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Review Article

Advances and application of radioimmunotherapy in non-Hodgkin lymphoma

Patrick L Stevens, Olalekan Oluwole, Nishitha Reddy

Division of Hematology and Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.

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Abstract: The activity of radio-immuno conjugate in Non-Hodgkin Lymphoma (NHL) has resulted in FDA approval of two antibodies, Y^{90} Ibritumomab tiuxetan and I^{131} tositumomab. Both these agents target CD20, a receptor widely expressed in B-Cell NHL. These immunoconjugates deliver their radioactive payload to the malignant clone in the bone marrow and lymph node. Their use has been associated with modest improvement in survival end points among several lymphoma histologies. The promising effect on disease control as well as their efficacy in disease relapse is encouraging in low grade lymphoma. Radioimmunotherapy (RIT) is increasingly being explored in the setting of consolidation as well as conditioning regimens prior to stem cell transplantation. Here, we summarize the clinical use, complications and future applications of RIT in NHL.

Keywords: Radioimmunotherapy, non-Hodgkin lymphoma, stem cell transplantation, CD20 target

Introduction

Non-Hodgkin lymphoma (NHL) is a group of heterogeneous histologies, with variable clinical outcomes [1]. Chemotherapy, immunotherapy and radiation therapy have been the main modalities of treatment in this disease. With the advent of monoclonal antibodies, especially the CD20 directed rituximab in combination with multi agent chemotherapy, high rates of initial response can be achieved. Fewer patients however, attain a cure and many eventually relapse with disease that is often less sensitive to chemotherapy. Pre-clinical data supports that along with development of rituximab resistance, chemotherapy resistance emerges [2]. The effectiveness of Immunotherapy alone in the setting of relapse suggests an intact target and host immune function [3].

The ability to deliver radioactivity directly to the tumor via an antigenic target was the rationale for developing Radioimmunotherapy (RIT). RIT in lymphoma acts as a means of reaching the target with its radioisotope payload, rather than invoking antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity [4, 5]. The two chemo immunotherapy agents approved for use in NHL are yttrium Y^{90} Ibritumomab tiuxetan (Y^{90}I, Zevalin) and I^{131} Tositumomab (I^{131}T, Bexxar). The characteristics of the two antibodies are compared in **Table 1**.

Mechanisms of action

While delivering RIT, the amount of radiation that reaches the target can be accurately determined. It is thus possible to administer higher doses of tumor site specific radiation. In addition, the amount of off target radiation to major organs is predictable and therefore measured for toxicities. The radioactive conjugates are concentrated on the cell surface because of the antigen density. Radioactive particles can deliver their effects over distances of 1-5mm.

The major mechanism of action of RIT is direct apoptosis. Pro apoptosis signals are up regulated including CD95 ligand and CD95 receptor both of which activate caspases which effect apoptosis through the extrinsic pathway [6]. Furthermore, mitochondrial damage caused by radiation leads to release of cytochrome c which in turn leads to apoptosis via the intrinsic path-

Table 1. General Characteristics of Radioimmunotherapy antibodies

Radioisotope	Y90- Irbitumomab Tiuxetan	I131-Tositumomab
Emission	Alpha	Gamma
Link Type	Covalent	Ionic
Range	11.3 mm	2.3mm
Energy (KeV)	2284	606
Immunoglobulin Type	IgG1	IgG2 alpha
Half Life	64 hrs	193 hrs
FDA approval	2002	2003
Indications	Relapsed/refractory CD20+ve low grade NHL or PR after initial therapy	Relapsed/refractory CD20+ve Low grade NHL, or TL

NHL- Non-Hodgkin's lymphoma, PR- partial response, TL- transformed lymphoma

Table 2. Select Clinical Trials utilizing radio-immunotherapy in refractory Low Grade NHL

