeted Therapy for B-cell Non-Hodgkin Lymphoma: A Review

Hastono Ridwansyah[1], Achmad Hussein S. Kartamihardja*[2], and Muhammad Hasan Bashari[3], Bethy Suryawathy Hernowo[4]

[1]Graduate School of Biomedical Science, Faculty of Medicine, Universitas Padjadjaran, Jl. Eijkman 38, Bandung, Indonesia, Email: ridwansyah19001@mail.unpad.ac.id

[2]Department of Nuclear Medicine and Molecular Imaging, Faculty of Medicine, Universitas Padjadjaran, Jl. Eijkman 38, Bandung, Indonesia, Email: husseinkartamihardja@gmail.com

[3]Department of Pharmacology and Therapy, Faculty of Medicine, Universitas Padjadjaran, Jl. Eijkman 38, Bandung, Indonesia, Email: bashari@unpad.ac.id

[4]Department of Anatomical Pathology, Faculty of Medicine, Universitas Padjadjaran, Jl. Eijkman 38, Bandung, Indonesia, Email: bethy.suryawathy@unpad.ac.id

***Author for Correspondence**: Achmad Hussein S. Kartamihardja
Email: husseinkartamihardja@gmail.com

ABSTRACT

The treatment of B-cell non-Hodgkin lymphoma (NHL) still has the problems, such as a high rate of relapse and refractory case. The use of radioimmunotherapy (RIT) appears to be a treatment modality expected to resolve the problem. However, RIT remains underused in a clinical practice setting for B-cell NHL treatment. This study was conducted to find out the treatment potency of RIT in patients with B-cell lymphoma, particularly in indolent or aggressive NHL patients. This literature review was conducted in a systematic review from many kinds of literature published from 2010 to 2020 using keyword combinations, including "radioimmunotherapy", "aggressive lymphoma", "diffuse large B-cell lymphoma", "indolent lymphoma", and "follicular lymphoma". Those keywords were entered in the advanced search of Cochrane Library and Pubmed. There were 84 articles collected based on those keywords and among them, only 30 articles containing antibody anti-CD20 fulfilled the inclusion and exclusion criteria. Articles reporting the efficacy and safety of RIT as the first-line and consolidation of aggressive and indolent lymphoma were 5 and 11 articles respectively, and as relapsed/refractory treatment were 9 and 5 articles, respectively. Radiopharmaceuticals used were ^{90}Y-ibritumomab-tiuxetan, ^{131}I-tositumomab, and ^{131}I-rituximab. The conclusion is that RIT, mainly ^{90}Y-ibritumomab tiuxetan, has shown favorable and safe clinical outcomes for indolent and aggressive B-cell NHL, and it has a greater opportunity of being used as B-cell NHL treatment to improve ORR and overall patient survival in a clinical practice setting.

Keywords: *H*igh-grade lymphoma, low-grade lymphoma, non-Hodgkin lymphoma, radioimmunotherapy

Correspondence:
Achmad Hussein S. Kartamihardja
Department of Nuclear Medicine and Molecular Imaging, Faculty of Medicine, Universitas Padjadjaran, Jl. Eijkman 38, Bandung, Indonesia
Email: husseinkartamihardja@gmail.com

INTRODUCTION

Lymphoma is a malignant tumor arisen from the lymphoid organ. It is divided into two types, such as Hodgkin and non-Hodgkin lymphoma. Non-Hodgkin lymphoma (NHL) is the most common type of lymphoma, which affects over 500,000 people, and causes 248,724 deaths worldwide in 2018[1]. An estimated 5-year relative survival for non-Hodgkin and Hodgkin lymphoma (HL) is 72.7% and 87.4% respectively. The mortality rate of NHL is higher than HL. Although lymphoid malignancy can be derived from T-cells. About 90% of all lymphoma diseases are of B-cell origin[2,3].

Rituximab, cyclophosphamide, hydroxidaunorubicin, oncovin, and prednisone (R-CHOP) are the standard regimen for B-cell NHL treatment. Each drug of this regimen has a different mechanism of action, but it synergizes in inhibiting the development of B-cell lymphoma at different phases[4,5]. Although CHOP regimen seemed to be effective initially for the treatment of B-cell NHL, only 45-55% showed complete remission and cured about 30% of patients[6]. The results were unsatisfactory because relapses were frequent and the prognosis of relapsing patients was poor.

The mechanism underlying the relapse and treatment failure may be due to drug resistance. The molecular mechanism of resistance to alkylating agents is consisting of intrinsic and extrinsic mechanisms including pre, on, and post-target mechanisms. The lymphoma cells are responsible for the intrinsic mechanism of drug resistance. Chemotherapy agent cannot work properly in the lymphoma cells due to one or more factors, such as inhibition of active drug transport, inhibition of pro-drug activation into active metabolites, increased drug degradation, and drug efflux, interference with drug mode of action, and disruption of DNA damage response pathways[7,8].

The extrinsic mechanisms do not come from lymphoma cells but the microenvironment around the cells, such as hypoxia, acidosis, increased release of pro-survival cytokines or growth

factor, cell-to-cell contact, and changes in the component of the extra-cellular matrix. Both intrinsic and extrinsic mechanisms may be responsible for CHOP regimen, but the exact mechanism leading to the drug resistance in B-cell NHL requires further investigation[8].

The discovery of anti-CD20 monoclonal antibody (mAb) has changed the survival of lymphoma patients. This mAb showed tolerable safety, pharmacokinetic, and favorable efficacy in NHL patients[9,10]. Rituximab was the first anti-CD20 approved by food and drug administration (FDA) to treat B-cell NHL[11]. Rituximab works specifically by targeting the CD20 protein expressed on the superficial membrane of B-cell lymphoma. Rituximab has the primary function of recognizing mature B-cells but not pre-B cells or plasma cells, so the specificity of this monoclonal antibody is beyond doubt.

