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Current concepts of radioimmonotherapy for lymphoma

Aktuelni koncepti radioimunoterapije za limfom

Jasna Mihailović*†, Milan Ubavić‡§, Jasna Trifunović‖¶

***Department of Nuclear Medicine, ‖Department for Medical Oncology, Oncology Institute of Vojvodina, Sremska Kamenica, Serbia; †Technical Faculty "Mihajlo Pupin" Zrenjanin, University of Novi Sad, Zrenjanin, Serbia; ‡Health Care Institution for Laboratory Diagnostics "Medlab", Novi Sad, Serbia; §Faculty of Pharmacy, European University, Novi Sad, Serbia; ¶Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia;**

Abstract

Key words:
lymphoma, non-hodgkin; radioimmunotherapy; clinical protocols; remission induction; treatment outcome.

Apstrakt

Ključne reči:
limfom, nehodžkinov; radioimunoterapija; protokoli, klinički; remisija, indukcija; lečenje, ishod.

Introduction

Non-Hodgkin's lymphoma (NHL) represents a heterogeneous group of lymphocyte malignancies. In general, despite being sensitive to radiation therapy and chemotherapy, low grade NHL remains an incurable disease. In most cases, patients respond to the initial treatment, but half of those relapse within 10 years. Relapsed patients are retreated but there is often a shorter duration of each remission. In addition, some patients become refractory to the treatment regimen [1–3]. A great deal of effort has been made to improve the treatment of NHL to achieve a longer duration of response.

However, despite new chemotherapeutic agents that have been introduced and established into the clinical treatment during the last several decades, overall survival for NHL patients has not essentially changed over the past 40 years [4]. In the 1970's, Köhler and Milstein [5] developed the technique for large-scale production of monoclonal antibodies making possible the anti-tumor therapy using monoclonal antibodies. The first B-cell specific antibody B1 was identified in 1981 by Nadler et al. [6]. Subsequent investigations demonstrated the therapeutic potential of anti-CD 20 immunoglobulins [7, 8]. In the late 1990's, another anti-CD 20 monoclonal antibody, rituximab, was developed and subsequently approved by the United States Food and Drug Administration (FDA) for treatment of patients with low grade B-cell lymphoma who have relapsed. Rituximab is a chimeric monoclonal antibody which is derived from the murine antibody, ibritumomab, and is marketed as Rituxan®/Mab Thera®. Initially, rituximab was used in combination with standard chemotherapeutic options and as a single agent for treatment of elderly NHL patients. The results showed improvement in outcome, overall response rate and duration of remissions [9–12].

Recent advances in molecular medicine have provided a novel approach to the treatment of NHL. During the early decades of the 21st century, therapy with radiolabeled monoclonal antibodies became a treatment option. Radioimmunotherapy (RIT) is based on the concept of conjugation of a radionuclide to a monoclonal antibody that would deliver localized radiation to an antigen that is expressed on tumor cells. RIT targets the cytotoxic radiation to the tumor cells with minimal irradiation of normal cells. RIT the most appropriate for treatment of multiple tumor sites that cannot be readily excised surgically or irradiated using external beam radiation or brachytherapy.

The US FDA has approved 2 RIT protocols: the first in 2002, Zevalin® – rituximab and ^{90}Y-ibritumomab, and the second in 2003, or Bexxar® – tositumomab and ^{131}I-tositumomab. The primary indication for these agents was treatment of relapsed, refractory, or transformed CD20+B-cell NHL. Treatment with either agent is based on monoclonal antibodies specific for the CD20 surface antigen found on normal B-cells and more than 90% of B-cell NHL. In fact, CD20 is an epitope (antigen) expressed on pre-B and mature B-cells, but not on early precursors, stem cells or

Correspondence to: Jasna Mihailović, Department of Nuclear Medicine, Oncology Institute of Vojvodina, University of Novi Sad, Put dr Goldmana 4, Sremska Kamenica, 21 204, Serbia. Phone: +381214805459. E-mail: jasnans@eunet.rs

plasma cells [13–17]. This represents an excellent target as B-cell precursors and plasma cells are not targeted by anti-CD20 antibodies [18]. Moreover, the bound antibody is not shed and is minimally internalized resulting in antibody-dependent and complement-mediated cytotoxicity as well as apoptosis [19–21].