Author/year	Type of RIT	Phase	Number of patients	Stage	Median Prior Rx	Response rate ORR/CR	Toxicity Grade 3-4
Witzig 1999	$Y^{90}I$	I/II	51	Any	2	67%/26%	Neutropenia-27%, Thrombocytopenia-10%
Witzig 2002	$Y^{90}I$	II	57	Any	4	74%/ 15%	Neutropenia-35%, Anemia-4%, Thrombocytopenia-9%, AML-2%
Witzig 2002	$Y^{90}I$	III	143	Any	2	80%/30% vs. 56%/ 16%	Neutropenia-55%, Anemia-2%, Thrombocytopenia-57%
Wiseman 2003	$Y^{90}I$	II	30	Any	-	83%/37%	Neutropenia-33%, Thrombocytopenia-13%
Gordon 2004	$Y^{90}I$	I/II	51	Any	2	73%/29%	MDS-4% at 3 years,
Zinzani 2010	$Y^{90}I$	II	57	III/IV	3	93%/70%	Neutropenia-67%, Anemia-35%, Thrombocytopenia-79%
Kaminski 2001	I^{131} T	III	60	III/IV	4	65%/ 20%vs. 28%/ 3%	Neutropenia-18%, Thrombocytopenia-22%
Davis 2004	I^{131} T	III	78	Any	2	55%/35% vs. 19%/8%	Neutropenia 33 %, Thrombocytopenia 33%
Horning 2005	I^{131}T	II	40	Any	4	65%/38%	Neutropenia-42.5%, Anemia-10%, Thrombocytopenia-25%, Pneumonia-10%
Kaminski 2005	I^{131}T	II	32	III/IV	4	56%/25%	Neutropenia 50%, Thrombocytopenia-43%, Hyopthyroidism-12%

way [6, 7].

Clinical implication in NHL subtypes

Clinical trials evaluating the role of RIT in various histological subtypes of NHL are detailed in **Table 2**. Here we summarize the results of major clinical trials [8-17].

Clinical experience of RIT in Low grade Lymphoma

Follicular lymphoma (FL), a relatively indolent yet incurable disease, was the target for early

development of RIT. The quest for safer mechanisms of therapy including targeted agents is an attractive strategy. The natural history of this disease is for more mutant and chemotherapy resistant clones to evolve as the disease is re-treated with multi agent chemotherapy. In FL, where the malignant clone retains the expression of CD20, RIT is an additional option to be considered. Furthermore as described previously, proximity to the cell (assured through binding of the CD20 receptor) is critical for activity.

RIT in relapsed lymphoma

The encouraging results of several phase I/II trials led to conduct phase III trials.

In a randomized study of 143 patients with mainly FL histology, patients were treated with rituximab or $Y^{90}I$ with median number of 2 prior regimens [12]. The overall response rate (ORR) was statistically significant between the two groups 80% versus 53% with the most notable response of 86% in the FL group. Furthermore, patients who were randomized to receive RIT achieved a complete response (CR) of 30% versus 16% among patients receiving rituximab (p=0.04). The median duration of response was 14.2 months with 12.6 months to time to progression (TTP) in the $Y^{90}I$ group.

RIT has also shown efficacy in patients with no response to rituximab. A prospective phase II trial by Horning et al [14] explored the use of $I^{131}T$ in 40 patients of whom 60% had been rituximab non-responders. The ORR was 65% with 38% achieving CR. At 3 year follow-up the median progression free survival (PFS) was 10.4 months in all patients and 24.5 months in responders. Of note, follicular grade 1 or 2 patients with tumors ≤ 7 cm (n = 21), the ORR and CR rates were 86% and 57%. In this subgroup the estimated 3-year PFS was 48%. A study by Kaminski et al. [17] explored re-treatment of 32 patients with $I^{131}T$ who previously had a response of greater than 3 months. These patients showed an ORR 53% with 25% CR. Interestingly the median duration of response was similar with 13.6 months initially versus 15.2 months in the retreatment group. These patients experienced similar Grade 3-4 hematologic toxicities as compared with previous studies (neutropenia 50%, thrombocytopenia 43%).

In a phase 3 cross-over trial by Davis et al [16], 78 patients with relapsed refractory NHL were randomized to tositumomab alone (without radioactive conjugate) or $I^{131}T$. Response rates were higher in the RIT arm (55% compared to 19% p =.002), CR 33% compared with 8% (p =.012) and the median duration of response was not yet reached in the $I^{131}T$ arm. In the cross-over group the CR rates were 42% versus 0% with OR of 68% versus 16% (p =.002) Toxicity pattern was similar as previous studies with grade 3-4 neutropenia seen among 33% in the RIT arm compared with 8% in the tositumomab alone arm. No thrombocytopenia was seen among those who had tositumomab as a single agent compared with 33% in the $I^{131}T$ arm.