Once rituximab binds to CD20 on the surface of the B-cell membrane, this can cause cell death through certain mechanisms, such as antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cellular cytotoxicity (CDC), induction of apoptosis, CD20 redistribution to lipid rafts, and modulation of B-cell signaling[12,13].

Rituximab is recommended in combination with CHOP regimen as the first-line treatment in B-cell NHL to promote clinical improvement[14]. Some reports of studies to compare the efficacy of CHOP regimen and R-CHOP showed consistent results. R-CHOP has a significantly better effect on clinical improvement in patients with high and low-grade B-cell NHL[15,16]. Research conducted by salles et al. showed that 2 years of the administration of rituximab maintenance following initial R-CHOP in patients with follicular lymphoma can significantly improve the progression-free survival (PFS)[17].

With the long-term use of CHOP regimen, many patients cannot tolerate the side effects of the chemotherapy due to the long-term use of CHOP regimen, particularly the elderly or patients with specific comorbidities. Some patients also feel uncomfortable due to nausea, neuropathy, hair loss, gastric, and mucositis [16].

One of the non-chemotherapeutic modalities for B-cell NHL is radioimmunotherapy. The researchers combine the mAb with a radioisotope. The mAb serves as a radioisotope carrier molecule to the target cell. The first radiopharmaceutical approved by FDA for patients with relapsed or refractory B-cell NHL was Zevalin (Yttrium-ibritumomab) in 2002 and followed by Bexxar (Iodine131-tositumomab)[18]. RIT using radiopharmaceuticals showed favorable outcomes in low-grade B-cell lymphoma patients in form of increased response rate and long-lasting remission, but this method has received less attention from the medical community[19–22]. RIT containing tositumomab was withdrawn from the market in 2014 due to [23].

Ibritumomab and tositumomab are murine monoclonal antibodies that often cause rejection or clearance from the human body by immune cells. To overcome this problem, rituximab as a chimeric human-mouse monoclonal antibody was introduced to be labeled with a certain radioisotope agent to form a better radiopharmaceutical. In the last decade, there are many RIT drugs based on rituximab and various chelators to conjugate radioisotope with the antibodies as the new radiopharmaceutical innovations that are more stable, effective, tolerable, and optimal half-time[24–26].

Radiopharmaceuticals for RITs containing anti-CD20 mAb have not been used routinely for the treatment of patients with B-cell lymphoma. National Comprehensive Cancer Network (NCCN) recently published guidelines for treating B-cell NHL involving immunotherapy, chemotherapy, radiotherapy, radioimmunotherapy, and autologous stem-cell transplantation (ASCT)[14].

Many studies on the use of RIT have shown good results, and a certain radiopharmaceutical has been approved by FDA for use in patients with relapsed and refractory follicular lymphoma. However, the utilization of RIT remains unclear and underutilized for low- and high-grade B-cell lymphoma in a clinical practice setting[27,28].

This review article will describe whether a particular RIT can be recommended as an effective first-line and consolidation for previously untreated patients or as a relapsed/refractory treatment for B-cell NHL patients in clinical practice settings. It also describes what types of RIT can provide the most promising results for indolent and aggressive B-cell NHL patients.

MATERIAL AND METHODS

Study Design and Protocol

The PRISMA checklist guided the reporting of this systematic review[29]. The study protocol began with collecting data and references relevant to the efficacy and safety of using RIT for the treatment of patients with B-cell NHL, assessing and elaborating the literature, providing analysis-synthesis results, and drawing some conclusions.

Eligibility criteria

Articles reporting the efficacy and safety of using RIT in phase-II or -III clinical trials in patients with indolent and aggressive B-cell NHL were included in this review article. Those studies should involve humans as subjects, have ethical approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), and be published within the past decade. The articles that were excluded were review articles and systematic review articles, as well as articles from studies that did not use anti-CD20 mAb.

Search strategy and data collection

The data collection was carried out by searching for relevant literature published in the last 10 years in the Pubmed and Cochrane library. A further search was by entering the following keywords: "radioimmunotherapy" AND "diffuse large B cell lymphoma", "radioimmunotherapy" AND "aggressive lymphoma", "radioimmunotherapy" AND "follicular lymphoma", as well as "radioimmunotherapy" AND "slow lymphoma". The google scholar search engine is used to get the full text of literature.