Both RIT agents target the CD surface antigen. Zevalin® utilizes ^{90}Y, and is a pure β emitter with a 2.7 days of half-life, energy of 2.3 MeV, and maximal tissue penetration of 5 mm. Since there are no gamma emissions in the decay spectrum of this isotope, it is poorly visualized on gamma cameras. Therefore, ^{111}In was used until recently in the US for pretreatment imaging and evaluation of biodistribution. In contrast, Bexxar®, is a directly radiohalogenated β and γ emitter; with a γ emission spike of 0.36 MeV, β energy emission of 0.6 MeV. Thus, it can be readily visualized on a gamma camera. Furthermore, Bexxar® involves a covalent bond between I-131 and monoclonal antibody, while Zevalin® uses chelation complex thus providing non-covalent linkage for the radiometal (Table 1) [22].

Zevalin® increases the efficacy of anti-CD20 antibody therapy due to the conjugation of monoclonal antibody with a beta-emitting radionuclide (^{90}Y) [15, 23, 24]. This specific treatment is based on direct toxicity delivered to the cell bound by the antibody and to the neighboring tumor cells *via* cross-fire effect. Beta particles thus kill cells in the nearby environment which are either not accessible to the monoclonal antibody, or may not express CD20, and/or that may be resistant to the immune-mediated or direct apoptotic effects of the unlabeled antibody [25].

Two products, Bexxar® and Zevalin® had been approved in the US and Canada for the treatment of refractory low grade and transformed intermediate grade NHL (follicular lymphoma). Zevalin® regimen is available only in Europe. Both products involve infusions of both unlabeled (cold) antibody and a radiolabeled (hot) antibody: Zevalin® consists of rituximab and ^{90}Y-ibritumomab tiuxetan. Rituximab is non-labeled component of Zevalin®. Ibritumomab is a murine monoclonal antibody component of Zevalin® – labeled with ^{90}Y. Bexxar® consists of tositumomab and ^{131}I-tositumomab. Tositumomab is a murine monoclonal antibody component of Bexxar® – labeled with ^{131}I. In fact, both regimens include the combination of cold, unlabeled antibody infusions followed by infusion of radiolabeled antibody (Zevalin® includes ^{90}Y-labeled anti-CD20 antibody ibritumomab; while Bexxar® includes the ^{131}I-labeled anti-CD20 antibody tositumomab) [18].

Nevertheless, despite the excellent clinical responses, the utilization of these products has been disappointing. Consequently in early 2014, Bexxar® was withdrawn from the market by the manufacturer and is no longer available.

Table 1

Chemical and physical characteristics of Zevalin® and Bexxar® [22]

Characteristics	^{90}Y Ibritumomab Tiuxetan (Zevalin®)	^{131}I Tositumomab (Bexxar®)
Epitope	CD20	CD20
Antibody used for labeling	Ibritumomab-murine Ab	Tositumomab-murine Ab
Linking molecule	Tiuxetan-chelation complex (noncovalent bond)	None (direct halogenization) (covalent bond)
Pretreatment imaging	Optional one	Requested, three
Cold antibody	Chimeric rituximab	Murine tositumomab
Imaging agent	^{111}In ibritumomab tiuxetan	^{131}I tositumomab
Aim of pretreatment imaging	Biodistribution	Dose estimation

Eligibility criteria

RIT is approved for patients with low-grade follicular lymphoma that relapsed after the treatment with rituximab or are refractory or failed to respond to rituximab. As stated, recently the indications for use have been extended to include consolidation therapy in patients with a complete response or at least partial response. This treatment is also used in patients with large B-cell lymphoma that express the CD-20 epitope. Before administration of RIT, patients have to meet the following criteria: initial biopsy confirmation of NHL with the expression of CD20 epitope; recent (within 4-6 weeks) bone marrow biopsy to confirm less than 25% involvement, because treatment of patients with 25% or more bone marrow involvement is associated with severe bone marrow toxicity; history of allergies or medications; and recent (within 1-2 weeks) complete blood count (a platelet count greater than 150,000 justifies full dose, while platelet counts between 100,000 and 150,000 require a modified amount of radiolabeled antibody). This treatment should not be performed in patients younger than 18 years or pregnant and lactating women [18].