RIT in newly diagnosed low grade lymphoma

The updated results of I^{131} T as initial monotherapy in 76 patients for previously untreated advanced stage FL were recently reported [17]. The 10 year overall survival was 82% and median PFS was 10.9 years in patients who attained CR. Notably in this trial PCR for Bcl-2 rearrangements were run on patients in CR and showed that 80% achieved a molecular response. While there was some hematologic toxicity, mainly Grade 3 neutropenia and thrombocytopenia, 34% and 17% respectively, no patients required growth factors or transfusion support. This data is convincing to support the use of RIT in a selected group of patients with newly diagnosed low grade NHL.

RIT as consolidation in FL

Among rituximab naïve patients, RIT used as consolidation therapy chemotherapy with CHOP, CVP or fludarabine based regimens, CR rates were notably improved. The FLUMIZ trial [18] studied the use of ^{90}Y-ibritumomab tiuxetan following 6 cycles of Fludarabine and Mitoxantrone in 57 stage III/IV patients. Of the 14 patients who had PR after initial chemotherapy, 12 achieved CR (96.5%). The 3-year PFS and overall survival (OS) rate were 76% and 100% respectively. The Grade 3-4 hematologic toxicities were most notably 52% neutropenia and 63% thrombocytopenia with 23% receiving colony stimulating factors. A follow-up study by Zinzani et al [19] studied consolidation $Y^{90}I$ following 4 cycles of Fludarabine, Mitoxantrone, and Rituximab in a population of 55 patients with Stage III/IV disease. Following therapy there was a

100% ORR with 81% attaining CR. The 3 year PFS and OS were 81% and 100% respectively.

Jacobs and colleagues [20] studied R-CHOP therapy followed by $Y^{90}I$ and extended dosing rituximab in a population of FL patients with Stage III-IV disease. After RIT, the CR rate was noted to be 89% by PET. The 2 year ORR was 73%. Hainsworth et al observed the response of 41 patients following R-CHOP (88%) and CVP-R (12%) combined with $Y^{90}I$ 4 weeks later. The ORR and CR were measured at 95% and 72% respectively with 39% Grade 3-4 neutropenia and 36% Grade 3-4 thrombocytopenia. The OS and PFS at 5 years were documented to be 96% and 64% [21].

The international phase III study (FIT) evaluated the role of $Y^{90}I$ following initial response to chemotherapy. Patients who achieved a partial response (PR) following initial therapy appear to benefit the most with consolidation RIT. In this study only 14% of patients received rituximab with induction chemotherapy. Initially, Morschhauser et al [22] reported the results on 414 previously treated patients with FL were randomized to $Y^{90}I$ versus observation following chemotherapy. $Y^{90}I$ was effective with PFS 36.5 versus 13.3 months in the observation arm at a median follow up of 3.5 years. At an extended follow up of this study, the median PFS at 5.5 years was 49 months vs. 14 months. The median PFS was prolonged for all subgroups examined including those in PR, CR and all International Prognostic Index (IPI) groups. There was however no significant difference in OS among both the groups. The incidence of MDS/AML was 3% in the consolidation arm.

The results of the phase III intergroup study (S0016) presented by Press et al. evaluated the role of rituximab and CHOP therapy versus CHOP followed by $I^{131}T$ in patients in newly diagnosed FL with a primary end point of PFS. Of the 554 patients enrolled in this study, the 2-year estimate of OS was 97% in the CHOP-R arm and d 93% in the CHOP-RIT arm (p=0.08). There were no significant differences in the incidence of hematological toxicities or ORR [23].

In summary, RIT appears to play a significant role in upfront, consolidation or relapsed FL. The most benefit of such treatment is likely to be obtained when considered early on in the natural history of disease with the likelihood of targeting radiologically detectable disease among those achieving PR to induction therapy. The improvements seen in patients who have attained a CR, argues for its role in targeting minimal residual disease.