RESULTS

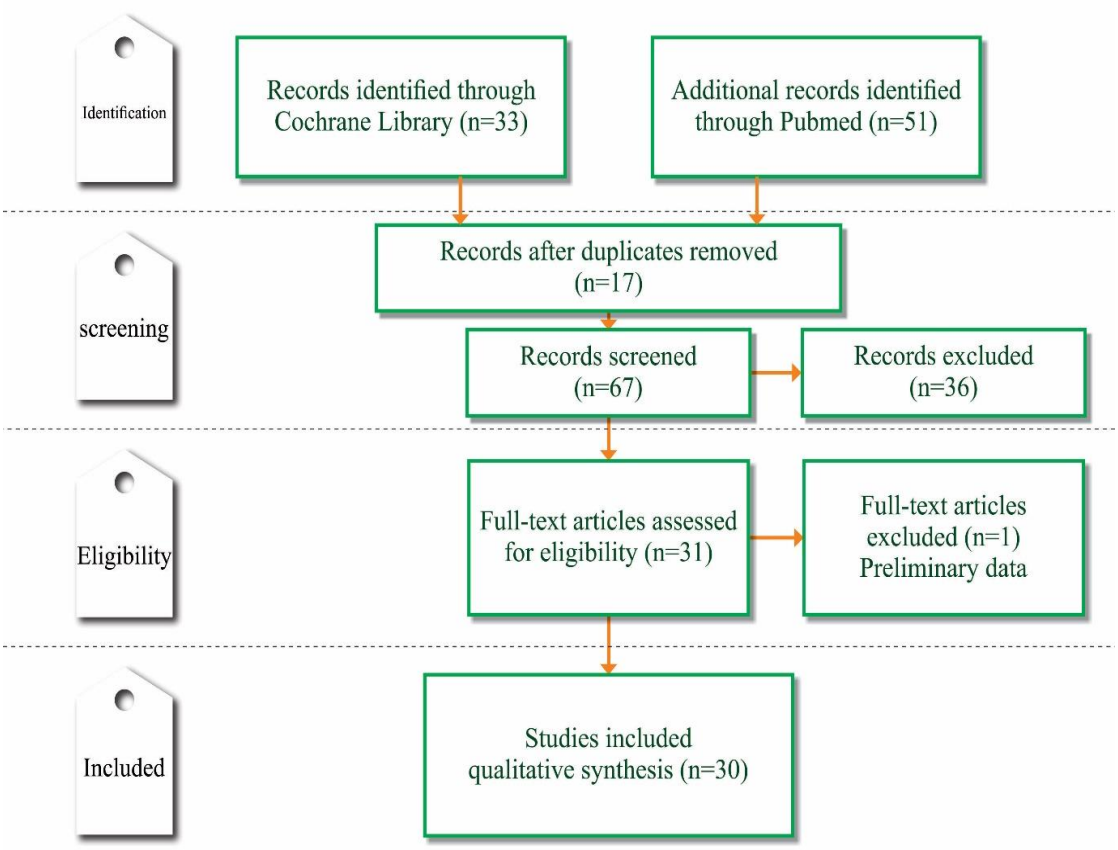

Figure 1. The result of the search reported through PRISMA flow diagram

The identification process for eligible studies is shown in Figure 1. Thirty of 84 related articles collected were included in the content analysis. Seventeen articles were excluded due to duplication, and 36 articles were excluded because 16 of them did not address RIT containing CD20 mAb, 7 articles were non-clinical trial studies, 5 articles were a phase-I trial, 4 articles lack efficacy data, and 4 are ongoing studies. Articles reporting the efficacy and safety of RIT as the first-line and consolidation treatment for previously untreated patients with aggressive and indolent B-cell NHL were 5 and 11 articles respectively, and as relapsed/refractory treatment were 9 and 5 articles respectively.

RIT as the first consolidation and relapsed/refractory treatment for aggressive B-cell lymphoma

A variety of radionuclides and anti-CD20 antibodies have been used for RIT in the last decade. The efficacy of using RIT as the consolidation treatment and in relapsed/refractory patients with aggressive NHL is shown in Table 1 and 2, respectively.

The safety of using RIT for aggressive lymphoma is shown in Supplementary Table S1 and S2. The side effects of using RIT are divided into two types of manifestations, such as hematological and non-hematological manifestations. Most of the side effects related to ^{90}Y-ibritumomab tiuxetan were less severe than standard chemotherapy for B-cell NHL. The majority of the symptoms of these events are reversible and manageable. Therefore, in the last decade, this approved RIT has been showing effective and tolerable results in B-cell NHL patients.

RIT ^{131}I-tositumomab, such as ^{90}Y-ibritumomab tiuxetan, showed tolerable side effects based on several studies. When RIT was given with chemotherapy regimen, the majority of infections appeared more frequent in the chemotherapy groups (53% and 64%) than in the RIT groups (8%), and an incidence of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) was 15% patients within 96.5 months follow-up[30]. The safety of rituximab was compared to ^{131}I-tositumomab in a phase-III clinical trial and showed that there was no significant difference in the mortality rate and the incidence of side effects[31]. RIT ^{131}I-rituximab has the same radionuclide with ^{131}I-tositumomab but a different anti-CD20 antibody. Some of the side effects were hematological and non-hematological manifestations. Five deaths were reported in three phase-II clinical trials involving 70 participants due to MDS (2 patients), chronic obstructive pulmonary disease (COPD) (1 patient), pneumonia (1 patient), and one patient after receiving total body irradiation (TBI) and autologous stem-cell transplantation (ASCT)[32–34]. Most of the participants experienced only reversible side effects. This RIT can cause the worst side effects if it was administered repeatedly. Among the 31 participants who received RIT more than once, two patients developed MDS and died a few weeks later[32,33]

Table 1. Data of RIT efficacy as the first consolidation treatment regimen for aggressive B-cell NHL

Design/Phase	NHL type	Median age	Number of patients	RIT regimens	Duration of *follow-up*	*Primary end-point*
Single-arm trial/II[a]	Advance stage DLBCL	64	84	RCHOP + CHOP + ^{131}I-tositumomab (consolidation)	3.9 years	ORR: 98%; 2-year-PFS: 69% 2-year-OS: 77%
Single-arm trial/II[b]	Early stage DLBCL	62	53	RCHOP+ ^{90}Y-ibritumomab tiuxetan (consolidation)	5.9 years	ORR: 98% 5-year survival: 94%
Open label/II[c]	DLBCL	60	20	RCHOP + ^{90}Y-ibritumomab tiuxetan (consolidation)	89.7 months	ORR 100%
Single-arm trial/II[d]	High-risk DLBCL High-risk MCL	60	39	High-dose chemotherapy + ^{131}I-tositumomab	75.9 months	ORR: 92.3% 5-year OS: 59.6%
Single-arm trial/II[e]	High-risk DLBCL	54	11	R-CHOP+IVAM/ICE+^{90}Y-Ibritumomab+BEAM+PBSCT	18.1 months	2-year-PFS: 18.2% OS: 36.4%

[a]Ref. [35]; [b]Ref. [36]; [c]Ref. [37]; [d]Ref. [30]; [e]Ref. [38]