Pretreatment imaging and predosing

Until recently, pretreatment imaging in the Zevalin® regimen was required in the US to confirm normal biodistribution despite the fact that altered biodistribution had been reported in less than 1% of patients. The imaging protocol involved administration of rituximab and ^{111}In ibritumomab tiuxetan [2]. Since 2013, this imaging requirement has been abandoned in the US. In Europe, the imaging component of the Zevalin® regimen was never required but predosing with rituximab one week prior to the combination of rituximab and ^{90}Y ibritumomab remains a component of the Zevalin® protocol.

For both regimens, Zevalin® and Bexxar®, an initial infusion of cold, unlabeled anti-CD20 antibody is necessary to

saturate binding sites on normal lymphocytes and improve the more specific targeting to the malignant cells [22]. Without prior infusion of cold antibody, administration of radiolabeled antibody would result in rapid binding of activity by circulating lymphocytes and clearance by those stored in the spleen. When the radiolabeled antibody is injected after the cold antibody, the sites in the spleen have been already saturated and a greater portion of injected labeled antibody remains in the circulation and increases the percentage of the administered dose in tumor [18].

Treatment regimens

The protocol of the Zevalin® regimen is described in detail in our previous reviews [26, 27]. The dosing regimen for treatment with Zevalin® starts with a pre-dose of rituximab 250 mg/m^2 on the first day. The same dose of rituximab (250 mg/m^2) is repeated one week later, followed by the ^{90}Y-ibritumomab tiuxetan infusion in a dose dependent on the platelet counts (30 MBq/kg if platelets exceed 150,000/mL; 22.5 MBq/kg if platelets are > 100,000/mL, < 150,000/mL). The maximum dose should not exceed 1.18 GBq (Figure 1).

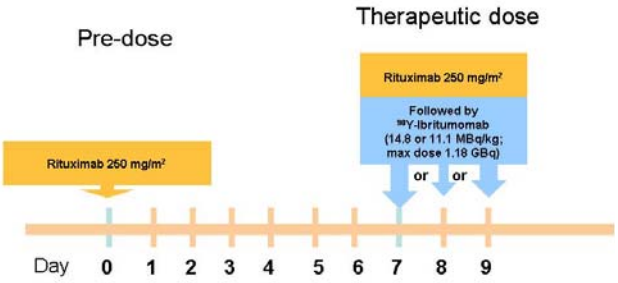

Fig. 1 – The Zevalin® treatment regimen for non-Hodgkin lymphoma.

Patients receiving Bexxar® should be premedicated with a saturated solution of potassium iodide, to block or to reduce thyroidal iodine uptake (3 drops saturated solution of potassium iodide diluted in water 2 times per day, beginning the day before the protocol initiation and continuing for 3 weeks). The Bexxar® regimen consists of 2 steps, the first being, dosimetric and the second, therapeutic [27]. The dosimetric phase involves 3 whole body scans (24–48 h apart) during the week after a dosimetric dose of 185 MBq of ^{131}I-tositumomab preceded by an infusion of 450 mg of unlabeled tositumomab. The Bexxar® regimen is completed seven to nine days after the initial infusion, with the infusion of 450 mg of unlabeled tositumomab followed by the ^{131}I-tositumomab therapeutic dose (Figure 2). For dosimetry, whole body counts are calculated from the total counts on the anterior and posterior whole body scans performed one h after the infusion, 2 and 4–5 days after the initial infusion. The residency time is determined by setting the initial whole body counts as 100% and plotting the other data on a semilog plot. Residence time is at the 37% intercept. This value is used in the calculation of the dose of radioactivity to be administered. Patients with a platelet count exceeding 150,000/mL would receive the maximum tolerated dose of 75 cGy whole-body radiation absorbed dose, while 65 cGy whole-body radiation absorbed dose is optimal for patients with platelet counts between 100,000/mL and 150,000/mL [18].

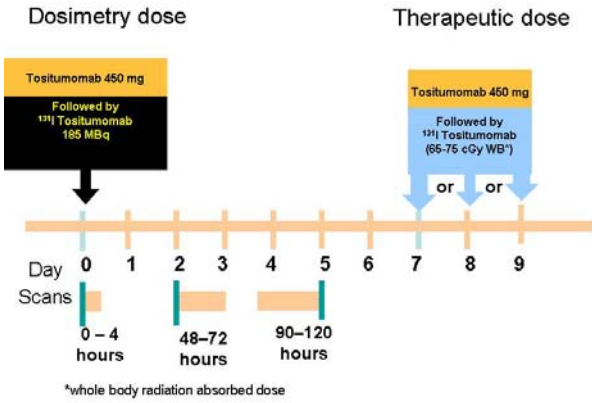

Fig. 2 – The Bexxar® treatment regimen for non-Hodgkin lymphoma.