Intermediate grade lymphoma and RIT

The kinetics of RIT include a long half-life (64 hours for $Y^{90}I$ and 193 hours for $I^{131}T$) with relatively slower onset of action. These characteristics may limit its utility in the setting of an aggressive lymphoma with a rapid doubling time. Nonetheless, $Y^{90}I$ and $I^{131}T$ have been used as consolidation therapy in de-novo and transformed diffuse large B cell lymphoma (DLBCL). Often times, it has been used as an adjunct with high dose chemotherapy and stem cell rescue. Clinical trials in this histological subtype are limited to phase II studies. A summary of the trials in DLBCL or transformed lymphoma are detailed in **Table 3** [24-29].

A phase II trial by Yang and associates (24) studied the use of $Y^{90}I$ in Stage I/II DLBCL patients (n=21) with bulky disease. Patients were treated with six cycles of R-CHOP chemotherapy; patients with either PR or CR were then given $Y^{90}I$. The ORR was noted to be 81%. After 28 months the 3 year PFS and OS were 75% and 85% respectively.

A further study examined the use of $Y^{90}I$ in elderly patients (n=104) who had either failed chemotherapy with or without rituximab or relapsed after achieving a CR [26]. Patients were stratified into 2 groups, one group that failed chemotherapy without rituximab (A) and one that failed therapy with rituximab (B). The non-rituximab group was further stratified into those who failed initial therapy (A1) and those who achieved complete response and relapsed (A2). In patients in group A1 the ORR was 67% with 24% experiencing progressive disease and 9% with stable disease. In group A2 there was a 100% ORR with 93% CR. Finally in group B, there was an OR of 65% with 38.5% CR; progressive disease was documented in 35% of patients. The median survival documented at median follow-up of 21.7 months was 21.4, 22.4, and 4.6 months respectively in Groups A1, A2, and B. The major hematologic toxicity was Grade 3-4 thrombocytopenia in 79% of patients with 2 deaths in study attributed to intracranial hemorrhage related to thrombocytopenia.

Table 3. Select clinical trials of radio-immunotherapy in intermediate grade NHL

Author/ year	Type of RIT	Phase	Study Group	Patients	Response rate	PFS/OS	Toxicity Grade 3-4
Kaminski 2000	$I^{131}T$	I/II	Relapsed/ Refractory DLBCL	17	ORR - 41% CR - 0%	12 month PFS 0%	Not specifically listed by subgroup
Tsimberidou 2004	$Y^{90}I$	II	Richter's Transformation	7	OR - 0%	Median TTP - 41 days	Neutropenia 29%, thrombocytopenia 71%
Wang 2007	$Y^{90}I$	II	Relapsed/ refractory MCL	34	ORR - 67% PR - 15.5% CR - 15.5%	EFS - 6 months OS - 21 months	Neutropenia 32%, thrombocytopenia 24%
Zinzani 2008	$Y^{90}I$	II	Consolidation R-CHOP in elderly with DLBCL	20	ORR - 100% CR - 95%	PFS - 75% OS - 95%	Neutropenia 60%, thrombocytopenia 35%
Morschhauser 2009	$Y^{90}I$	II	Relapsed/ Refractory DLBCL A1: No CR A2: Relapsed B: Relapsed	104 A1:33 A2:43 B:28	A1:ORR - 67% A2:ORR - 100% B:ORR - 65%	Median Survival: A1 - 21.4 months A2 - 22.4 months B - 4.6 months	Neutropenia 17-24% Thrombocytopenia 76-79% 2 deaths from thrombocytopenic ICH
Yang 2011	$Y^{90}I$	II	Consolidation DLBCL	21	ORR - 80.9% PD - 28.6%	PFS - 75% OS - 85%	Neutropenia 60%, thrombocytopenia 35%

DLBCL: diffuse large B cell lymphoma, MCL: Mantle cell lymphoma, A1: patients not achieving a CR following chemotherapy alone, A2: patients with initial response but with disease relapse following chemotherapy, B: patients with disease relapse following rituximab based chemotherapy.

A single arm study at the University of Michigan [27] examined the use of $I^{131}T$ for relapsed/ refractory disease included 17 patients with either intermediate or high grade lymphoma. Forty-one percent of patients achieved a response; however none of these patients achieved CR. Intermediate grade histology was revealed in subgroup analysis to be a risk factor for shortened PFS (relative risk [RR] = 4.8, p <.0001).