Table 2. Data of RIT efficacy as the relapsed/refractory aggresive NHL treatment

Design/phase	NHL type	Median age	Number of patients	RIT regimens	Duration of *follow-up*	*Primary end-point*
Single-arm trial/II[a]	DLBCL	63	11	^{131}I-rituximab	55 months	ORR: 9%
Single-arm trial/II[b]	DLBCL FL, MCL, MZL	55	16	BEAM + ASCT + ^{131}I- Rituximab +ASCT	50.4 months 39.7 months	4-year-OS: 67% 4-year-PFS: 64%
Single-arm trial/II[c]	DLBCL, FL, MCL, CLL	58	40	^{90}Y-ibritumomab tiuxetan+ fludarabine+ TBI+ PBSCT	52 months	ORR: 83% 2-year PFS: 31% 2-year OS: 54%
RCT/III[d]	DLBCL	57-58	224	^{131}I-Tositumomab + BEAM Rituximab + BEAM	25.5 months	PFS: 48.6% (B-BEAM), PFS: 47.9% (R-BEAM)
Single-arm trial/II[e]	DLBCL, MCL, BL, FL, MZL	63	31	^{131}I-rituximab (repeated administration)	21.8 months	ORR: 68%
Single-arm trial/II[f]	DLBCL	53	30	^{90}Y-ibritumomab+ chemotherapy regimen+ASCT	31 months	ORR: 70% 3-year-PFS: 61% 3-year-OS: 63%
Single-arm trial/II[g]	DLBCL, MCL, BL	50	18	^{90}Y- ibritumomab+ fludarabine+ melphalan+ thiotepa+ ASCT	46 months	ORR: 71.5% 4-year PFS: 44.4% 4-year OS: 44.4%
Single-arm trial/II[h]	DLBCL, FL, MCL	57	116	^{90}Y-ibritumomab+ High-Dose BEAM	48.6 months	2-year PFS: 78% 3-year OS: 82%
Single-arm trial/II[i]	DLBCL	70	62	R-PECC + ^{90}Y- ibritumomab (consolidation)	59 months	5-year OS: 62%

[a]Ref. [32]; [b]Ref. [34]; [c]Ref. [39]; [d]Ref. [31]; [e]Ref. [33]; [f]Ref. [40]; [g]Ref. [41]; [h]Ref. [42]; [i]Ref. [43]

RIT as the first-line, consolidation, and relapsed/refractory treatment for indolent B-cell lymphoma

The efficacy of using RIT use as the first-line, consolidation, and relapsed/refractory treatment for indolent NHL is shown in Tables 3 and 4. The safety of RIT for indolent lymphoma is shown in Table S3 and S4. RIT ^{90}Y-ibritumomab tiuxetan has been studied as a single therapy, consolidation with first-line chemotherapy, and combination with fludarabine, mitoxantrone, rituximab (FMR) regimens, and maintenance rituximab. Five patients died in those three studies involving 150 patients during follow-up. In RIT, which was administered as a single treatment for patients with indolent lymphoma which could lead to manageable myelosuppression, there were 2 deaths due to spontaneous intracerebral hemorrhage and pulmonary embolism. This incident was not related to the RIT administration since the onset was late. There was no incidence of myelodysplastic syndrome during the follow-up, but there were 4 patients who developed secondary neoplasm consisting of 2 prostate cancer, 1 renal cell carcinoma, and 1 bladder carcinoma.

Most of the previously untreated patients experienced a mild grade of side effects after administration of RIT. Several secondary malignancies were found in 5 patients receiving RIT and first-line chemotherapy, These malignancies are renal cell carcinoma, oral cancer, and adenocarcinoma of the caecum.

Serious adverse events were found to be higher in lymphoma relapsing patients receiving RIT and chemotherapy compared to those who were not previously treated groups. There were 3 deaths reported from one article, and two other articles did not mention the number of deaths. After the administration of combination R-CHOP or rituximab, cyclophosphamide, vincristine, prednisone (R-CVP) with RIT, there were 30 serious side effects and 7 of them were related to RIT. Etoposide, Solu Medrol, high-dose Ara-C, Platinol (ESHAP), and RIT also contributed to the occurrence of 6 serious side effects in lymphoma patients, such as duodenal ulcer, nausea, vomitus, diarrhea, and 2 patients experiencing MDS.

The safety evaluation of ^{131}I-tositumomab-CHOP and R-CHOP is shown in Table S3. The mortality, secondary malignancy and MDS / AML rates of ^{131}I-tositumomab-CHOP were 2%, 8% and 3% respectively, whereas those for R-CHOP were <1%, 9% and MDS / AML 1% respectively. These results did not differ significantly between the two groups. When 131I-tositumomab was combined with R-CHOP as consolidation therapy, most side effects were mild, and only <2% grade-III. The overall side effects are shown in Table S3[44].

Besides tositumomab, rituximab also was used with radionuclide for therapy as ^{131}I-rituximab. The safety profile of this RIT is shown in Table S3 and S4. The majority of indolent lymphoma patients receiving ^{131}I-rituximab experienced mild side effects, and one of 210 patients was reported developing AML.

Table 3. Data of RIT efficacy as the first-line and consolidation treatment for Indolent B-cell NHL