Clinical efficacy

For both Zevalin® and Bexxar® there are similar clinical outcome. The overall response rates vary between 60% and 80%, with a complete response (CR) of 20–50%, and with one year duration of response for indolent B-cell NHL [16]. Iagaru et al. [28] compared treatment with Bexxar® and Zevalin® in 67 patients with low-grade refractory/relapsed NHL. Objective responses were similar: 70.9% for Bexxar® *vs* 77.8% for Zevalin®. In this report, however, Zevalin® induces more CR than Bexxar® (41.7% *vs* 35.5%).

Clinical efficacy results in several studies using the Zevalin® regimen in NHL patients are shown in Table 2. A single-arm phase II clinical trial was performed on 57 follicular B-cell NHL patients who relapsed or were refractory to the prior rituximab treatment. Patients achieved 74% overall response rate (ORR) and 15% CR. Estimated median duration of response (MDR) was 6.4 months and time to progression (TTP) was 6.8 months for all patients and 8.7 months for responders [24]. A randomized, phase III multicenter study involving 27 institutions and 143 patients with relapsed or refractory low-grade, follicular, or transformed NHL was performed. All patients had advanced disease with a median of two prior chemotherapy regimens. Seventy three patients received Zevalin®, and 70 patients received 4 doses of rituximab. RIT group was pretreated with two rituximab doses to improve biodistribution. An 80% of ORR for Zevalin® group *vs* 56% for the rituximab group ($p = 0.002$), and CR of 30% for Zevalin® group *vs* 16% for rituximab group ($p = 0.04$) were observed. The median duration of response was 14.2 *vs* 12.1 months while TTP was 11.2 months or 10.1 months for Zevalin® *vs* rituximab, respectively [15]. Updated results of the trial reported in 2004 indicated 80% ORR and 56%, and CR rates of 34% *vs* 20%, for Zevalin® compared to rituximab, respectively. Results of this trial suggested a longer estimated MDR (16.7 *vs* 11.2 months) and median TTP (15 *vs* 10.2 months) in the Zevalin® group

Table 2

Clinical efficacy of the Zevalin® regimen in treatment of patients with non-Hodgkin's lymphoma (NHL)

Study	Patients (n)	ORR (%)	CR (%)	MDR (months)	TTP (months)
Witzig et al, 2002. [24]	57	74	15	6.4	6.8
Rituximab-refractory follicular NHL					8.7*
Witzig et al, 2002[15]					
Rituximab-refractory follicular or transformed NHL	143				
Zevalin group	73	80	30	14.2	11.2
Rituximab group	70	56	16	12.1	10.1
Gordon et al, 2004. [29]					
Rituximab-refractory follicular or transformed NHL	143				
Zevalin group	73	80	34	16.7	15
Rituximab group	70	56	20	11.2	10.2
Gordon et al, 2004. [30]					
Follicular and diffuse large B-cell lymphoma, low-grade or mantle-cell lymphoma	51	73	51	11.7*	12.6*
Wieseman et al, 2005. [31]					
Relapsed, refractory or transformed indolent CD20+ B-cell NHL	211	73–83	15–51	6.4–13.9	NA
phase I/II	51	73	51	11.7	
phase II	30	83	47	11.5	
phase II	54	74	15	6.4	
phase III	73	80	34	13.9	
Emmanoulides et al, 2007. [32]					
Relapsed or refractory CD20+ B-cell NHL	211				
patients <60 years	113	78	35	9.9	9.3
patients 60–69 years	58	71	33	11	8.4
patients ≥70 years	40	80	38	9.4	8.8
Vaes et al, 2012. [33]					
Previously treated CD20+follicular B-cell NHL	26	88	65	8.7*	29.6