A study by Wang et al [28] examined use of $Y^{90}I$ in patients with relapsed/refractory mantle cell lymphoma (MCL). Patients with Stage I-IV disease had failed an average of 3 prior chemotherapy regimens including 94% with prior Rituximab based therapy. Sixty-seven percent achieved some reduction in tumor bulk while there was a 15.5% CR. The OS was 21 months while the event free survival (EFS) was 6 months; notably patients who had achieved a CR/PR had a measurably increased EFS (21 months versus 3 months p<0.0001).

A study by Tsimberidou [29] et al examined the use of $Y^{90}I$ in Richter's transformation from CLL. These patients had received a median of 5 therapies with one occurring after transformation. Of note, none of the patients had a response except for interval decrease in lymphadenopathy. Patient's median time to progression was measured at only 41 days.

A multicenter, randomized study is evaluating the role of $Y^{90}I$ following R-CHOP therapy in patients with DLBCL (ZEAL study). Based on the listed studies, RIT appears to have a role as consolidation therapy as well as relapsed intermediate grade lymphomas.

RIT in stem cell transplant (SCT)

The perceived role of RIT in SCT was to deliver a myeloablative dose to the patient thereby eliminating residual NHL and marrow reconstitution by stem cell rescue. RIT is able to deliver radiation directly at the tumor site unlike Total Body Irradiation (TBI) which delivers same dose of radiation to all organs of the body at a significant cost in terms of side effects. Several studies were undertaken to evaluate the feasibility of adding RIT to chemo and whether that mechanism may be as effective with fewer side effects as compared with TBI. An additional advantage with $I^{131}T$ was that its bio-distribution, metabolism and half-life differed significantly among patients. These parameters can be reliably measured and exploited to provide patient specific (individualized) dosing to accentuate therapeutic effect against the cancer cell [30-38]. Pertinent trials involving RIT and stem cell transplant are listed on **Table 4**.

Table 4. clinical trials utilizing RIT in peri-transplant setting

Author	Phase	Patients	RIT	Outcome % (95%CI)	Conclusion
Press 2000	I/II auto-SCT	55	$I^{131}T$	2 yr OS:83% 2 yr PFS:68%	Multivariate analysis showed that PFS and OS were superior in the $I^{131}T$ treated group. Suggests that RIT is superior to non-targeted external beam TBI
Namandee 2005	I/II auto-SCT	31	$Y^{90}I$	2 yr OS:92% 2yr RFS:78%	High-dose 90Y-ibritumomab tiuxetan can be combined safely with high-dose etoposide and cyclophosphamide without an increase in transplant-related toxicity, patients with Follicular Lymphoma achieved best outcomes
Gopal 2007	II auto-SCT	24	$I^{131}I$	3yr OS:59% 3 yr PFS:51%	4 (17%) who had 3-8 prior regimens had features of MDS/AML. $I^{131}T$ was revealed to be a safe regimen for patients of older age requiring transplantation for refractory disease
Krishnan 2007	II auto-SCT	41	$Y^{90}I$	2yr OS:87.9% 2 yr PFS:68.8%	RIT did not add to toxicity profile when used in conjunction with BEAM. Older patients benefited most, patients with DLBCL had encouraging PFS
Shimoni 2007	II auto-SCT	23	$Y^{90}I$	2yr OS:67% 2 yr PFS:52%	Y90 was able to be safely combined with SCT and the stem cell rescue helped to attenuate the expected myelotoxicity with the use of $Y^{90}I$
Kang 2010	II auto-SCT	19	$Y^{90}I$	3yr OS:52.6% 3yr EFS: 26.3%	Bu/Cy/E was revealed to be a feasible regimen when combined with RIT with limited serious toxicities. However revealed relatively high relapse rate.
Bethge 2010	II allo-SCT (RIC)	40	$Y^{90}I$	2 yr OS: FL 67% CLL 49% MCL 37%	All patients received GCSF. All engrafted by D+18. This study revealed that the use of RIT showed similar toxicity compared to historical controls
Gopal 2011	II allo-SCT	40	$Y^{90}I$	2 yr OS:54% 2 yr PFS:31%	This study shows RIT may induce early responses and prolonged survival in high-risk B-NHL patients with persistent disease