Design/phase	NHL type	Median age	Number of patients	RIT regimens	Duration of *follow-up*	*Primary end-point*
Single-arm/II[a]	Advance FL MZL	55	20 2	fludarabine/ mitoxantrone/ rituximab (FMR) + ^{90}Y-ibritumomab+ rituximab maintenance	49.6 months	ORR: 95% (FMR) ORR 100% (FMR + RIT)
Single-arm/II[b]	Advance FL	56	55	FMR+^{90}Y-ibritumomab	28 months	ORR: 96% 3-year-PFS: 81% 3-yr-OS: 100%
Single-arm/II[c]	Advance FL	60	50	^{90}Y-ibritumomab	38.8 months	ORR: 94% 3-year-PFS: 63.4% 3-year-OS: 90%
Randomized-trial/III[d]	Advance FL	53.3	554	CHOP + rituximab CHOP + ^{131}I- tositumomab	4.9 years	2-year-PFS: 76% (RCHOP) 2-year-PFS: 80% (RIT+CHOP) 2-year-OS: 97% (RCHOP) 2-year-OS: 93% (RIT+CHOP)
Randomized-trial/III[e]	Advance FL	55 53	409	First-line chemotherapy + ^{90}Y-ibritumomab	7.3 years	8-year-PFS RIT: 41% 8-year-PFS without RIT: 22%
Single-arm/II[f]	FL	66	59	^{90}Y-ibritumomab	30.6 months	ORR: 87% 2-year-PFS: 54%
Single-arm/II[g]	FL MZL	57	20 11	^{90}Y-ibritumomab	56 months	ORR: 100%
Single-arm/II[h]	Advance FL	61	72	^{90}Y-ibritumomab (fractionated)	3.1 years	ORR: 94.4% 3-year-PFS: 58% 3-year-OS: 95%
Single-arm/II[i]	Advance FL	31-89	68	^{131}I-rituximab	4 years	ORR: 99%
Single-arm/II[j]	Advance FL	52	84	R-CHOP+^{131}I-tositumomab+rituximab/3months	5.6 years	ORR: 99% 3-year-PFS: 90%; 5-yr: 84% 3-year-OS: 96%; 5-yr: 94%
Randomized-trial/III[k]	Advance FL	53.3	531	CHOP+ rituximab CHOP+ ^{131}I-Tositumomab	10.3 years	10-year-PFS: 56% (RIT-CHOP) 10-year-PFS: 42% (R-CHOP) 10-year-OS: 75% (RIT-CHOP) 10-year-OS: 81% (R-CHOP

[a]Ref. [45]; [b]Ref. [46]; [c]Ref. [47]; [d]Ref. [48]; [e]Ref. [49]; [f]Ref. [50]; [g]Ref. [51]; [h]Ref. [52]; [i]Ref. [53]; [j]Ref. [54]; [k]Ref. [44]

Table 4. Data of RIT efficacy as the relapsed/refractory indolent NHL treatment

Design/phase	NHL type	Median age	Number of patients	RIT regimens	Duration of *follow-up*	*Primary end-point*
Single-arm/ II[a]	FL, MALT, MCL, SLL	61	142	^{131}I-rituximab	32 months	ORR: 68% 8-year-OS: 48%
Single-arm/II[b]	FL	53-55	47	FCR+ ^{90}Y-ibritumomab	107 months	11-year-OS: 78% 11-year-PFS: 72%
Single-arm/ II[c]	FL	62	50	R-CHOP atau R-CVP+^{90}Y-ibritumomab	5 years	ORR: 98% 5-year-OS: 77.5%
Randomized-trial/III[d]	FL	53.3	506 (14)	Rituximab Tositumomab + ^{131}I-tositumomab	62 months 91.5 months	2-year PFS: 75% 5-year OS: 50%
Single-arm/II[e]	FL	61	28	ESHAP+ ^{90}Y-ibritumomab	73 months	ORR: 72% 2-year-PFS: 27% 5-year OS: 62.5%

MALT: mucosa-associated lymphoid tissue; MCL: mantle cell lymphoma; SLL: small lymphocytic lymphoma
[a]Ref. [55]; [b]Ref. [56]; [c]Ref. [57]; [d]Ref. [58]; [e]Ref. [59]

DISCUSSION

RIT Use As The Consolidation Therapy For Aggressive B-cell NHL

Diffuse large B-cell lymphoma (DLBCL) is one of the subtypes of aggressive B-cell lymphoma that frequently occurs, accounting for 30-85% of total NHL[60]. If the patients do not receive proper therapy, DLBCL often causes death due to its aggressiveness. The majority of the literature describes the results of clinical trials involving high-risk DLBCL patients. Based on the international prognostic index (IPI), the high-risk patients appear to have a higher risk of relapsed and the worst survival rate[61]. R-CHOP is the standard regimen for DLBCL patients. The five-year survival rate of high-risk DLBCL patients is getting lower, around 26%[61]. The overall response rate (ORR) and 2-year overall survival (OS) of R-CHOP in the general population of DLBCL patients were 91% dan 82.7%, respectively[62]. However, in high-risk DLBCL patients, the ORR and the 2-year OS became 83% and 65% respectively[63]. It showed that R-CHOP had a problem when given to the high-risk aggressive lymphoma patients. Horvat et al. mentioned that the efficacy of R-CHOP for high-grade NHL in the last decade was ORR 90%, 2- and 5- year PFS 82%, 80%, and 2- and 5-year OS 74% and 63%, respectively[64]. RITs are considered to have beneficial results if they provide better ORR, PFS, or OS compared to the efficacy data of the existing chemotherapy. Among 5 studies, four showed that RIT as consolidation therapy resulted in the benefit for patients with high-grade NHL[30,35–37]

Karmali et al. reported the results of their studies on the effectivity of R-CHOP in combination with RIT ^{90}Y-ibritumomab tiuxetan for high-risk DLBCL patients. The result of 2-year OS was 86% compared to R-CHOP alone 65%[37]. Another clinical trial showed the clinical outcome of 5-year OS increased to 94% (95%CI, 88-100%) when RIT combined with R-CHOP[36]. Another RIT, ^{131}I-tositumomab is not better than ^{90}Y-ibritumomab. The results of trials in which R-CHOP, CHOP, and ^{131}I-tositumomab were administered showed 2-year OS in only 77%[35]. This result is lower than that of ^{90}Y-ibritumomab but higher than that of R-CHOP alone. Furthermore, the toxic effect was poor for patients, so this RIT as a standard therapy for aggressive B-cell NHL has not been recommended. Safety aspects must be considered after RIT ^{90}Y-ibritumomab tiuxetan is known to provide benefits. Most of the side effects were hematologic related including thrombocytopenia and neutropenia, whereas the non-hematologic side effects were nonspecific. Overall, these side effects can be managed well. With its low mortality and safety profile, this RIT can be recommended for use in phase-III clinical trials.