***Responder patient population; ORR – overall response rate; CR – complete response; MDR – median duration of response; TTP – time to progression.**

vs rituximab group, respectively. CR were highly durable in the Zevalin® group with a median TTP of 24.7 months compared to TTP of 13.2 months in rituximab group with ongoing responses of more than 5 years [29]. The same authors [30] performed a clinical phase I/II trial on 51 patients with follicular and diffuse large B-cell lymphoma, low-grade or mantle-cell lymphoma with a long-term follow-up of more than 5 years. They showed 73% ORR and 51% CR, with the mean TTP and the duration of response in responders of 12.6 and 11.7 months, respectively [30]. Wiseman et al. [31] reported durable long-term responses in 37% of 211 patients with relapsed, refractory or transformed indolent B-cell NHL who were treated with Zevalin® in 4 clinical trials. They obtained ORR of 73–83%, CR of 15–51%, with MDR of 6.4–13.9 months. Patients with TTP of 1 year or longer were characterized as long-term responders; 65% of those patients achieved CR with median TTP of 31 months. Emmanoulides et al. [32] analyzed data from clinical trials of Zevalin® performed in a total of 211 relapsed or refractory NHL treated in 4 different centers. Patients were divided into there different age groups: < 60; 60–69; and ≥ 70 years. The authors obtained different results in different age groups: ORR, between groups ranged from 71–78%; CR, 33–38%; MDR, 9.4–11 months; and TTP, 8.4–9.3 months. In a study performed on 26 patients (CD 20+ B-cell lymphoma), ORR was 88%, CR was 65%, while estimated median progression-free survival (PFS) was 9.1 months after a median follow-up of 29.6 months. Responders had estimated MDR of 8.7 months [33].

Morschhauser et al. [34] studied 414 patients with advanced stage follicular lymphoma who had been enrolled in 77 centers. A large group of 208 patients who received consolidation therapy [chemotherapeutic induction of CR and partial response (PR)] in contrast to a similar group of patents after first line induction treatment without additional treatment were compared. They detected that consolidation induced significantly longer median PFS in the control group (36.5 *vs* 13.3 months). Moreover, 77% of patients with PR after induction treatment converted to CR after consolidation treatment. The final CR rate was 87.4% after consolidation with Zevalin® compared to 53.3% to the control group.

Table 3 shows the clinical efficacy in several single arm trials on the Bexxar® regimen in previously treated NHL patients. Kaminski et al. [35] performed a pivotal study on 60 patients with chemotherapy-refractory low-grade or transformed low grade B-cell NHL. They compared the efficacy of Bexxar® regimen to the last qualifying chemotherapy obtaining ORR of 65% *vs* 28%, respectively. Twenty percentage of patients achieved CR on ^{131}I tositumomab with MDR of 6.5 months and TTP of 8.4 months. Fisher et al. [36] enrolled 250 previously treated relapsed or refractory low-grade, follicular, or transformed low-grade NHL patients in five clinical trials. Bexxar® regimen was administered in NHL patients who were previously treated with chemother-

Table 3

Clinical efficacy of Bexxar® in previously treated patients with non-Hodgkin lymphoma (NHL)

Single arm trials with Bexxar® in previously treated NHL, without rituximab	Patients (n)	ORR (%)	CR (%)	MDR (months)	TTP (months)	Follow-up (months)
Kaminski et al, 2001[35] *Low-grade/ transformed low-grade CD20+ B-cell, at least 2 prior chemotherapy*	60	65	20	6.5	8.4	NR
Fisher et al., 2005 [36] *Relapsed or refractory low-grade, follicular, or transformed low-grade NHL*	250	56 (47–68)	30 (20–38)	12.9	15	41.5
	81*	100*	77*	45.8*	48.5*	61.2*
Kaminski et al. 2000 [37] *Relapsed/ refractory to chemotherapy,CD20+ B-cell NHLs*	59	71	34	NR	12	37.2
Vose et al. [38] *Low-grade/ transformed low-grade CD20+ chemotherapy relapsed/refractory*	47	57	32	9.9	11.6	NR
Davies et al. 2004. [13] *B-cell NHLs in first or second recurrence*	41	76	49	15	9.6	36