NRM: Non Relapse Mortality; MDS: Myelodysplastic Syndrome; DLBCL: Diffuse Large B cell Lymphoma; SCT: Stem cell transplant; RIC: Reduced intensity conditioning; MCL: Mantle cell lymphoma; MZL: Marginal zone lymphoma, CLL: Chronic lymphocytic leukemia

A phase I/II study by Nademanee et al [31] studied the use of $Y^{90}I$ in conditioning for autologous stem cell transplant when combined with high-dose etoposide (VP-16) 40 to 60 mg/kg (day -4) and cyclophosphamide 100 mg/kg (day -2). Patients received dosimetry on day- 21 followed one week later with $Y^{90}I$. Day -7 bone marrow was conducted to estimate delivery of radiation; patients were redosed if total irradiation was deemed to be less than 5 cGy. The study group included 31 patients who had a median of 2 previous lines of therapy with histology notable for FL (*n* = 12), DLBCL (*n* = 14), and MCL (*n* = 5). Following stem cell infusion, the median time to neutrophil and platelet recovery were 10 and 12 days respectively. The major Grade 3-4 toxicities were most notably Infection 74% and mucositis 34%. The estimated two year OS and relapse free survival (RFS) were 92% (95% CI, 82%-100%), and 78% (95% CI, 61%-96%) respectively. The best survival was noted in patients with FL histology (100% 2 year OS/RFS).

A recent phase II study by Kang et al [32] studied the use of $Y^{90}I$ when combined with intravenous busulfan, cyclophosphamide, and etoposide (Bu/Cy/E) followed by auto-SCT in patients with relapsed/refractory B-cell lymphoma. The majority of patients in this population had DLBCL (*n* = 14), with FL and MCL (*n = 2)*. The regimen involved giving rituximab 250 mg/m^2 on day -21 with $Y^{90}I$ on day -14 at dose of 0.4 mCi/kg followed by busulfan (IV, 0.8 mg/kg every 6 h from day -7 to day -5), Cyclophosphamide (IV, 50 mg/kg on days -3 and -2), and etoposide (IV, 200 mg/m2 every 12 h on days -5 and -4). The major non-hematologic toxicities observed were Grade 3 diarrhea and nausea in 15.8% with no Grade 4 toxicities. At a median follow up of 29.4 months, 12 patients (63.2%) had relapsed with 8 deaths. The estimated 3-year OS and EFS rates were 52.6% and 26.3% respectively.

Krishnan et al [33] conducted a study of $Y^{90}I$ in combination with high dose chemotherapy and stem cell rescue using carmustine, cytarabine, etoposide and melphalan (BEAM). Eligible patients had CD20 positive refractory FL, poor risk

MCL (requiring two or more regimens to achieve PR or CR), DLBCL (represented half of the population) or transformed DLBCL. Stem cells were collected and they were treated in the outpatient setting with the dose of $Y^{90}I$ capped at 40mCi. $Y^{90}I$ was administered on day -14 and the protocol for auto-SCT was initiated on day -7. Disease status was evaluated at days 30, 100, 180 post-transplant. The two year OS was 87.9% (95% CI 68.8 - 96.9). Elderly patients benefited from treatment and therapy was safely administered in the outpatient setting.

Another study by Shimoni et al [34], evaluated the role of $Y^{90}I$ in conjunction with BEAM. These patients were similar to the previous with two year OS 67% (95% CI 46 - 87%) and PFS 52% (95% CI 31 - 72%). This study confirms that $Y^{90}I$ can be safely combined with conditioning regimen prior to SCT.

The response of elderly patients to conditioning with RIT was studied by Gopal et al. [39]. This study examined 24 patients with DLBCL *(n = 9), MCL (n = 7)* and FL (*n* = 8) with a median age of 64 who were treated with an $I^{131}T$ infusion only. Patients received dosimetric infusion on day -24 followed by therapeutic infusion on day -14 (median, 19.4 Gbq [525 mCi]; range, 12.1 to 42.7 Gbq [328 to 1,154 mCi]) to deliver 25 to 27 Gy. At a median follow-up of 29 months the OS and PFS were 59% (CI 95%, 37 - 80%) and 51% (CI 95%, 30 - 72%) respectively. Patients with DLBCL had inferior OS amongst the groups, whilst MCL had poor PFS.