Most of the literature analyzed in this article showed the favorable potential of RIT, but they were based on a phase-II clinical trial in the last decade, and so it has not been recommended yet for use in aggressive B-cell NHL patients. More substantial phase-III clinical trials are needed to adequately prove the efficacy of ^{90}Y-ibritumomab tiuxetan and R-CHOP vs R-CHOP alone as a standard regimen for aggressive lymphoma patients.

RIT Use As A Standard Treatment For Relapsed/ Refractory Aggressive B-cell NHL

Relapsed/refractory aggressive lymphoma has a poor prognosis, and it can be determined by using IPI[28]. This has prompted many clinicians and researchers to investigate the use of RIT for the disease. DLBCL as an aggressive lymphoma is well-known as a chemosensitive disease, but in certain cases, it can be relapsed or refractory. The standard therapy for the disease is a regimen of high-dose or second-line chemotherapy followed by a stem-cell transplant. If chemotherapy fails to clear the tumor cells, the transplant will also fail, so the therapeutic programs must be effective in killing the cancer cells for better transplant results [14,31].

R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) is a regimen commonly used for relapsed/refractory aggressive B-cell NHL followed by a stem-cell transplant. Imhoff et al. reported that the efficacy of this regimen was 33% in ORR, 38% in 2-year PFS, and 26% in 2-year OS[65]. The majority (8 of 9) of studies described previously in this review showed more favorable ORR, 2-year PFS, and OS for relapsed/refractory

high-grade lymphoma. Most of them were ^{90}Y-ibritumomab tiuxetan[31–34,39–43].

A phase-III clinical trial comparing the efficacy of R-BEAM and ^{131}I-tositumomab-BEAM followed by hematopoietic cell transplant showed that both resulted in the same 2-year PFS and OS in relapsing DLBCL[31]. Based on these results, clinicians should have another reason to use ^{131}I-tositumomab-BEAM rather than R-BEAM. Yttrium-90 ibritumomab tiuxetan, one of the RITs provides several benefits for patients with recurrent lymphoma[40]. Unfortunately, it was a phase-II clinical trial with the single-arm protocol, so it must be further investigated in phase-III.

RIT Use As The First-line and Consolidation Therapy for Indolent B-cell NHL

Indolent lymphoma is still difficult to treat. This is of concern to many clinicians[54]. Stage-I and –II of NHL can be managed by 'watchful waiting' when the toxic effect of radiotherapy and systemic therapy is more harmful to the patients[14]. Overall survival and progression-free survival were the main outcomes to be measured in any indolent NHL trial. Overall survival of the patients receiving immediate and delayed chemotherapy was 5.9 years and 6.7 years respectively. It was not significantly different (p=0.84)[66].

The first-line treatments of indolent B-cell NHL are R-CVP, R-CHOP, or R-bendamustine. The efficacy of the first-line therapy for indolent lymphoma is shown in Table 5, while the efficacy of the RIT is mentioned in Table 3. RIT as single first-line therapy is not superior to R-CHOP. When RIT ^{90}Y-ibritumomab tiuxetan was used as consolidation with R-CHOP, it resulted in better ORR and PFS in a phase-III clinical trial compared to R-CHOP alone[49].

Table 5. Efficacy of R-CHOP and R-CVP as the first-line treatment for indolent B-cell NHL

RCHOP/ RCVP	Duration	PFS (%)	OS (%)
ORR: 94.5%[a]	2-year	86[b]	95[b]
	3-year	75[c]	94[b]
	5-year	71[a]	84[a]
	8-year	49[d]	83[d]

[a]Ref.[67]; [b]Ref.[68]; [c]Ref.[17]; [d]Ref. [69]

The efficacy of RIT is compared to the efficacy of existing chemotherapy. Among 11 studies, seven trials are showing more promising results for indolent NHL. Other RITs containing tositumomab and rituximab did not provide any better benefits than R-CHOP, so they cannot be recommended to be used in B-cell NHL patients. Iodine-131 used in RIT is more affordable, unfortunately, it has less beta energy[70]. This may explain why iodine-containing RITs are not superior to yttrium-containing RIT.

One of the most frightening side effects is secondary malignancy following RIT and chemotherapy. The study conducted by Sacchi et al. involving 563 indolent NHL patients for 62 months showed 39 (6.9%) of them experienced various secondary malignancies. Twelve of these patients were MDS/AML and 27 solid tumors. Based on this report, with or without RIT, secondary malignancies appeared more frequently in NHL patients than in the general population[71].

RIT Use As A Standard Treatment For Relapsed/ Refractory Indolent B-cell NHL

Advanced-stage indolent NHL has a median survival of 8-10 years, whereas it will be 4-5 years in the relapsed cases. The prolonged survival rate is the focus of many studies in NHL patients. Standard regimens of indolent NHL have not been established uniformly in the clinical setting. The NCCN lists several treatment options, such as R-bendamustine, R-lenalidomide, ibritumomab tiuxetan, and obinutuzumab. Each of them shows different results[14].

R-lenalidomide provided an ORR, 2-year PFS, 2-year OS, and 5-year OS 76%, 52%, 93%, and 40% respectively. It is better than lenalidomide alone with an ORR of 53% (p=0.0023), and it has a longer median survival (2 years). The phase-III clinical trial confirmed the effectiveness and safety of this regimen. Based on these clinical trials, the FDA approved the use of this regimen for indolent B-cell NHL in 2019[72,73]. Among 5 studies of RIT, Three studies reported favorable results of RIT administration for relapsed/refractory indolent NHL[56,57,59].