***Durable Response Population; NR – not reached; ORR – overall response rate; CR – complete response; MDR – median duration of response; TTP – time to progression.**

apy or rituximab (50% of them did not respond to the last treatment). Data of the integrated patient population indicated ORR and CR rates of 56% and 30%, respectively, with MDR of 12.9 months and median TTP of 15 months (in patients with a complete response, MDR was 58.4 months and TTP 48.5 months). ORRs and CR differ among each of five clinical trials, ranging from 47–68% and 20–38%, respectively; with the median follow-up of 41.5 months. For the durable response population (32% of the entire patient population), CR was 77%; MDR 45.8 months with a median follow-up of 61.2 months [36]. Updating the long-term data on chemotherapy-relapsed/refractory patients treated with Bexxar® in the phase 1–2 single-center study, Kaminski et al. [37] detected 71% ORR and 34% CR with TTP of 12 months during the follow-up of 37.2 months. They showed better ORR in transformed low-grade lymphoma compared to newly diagnosed intermediate-grade tumors (79% *vs* 41%), with 50% CR rate in a group of transformed NHL patients. A multicentric phase II study with a single dosimetric and therapeutic dose of Bexxar® was conducted in 47 patients with relapsed or refractory low-grade (79%) or transformed low-grade (21%) B-cell NHL. Patients were heavily pretreated with median of four prior chemotherapy cycles and showed extensive disease. The study obtained 57% ORR of all the treated patients and 32% CR. The median TTP was 11.6 months and MDR was 9.9 months [38]. Davies et al. [13] performed a phase II study to assess the efficacy of Bexxar® at first or second recurrence on 41 patients with indolent or transformed indolent B-cell NHL. During the follow-up of 3 years, they obtained ORR of 76%, CR of 49%, with 9.6 months of TTP and 15 months of MDR.

Table 4

Clinical efficacy of Bexxar® in previously untreated patients with non-Hodgkin lymphoma (NHL)

Single arm trials with Bexxar in previously untreated NHL	Patients (n)	ORR (%)	CR (%)	MDR (months)	TTP (months)	Follow-up (months)
Kaminski et al., 2001[39] *Follicular advanced stage*	76	95	75	NR	73.2	61.2
Press et al., 2003 [40] *Follicular, II–IV stage*	90	90	67	NR	NR	27.6
Leonard et al., 2004 (abs) [41] *Advanced low-grade*	35	100	83	NR	NR	52.8
Leonard et al., 2005 [42] *Stage III/IV follicular grade*	35	100	86	NR	NA	58
Wahl et al, 2004[43] *Relapsed NHL responders to Bexxar®*	32	56	25	35	NA	NA

NR – not reached; ORR – overall response rate; CR – complete response; MDR – median duration of response; TTP – time to progression; NA – not applicable.

The Bexxar® regimen was also performed in previously untreated NHL patients (Table 4). In a study on 76 previously untreated stage III or IV follicular NHL patients receiving Bexxar® as a sole treatment, after a median follow-up of 5.1 years, Kaminski et al. [39] observed a 95% ORR, 75% CR with a TTP of 73.2 months and a median PFS of 6.1 years. Among patients who achieved complete remission,

70% remained in remission for 4.3–7.7 years. Press et al. [40] conducted a phase 2 trial that included six cycles of CHOP chemotherapy followed by Bexxar® in 90 patients with advanced stage follicular NHL. The results of this trial shows 90% ORR and 67% CR, while 57% of patients who achieved less than CR with CHOP improved their response after Bexxar® therapy (49% patients converted from PR to CR/unconfirmed CR (Cru), while 4.9% patients changed from CRu into CR). With a median follow-up of 27.6 months, the 2-year PFS was estimated to be 81%, with 97% of the 2-year overall survival. Another Bexxar® trial in patients with previously untreated non-Hodgkin lymphoma reported 100% ORR and 83% CR with follow-up of 52.8 months [41]. In different study, Bexxar® regimen was administered after a short chemotherapeutic course of Fludarabine for 3 cycles in 35 previously untreated, stage III or IV follicular grade NHL CD20 lymphoma. The results of this study showed 100% of ORR to the complete regimen, and 86% of CR during the median follow-up of 58 months. The median duration of response was not reached. PFS was also not reached but was estimated to exceed 48 months [42]. A single-arm open-labeled multicenter phase II trial was performed on 32 patients who had initially responded to Bexxar® and were retreated with Bexxar® after relapse of the disease. Authors [43] reported 56% of ORR and 25% of CR, with 35 months of MDR in patients with CR. Retreatment with Bexxar® was also studied in 16 relapsed NHL patients who initially responded to the first regimen and achieved ORR and CR in 56% and 31% of patients, respectively [38].