Press et al conducted [36] a phase I/II study evaluating maximum tolerated dose (MTD) of $I^{131}T$ in combination with etoposide and cyclophosphamide among 55 patients. Patients were evaluated at months 1, 3, 6, and 12, and annually thereafter. All patients developed expected grade 4 neutropenia and the median duration of recovery (ANC > 500) was 10 days for peripheral blood and 13.5 days for bone marrow harvest. Platelet engraftment occurred at 13 days for peripheral blood and 23 days for patients who received bone marrow harvest. The maximum tolerated dose was achieved at dose level of 25Gy $I^{131}T$, Etoposide 60 mg/kg and cyclophosphamide 100 mg/kg). Multivariate analysis showed that PFS and OS were superior in the $I^{131}T$ treated group; however it was difficult to interpret due to the histologic differences between groups.

Fewer studies established the role of RIT in the setting of allogeneic stem cell transplantation (allo-SCT). The study by Bethge et al [37] was designed to evaluate the feasibility of adding RIT to allo-SCT. The primary objective of this study was to evaluate the feasibility and assess treatment related toxicities. A recent study by Gopal et al [38] examined the use of RIT in conditioning for a non-myeloablative allo-SCT. As in previous studies, patients received dosimetry on day -21 prior to dosing on day -14 with 250 mg/m^2 of rituximab before the therapy dose of 0.4 mCi/kg of $Y^{90}I$, with a maximum dose of 32 mCi. Fludarabine 30 mg/m^2 was delivered on day -7 to -5 with 2 Gy TBI on day 0. The treatment regimen revealed the expected myelosuppressive side effect profile with time to neutrophil > 500/μL was 17 days (range, 0-34 days) and platelets > 50 000/μL was 11 days (range, 0-147 days). At median follow-up of 1.7 years, the estimated 2 years OS and PFS were 54% (95% confidence interval [CI], 37%-68%) and 31% (95% CI, 16%-48%), respectively. Notably, univariate analysis revealed that patients with indolent histologies had better OS and PFS when compared with aggressive histology ($p < 0.01$).

The application of RIT in SCT offers the advantage of eradication of minimal residual disease and possibly even disease control until the effect of Graft versus lymphoma takes effect.

Current indications for approved use of RIT

The following are the FDA approved indications for the use of RIT

I131 T is approved for the treatment of relapsed or refractory CD20 positive, low-grade, follicular, or transformed NHL.

Y90 I is approved for the Treatment of relapsed or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL); treatment of follicular NHL in patients who achieve a response (partial or complete) to first-line chemotherapy.

Can RIT replace rituximab?

The recent intergroup trial (S0016) concludes that in patients receiving either CHOP-R or CHOP-RIT there are no significant differences in either arm and either arm is considered superior in patients with newly diagnosed follicular lymphoma. This is an important conclusion as

patients who are unable to tolerate rituximab infusions should be considered for $I^{131}T$ at the end of chemotherapy. This is further supported by a meta-analysis of RIT as consolidation for untreated patients with FL. Consolidative RIT appears to benefit patients with untreated FL and compares favorably with rituximab given after chemotherapy [40]. It is however unclear if this approach is comparable in patients who received R-chemotherapy as induction followed by rituximab maintenance. Among patients being considered for rituximab monotherapy as retreatment for relapsed low grade lymphoma, there appears to be an effective role for RIT.

Based on these data, RIT may not replace rituximab; however is an alternate promising anti-lymphoma approach.