Other chemotherapy regimens such as R-CHOP, R-CVP, or ESHAP in combination with RIT ^{90}Y-ibritumomab tiuxetan showed prolong OS and PFS in a phase-II clinical trial. NCCN includes the ibritumomab tiuxetan as one of many treatment options available for relapsed NHL. This means that this RIT can be recommended for relapsing patients with the specific regimens involved. As shown in previous studies, RIT ^{90}Y-ibritumomab demonstrated a favorable ORR, long-lasting remission, and tolerable adverse events[74,75]. Another report on the administration of RIT in over 200 relapsed patients resulted in 8-year PFS of 29.6% and 8-year OS of 54.5% with a wide range of acceptable toxicities[27].

Hematological and non-hematological side effects vary from grade-I to grade-IV. This can be managed with proper care. RIT is sometimes associated with the transformation of FL into the aggressive type and MDS/AML as well. Epperla et al. showed that the transformation in the RIT with fludarabine and the RIT-only group was 67% and 26% respectively (p=0.015). The incidence of MDS/AML in RIT combined with fludarabine and in the RIT-only group was 29% and 13% respectively. Based on this report, RIT should be administered with caution in patients receiving purine analog agents, such as fludarabine[76]. The result of this study indicates that ^{90}Y-ibritumomab tiuxetan is the FDA's most preferred radiopharmaceuticals. The effective dose of this radiopharmaceutical is 0.4 mCi/kg corresponding to 14.8 MBq/kg for both aggressive and indolent NHL[36,49]. Yttrium-90 as a radionuclide for RIT with a half-time of 64 hours and pure beta emission with an energy of 935 MeV is ideal for killing the tumor cells[70]. These physical properties explain why yttrium-90 provides promising clinical results for lymphoma patients.

Radiopharmaceutical yttrium-90 ibritumomab showed more favorable efficacy than rituximab did. It resulted in ORR in 80% of patients, whereas rituximab only showed ORR in 56% of patients (p=0.002)[75]. RIT can kill the tumor cells better than the chemo- or immunotherapy alone because of its bystander and cross-fire effect. These effects induce several types of cell deaths, such as apoptosis, autophagy, and necrosis which

depend on the level of the DNA damage. The more severe the deoxyribonucleic acid (DNA) damage, the more likely apoptosis, autophagy, and necrosis will occur. If the damage is smaller than it should be, the tumor cells can repair the damage and survive. Therefore, the radioactivity dose of radionuclides should be sufficient to kill the tumor cells and safe for the adjacent tissue or cells[77].

The phase-III clinical trials comparing RIT and standard regimens are not widely available. Therefore, this article can only compare the efficacy of RIT from one report to another report. Another reason why RIT is still underutilized relates to the license requirements to administer the radionuclides to the patients. Besides, hematologists or oncologists need to work closely with the nuclear medicine specialist when treating NHL patients with RIT. Unfortunately, many health centers do not have nuclear medicine facility [78,79].

Many clinicians consider the cost-effectiveness and convenience of treatment making it more difficult to apply RIT to lymphoma patients. However, some pharmacoeconomic studies have shown that RIT ^{90}Y-ibritumomab tiuxetan is not more expensive than standard chemotherapy and immunotherapy regimen for NHL patients[80,81]. Based on these considerations, RIT should have a greater opportunity of being used as B-cell NHL treatment to improve ORR and overall patient survival in a clinical practice setting.

CONCLUSION

Radioimmunotherapy has shown favorable and safe clinical outcomes for indolent and aggressive B-cell NHL. The most effective and safe RIT is ^{90}Y-ibritumomab tiuxetan. RIT ^{90}Y-ibritumomab tiuxetan (0.4 mCi/kg) can be used as consolidation therapy with standard therapeutic modalities. Further clinical trials (phase-III) are necessary to compare the RIT-regimen with the standard immunochemotherapy regimens. The use of RIT as treatment of lymphoma has the potential to be developed, beginning from in-vitro studies to find the most preferred radiolabelled antibodies, and in-vivo studies to compare them with the existing standard regimens. The results of those studies are expected to have an impact on increasing the ORR, PFS, OS of patients with lymphoma in a clinical practice setting.

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SUPPLEMENTARY MATERIALS

Table S1. Safety profile of RIT for previously untreated aggressive lymphoma patients

RIT	Other Therapies	Hematological side effects	Non-hematological side effects	Number of patients
^{90}Y-ibritumomab tiuxetan	R-CHOP[a]	Grade-III neutropaenia 36%, grade-IV neutropaenia 16%, grade-III thrombocytopenia 18%, grade-IV thrombocytopenia 29% (reversible)	Non-melanoma skin cancer (2%), primary thyroid cancer (2%), basal cell carcinoma(2%), GI tract symptom (2%), Colon (2%), dan myelodysplastic syndrome (2%)	53
	R-CHOP[b]	Grade-III or -IV : neutropaenia 60%, anemia 25%, thrombocytopenia 20%	GI tract symptoms, neuropathy, infection (>10%)	20
	R-CHOP+ IVAM/ICE+ BEAM+PBSCT[c]	Grade-III/IV neutropaenia 100%, thrombocytopenia 91%, anemia 36%	Increased body weight (63%), hypersensitivity (18%), hyperglycemia (9%), and neuropathy (9%)	11
^{131}I-tositumomab	Induction-I: CE-R Induction -II: Cytarabine and doxorubicin[d]	Grade-III/V neutropaenia 76%, thrombocytopenia 92%, febrile neutropaenia 12%	Grade-III/IV mucositis 4%, infection 8%, nausea 4%	39
	R-CHOP + CHOP[e]	Grade-IV toxicity: anemia 14%, leukopenia 56%, lymphoopenia 47%, neutropaenia 65%, dan thrombocytopenia 34%.	Grade ≥III toxicity: cardiovascular 10%, flu-like symptoms 12%, dehydration 1%, GI tract 1%, infection 26%, neuropathy 11%, renal failure 1%, AML (secondary malignancy) 1%.	84

CE-R: cyclophosphamide, etoposide, rituximab

[a]Ref. [36], [b]Ref, [37], [c]Ref. [38], [d]Ref. [30], [e]Ref. [35]