Safety

RIT using either molecular regimens, Zevalin® and Bexxar® seems to be a safe. The most frequent toxicity reported was bone marrow suppression, transient and reversible. Hematologic toxicity includes neutropenia and thrombocytopenia, was delayed in onset with nadir between 7–9 weeks after the regimen and recovery after 2–3 weeks. More than a half of treated patients show platelet nadir below 50,000 per mm^3, and approximately 20% will have a nadir below 25,000 per mm^3 and may require platelet transfusion. Absolute neutrophil counts below 500 per mm^3 may be detected in about 25–30% of treated patients with a month nadir duration. Hospitalization for febrile neutropenia or similar hematopoetic suppression develops in less than 10% [22]. Some authors [44] reported that Bexxar® causes significantly less severe declines in platelet counts than Zevalin® and thus may be better treatment option for patients with limited bone marrow reserve. Press et al. [40] conducted Bexxar® regimen and obtained grade 3–4 neutropenia, thrombocytopenia and anemia in 15.8%, 13.4% and 2.4%, respectively. In contrast, the most recent study with the Zevalin® regimen, reported 34% incidence of grade 3–4 neutropenia, 38% of thrombocytopenia and 8% of anemia, however, patients spontaneously recovered [33].

Compared to cytotoxicity caused by chemotherapy, nonhematologic adverse effects from either Zevalin® or Bexxar® are very mild. These toxicities are related mostly to minor allergic reactions to the protein components of the cold antibody, generally greater for patients treated with rituximab than those treated with tositumomab. In these situations, infusion should be adjusted to a slower rate. Asthenia or nausea was reported in about 20–40% after receiving either of the anti-CD20 compounds. Side effects such as hair loss, severe mucositis and persistent nausea or vomiting were not detected [44].

Potential long-term adverse effects might be hypothyroidism, development of human antimouse antibodies and secondary malignancies. Human antimouse antibody was reported in 10% of patients following Bexxar®; human antichimeric antibody was detected in about 1–2% following Zevalin® [22]. However, this adverse effect is without serious clinical consequences [38]. Hypothyroidism develops in about 10–20% of patients treated with Bexxar® despite the pretreatment of thyroid-blocking medications [22].

The most important late effect of RIT is secondary malignancy which includes myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Witzig et al. [45] reported 1–2% incidence of MDS/AML for lymphoma patients treated with Zevalin®. Emmanoulides et al. [46] detected annual incidence of 0.34% for MDS and 0.7% for AML since initial treatment with Zevalin® for the period 1993–2002. However, the review of the literature showed 4–8% rate of secondary malignancy in NHL patients treated with chemotherapy alone or combined with radiation therapy [47–49]. In a large study on 1,071 NHL patients treated with Bexxar®, MDS and AML was reported with an annualized incidence of 1.4% per year (95% CI; 1–2% per year) [50]. In another study, there were no cases of MDS or AML [13]. These late toxic effects of bone marrow occur late in patients with B-cell NHL no matter how they are treated. Patients treated with either regimen, Bexxar® or Zevalin®, did not show increased incidence of MDS/AML [22]. In the extensive literature review Cheung et al. [51] reported that secondary MDS and AML had been reported of 0–8% in treated patients, and 0–3% in untreated patients.

Radiation exposure

RIT with either agents, Zevalin® and Bexxar®, is generally considered an outpatient therapy in the US. This treatment, in general, should not be performed in children and adolescents under 18 years of age, in pregnant and in lactating women.

The Zevalin® regimen includes radionuclide ^{90}Y, which is pure beta emitter without gamma radiation. However, the bremsstrahlung emission radiation (which is emitted out of beta particle loosing energy process) is below the limit of exposure and is not hazardous for health personnel and family members. However, patients are provided by written instructions about contact with household members. They are suggested to avoid transmission of excretions such as saliva, blood, urine, seminal fluid and stool [52, 53]. According to the data published from another study, the Zevalin® regimen includes minimal exposure to treated patients (0.00295 mSv/h at 1 m immediately after dosing). Exposure to patient's fam-

ily members (first week 0.035 mSv) is in the range of European background radiation (0.04–0.15 mSv/week) [54].