Criteria for application of RIT

Due to the known hematological toxicities of RIT, it is recommended that prior to consideration of either of the approved agents, the marrow cellularity be at least at 15% with <25% involvement by lymphoma clone. It is also recommended that patient have an absolute neutrophil count > $1.5x10^9$/L and a platelet count of at least $150x10^9$/L. In relapsed patients however, a reduced dose of RIT can be considered in patients with a platelet count between 100-150 $x10^9$/L. A reduced dose of $Y^{90}I$ was studied in 30 patients with relapsed FL who received 2 prior therapies and with mild thrombocytopenia defined as platelet count between 100,000 to 149,000 [13]. Patients were excluded if they had prior RIT, Rituximab, or extensive BM involvement >25%. Statistical analysis on the data included relation of dosimetry to hematologic toxicity which displayed no significant relation in 21 out of 24 analyses, however in the remaining 3 subsets there was a relation between dosimetry and platelet nadir. The rate of complete response was 37% with Grade 4 thrombocytopenia noted in 13% of patients.

Cytogenetic testing of bone marrow is recommended prior to therapy with RIT to identify chromosomal abnormalities that may preclude the use of RIT. Tumor size may play a role while considering RIT. In a study by Gokhale et al., $Y^{90}I$ when administered to patients with tumor size >5cm had a higher local relapse rate as compared with tumor size <5cm (83% vs. 28%) [41]. Historically, in the trials with RIT, bulky disease was not included in the studies.

Complications

The majority of the clinical trials with RIT have demonstrated similar pattern of toxicity.

Early complications

Patients who receive RIT can have infusional reactions similar to those seen with naked monoclonal antibodies. Grade 1-2 infusion reactions are mild and consist of urticaria or hives only without bronchospasm. In most instances, infusion may only need to be temporarily held or rate reduced and patients can be safely re-challenged with the same drug if needed and premedication is indicated. In the event of grade 3 infusion reaction that causes cardiovascular collapse, bronchospasm and hypotension the antibody will need to be discontinued and may not be re exposed to the antibody. With RIT, grade 3-4 infusion reactions are rare (less than or equal to 2%) and at least partially preventable with premedication with steroids and H2 blockers. The risk of immunogenicity was higher in patients with no prior therapy [16].

The most significant sub-acute complications occur within days to weeks and have to do with marrow suppression which is expected since the radionuclides localize to the marrow. Severe (grade 3-4) marrow suppression occurs on an average of 22 - 75% and duration of grade 4 was 10 - 14 days in the stem cell transplant patient. In general, marrow suppression, especially neutropenia can persist for some time especially in the non SCT setting where patients may not be on growth factors. Concerning tositumomab, thyroid exposure can cause hypothyroidism. This can be effectively blocked with strict adherence to thyroid shielding and potassium iodide administration during treatment. Hypothyroidism may occur months after exposure therefore thyroid hormone levels should be monitored on a routine basis in patients treated with this drug [42].

Late complications

Late complications can occur from months to years after the administration of RIT. Some studies have looked at the development of myelodysplastic syndrome (MDS) and cases have been described up to 2.5-3% [43, 44]. It is

a difficult task to tease apart the causal effect of RIT in patients who have already been exposed to other multi agent chemotherapy drugs including purine analogs, which are known to cause MDS. In the first-line indolent trial, where RIT was used as consolidation, the incidence of MDS/acute myeloid leukemia was 3% as compared with 1% in the control group [44].

Summary

RIT is an effective treatment strategy in NHL. Despite its effectiveness, it has been underutilized. This is likely due to the complexity of administration that makes it less attractive for its wide-spread use. We however, believe that RIT should be considered early on in relapsed patients with low grade lymphoma given its excellent response. It also appears to be promising as a consolidative strategy in intermediate grade lymphoma, though further studies need to be performed to definitively establish its role. It has also shown encouraging results when used as conditioning regimen in patients undergoing SCT. A potential role is to consider its use after an attenuated course of chemotherapy.

Future directions

With advances in genetic engineering, pretargeted RIT using fusion proteins is an area of progress [45]. As the currently approved RIT drugs find their way to expand their use, the future of RIT is bright. Several antigen targets such as CD52, CD30, and CD22 are expressed in various histological subtypes of NHL and are being explored. Despite the promising preliminary phase results further confirmation in the setting of larger clinical trials are needed.

Address correspondence to: Dr. Nishitha Reddy, Division of Hematology and Oncology, Department of Medicine, Vanderbilt University Medical Center, 1301 Medical Center Drive; 3927 TVC, Nashville, TN-37232 Tel: 615-936-0381; Fax: 615-936-1812; E-mail: Nishitha.Reddy@Vanderbilt.Edu

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