Table S2. Safety profile of RIT for relapsed/refractory aggressive lymphoma

RIT	Other Therapies	Hematological side effects	Non-hematological side effects	Number of patients
^{90}Y-ibritumomab tiuxetan	Fludarabine+ TBI+ PBSCT[a]	Neutropaenia, thrombocytopenia	Sepsis dan multiorgan failure (12%), GVHD 78%, pneumonia (2%)	40
	FMT + ASCT[b]	N/A	diarrhea, cytomegalovirus enteritis, exacerbation of chronic renal failure, CHF, pleural effussion, dan lymphadenitis, septic shock, pneumonia.	18
	R-PECC[c]	Grade ≥III : thrombocytopenia 55%, neutropaenia 28%	Infection 21%, MDS (7%), NSCLC (3%), neuroendocrine malignancy (3%), and squamous cell carcinoma (3%)	62
	HD-BEAM[d]	Grade ≥III : lymphopenia (11 of 116 patients) on day-100 post-transplantation	Grade-II: stomatitis (28%), grade ≥III: infection (4%), GI tract toxicity (1%), pulmonary toxicity (1%)	116
	BEAM+ASCT[e]	Grade-I 1, grade-IV 3 consisting of neutropaenia dan thrombocytopenia	Sepsis (3%), cereberal hemorrhage, fever (76%), mucositis (83%), non-infective enteritis (10%)	30
^{131}I-Tositumomab	BEAM[f]	N/A	B-BEAM: Mucositis 52%, hypotension 10.7%, hypoxia 19.4%, dyspnea 28.2%, dan diarrhea 8.7%. MDS (0.5%)	224
^{131}I-rituximab	Monotherapy[g]	Grade-III/IV thrombocytopenia 33%, neutropaenia 21%	fatigue, nausea, myalgia, pneumonitis.	24
	Repeated dose[h]	Grade-III/IV thrombocytopenia 66%, neutropaenia 72%%, anemia 14%.	N/A	31
	BEAM+ ASCT[i]	Grade-IV toxicity: leukopenia, dan thrombocytopenia, grade-II: anemia 3 patients, febril neutropaenia 5 patients.	Pneumonitis 6%, mucositis 6%, hyperbilirubinemia 6%, increased creatinin 6%, MDS 6%.	16

[a]Ref. [39]; [b]Ref. [41]; [c]Ref. [43]; [d]Ref. [42]; [e]Ref. [40]; [f]Ref. [31]; [g]Ref. [32]; [h]Ref. [33];[i]Ref. [34]

Tabel S3. Safety Profile of RIT for previously untreated indolent lymphoma

RIT	Other Therapies	Hematological side effects	Non-hematological side effects	Number of patients
^{90}Y-ibritumomab tiuxetan	Monotherapy[a]	Grade-III/IV neutropaenia 30%, thrombocytopenia 26%	N/A	50
	Monotherapy[b]	Grade-III/IV: Thrombocytopenia 48%, leukopenia 34%, neutropaenia 32%, lymphopenia 20%, anemia 2%.	Grade-II: infection 20%, GI tract 10%, cardiovascular 5%, skin irritation 3%, and mucositis 2%.	59
	FMR+ rituximab maintenance	Grade-III/IV neutropaenia (55%), thrombocytopenia (42%), anemia (15%)	Febril neutropaenia (7%)	55
^{131}I-tositumomab	CHOP[d]	Grade-III/IV neutropaenia 51%, trombostiopenia 18%, anemia 3%	Grade-III/IV: infection 17%, GI tract 9%, cardiovascular 3%, fatigue 3%, febril neutropaenia 10%,	554
	CHOP[e]	N/A	N/A	531
	R-CHOP+ maintenance rituximab[f]	Grade-III/IV: neutropaenia 57%, thrombocytopenia 21%, leukopenia 41%, anemia 7%, lymphopenia 30%.	Grade-III/IV: fatigue 10%, nausea 4%, hiperglycemia 5%, sepsis 2%, and febril neutropaenia 16%,	84
^{131}I- rituximab	Monotherapy[g]	Grade-IV : thrombocytopenia 7%, neutropaenia 5%	Subclinical hypothyroidism 13%	68

[a]Ref. [47]; [b]Ref. [50]; [c]Ref. [46]; [d]Ref. [48]; [e]Ref. [44]; [f]Ref. [54]; [g]Ref. [53]

Tabel S4. Safety profile of RIT for relapsed/refractory indolent lymphoma

RIT	Other Therapies	Hematological side effects	Non-hematological side effects	Number of patients
^{90}Y-ibritumomab tiuxetan	FCR + stem-cell transplantation[a]	N/A	Grade-III GVHD (7%),	47
	R-CHOP or R-CVP[b]	Grade-III/IV: neutropaenia 36.5%, thrombocytopenia 38.5%, anemia 3.9%, MDS 1.9%	Grade-III/IV: infection 13.5%, febrile neutropaenia 1.9%, cardiovascular 1.9%, dermatology disorder 1.9%, syncope 5.8%.	50
	ESHAP[c]	Grade-III/IV: thrombocytopenia 61%, leukopenia 39%, neutropaenia 7%, anemia 14%	Grade-III/IV: fatigue 18%, nausea 4%, vomitus 7%, diarrhea 4%, dehydration 4%, febril neutropaenia 11%	28
^{131}I-Tositumomab	Tositumomab[d]	Thrombocytopenia (62%), leukopenia (50%), lymphopenia (50%).	headache (62%), nausea (62%), vomitus (50%), cough (50%)	14
^{131}I-rituximab	Monotherapy[e]	Grade-IV: neutropaenia 10%, thrombocytopenia 6%, anemia 1%	N/A	142

[a]Ref. [56]; [b]Ref. [57]; [c]Ref. [59]; [d]Ref. [58]; [e]Ref. [55]

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