According to the Nuclear Regulatory Commision and specific dose-calculations, virtually all patients can be released at the end of the therapeutic infusion. A study in Nebraska included family members of patients who had received 1–5 GBq of Bexxar® to deliver 30–75 cGy. Measurement of monitoring devices of 26 family members from 22 patients showed radiation absorbed dose differ from 17 to 409 mrem (below 500 mrem limit applicable to general public members), based on patients receiving Bexxar® (limit exposure to the total effective dose does not exceed 500 mR) [55].

Bexxar® therapeutic regimen can be administered safely with minimal additional exposure to healthcare professionals. Harwood et al. [56] studied exposure on professional workers who were involved in 300 administrations of Bexxar® treatment: radiopharmacists, nuclear medicine technologists, nurses and physicians at four different institutions during 2–4.5 years. They reported that additional average radiation monthly exposure per healthcare worker involved in Bexxar® regimen was 5.8 mrem. Before release, patients are given detailed instructions on the duration and proximity to others to minimize exposure such as: avoiding sleeping with other individuals for a week or more, not traveling by air for several days, and avoiding children and pregnant women for a week or longer. These instructions are based upon patient specific variables including administered dose, measured emission from the patient at the body surface and at 1 m, and biologic turnover rate calculated from dosimetry measurements [51].

Other radioimmunotherapy compounds

In Australia, due to the lack of availability of the RIT regimen, Zevalin® and Bexxar®, Leahy et al. [57] developed a new hybrid regimen consisting of rituximab as the cold antibody and rituximab labeled with ^{131}I in patients with indolent non-Hodgin's lymphoma. In a recent study, they achieved ORR of 76% and CR of 53% with a median survival over 4 years. At 6–7 weeks, they reported side effects such as grade 4 thrombocytopenia and neutropenia in 4%, and 16%, respectively.

Linden et al. [58] developed an anti-CD22 monoclonal antibody, radiolabeled with ^{90}Y and evaluated as ^{90}Y-Epratuzumab in combination with cold Epratuzumab for treatment of indolent NHLs. An ORR in 62% and CR in 25% of patients was achieved; ORR of 75% in indolent NHLs and 50% in aggressive NHL. Subsequently, Leonard et al. [59] reported a 24% response in patients with follicular NHL with median duration of the objective response of 79.3 weeks and median time to progression for responders of 86.6 weeks. The treatment was well tolerated with manageable hematologic toxicity.

Recently, a multicenter, fractionated dose phase I/II study with ^{90}Y-epratuzumab was performed on 64 patients with relapsed or refractory NHL. The results indicated that for 61 patients, a median PFS was 9.5 months, while ORR and CR were 62% and 84%, respectively. In addition, 17 patients previously treated with autologous stenc cell transplantation, ORR of 71% and 55% CR were achieved. On the other hand, in patients with indolent follicular lymphoma, the ORR was 100% with CR of 92% and a PFS of 18.3 months [60]. Sharkey et al. [61] suggested that combining anti-CD 20 and anti-CD 22 antibodies might be more efficient for NHL patients in future clinical trials. They also suggested the possible role of ^{177}Lu or an alpha particle emitter in the setting of minimal or occult disease.

Conclusion

Two radiolabeled antibodies (with different radiolabels) were approved as therapeutic agents in low grade non-Hodgkin's lymphoma. There was no direct comparison between the two agents and currently Bexxar® is unavailable. In general, clinical responses (complete response, partial response) with radioimmunotherapy after relapse are better, and of greater duration, than alternative or repeat chemotherapies. Radioimmunotherapy regimen is safe and effective even after multiple relapses following chemotherapy and/or rituximab (Rituxin®) therapy. The complete response and overall response rate is even better when used in conjunction with first-line chemotherapy ("consolidation" treatment). The principle toxicity is hematologic, secondary to bone marrow irradiation from labeled antibody in blood and specific deposition on tumor cells in the bone marrow. Radioimmunotherapy should not be performed in patients younger than 18 years, pregnant or lactating women. Radiation exposure of family members and health care personnel is low. In the event of relapse, patients tolerate subsequent therapy as well or better than equivalent populations who have not received radioimmunotherapy.

During the last few years, new agents for radioimmunotherapy have been developed such as ^{131}I-rituximab therapy and ^{90}Y-epratuzumab, showing impressive results. Hopefully, future trials should investigate the combination of immunoglobulins and introduce new radionuclides including alpha emitters for radioimmunotherapy of patients with non-Hodgkin lymphoma.

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