Radioimmunotherapy of Non-Hodgkin’s Lymphoma: From the ‘Magic Bullets’ to ‘Radioactive Magic Bullets’

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Radioimmunotherapy (RIT†) of lymphoma with Zevalin and Bexxar was approved by FDA in 2002 and 2003, respectively, for the treatment of relapsed or refractory CD20+ follicular B-cell non-Hodgkin’s lymphoma. In 2009, Zevalin was also approved for consolidation therapy in patients with follicular non-Hodgkin’s lymphoma that achieve a partial or complete response to first-line chemotherapy. For follicular lymphoma patients, the overall response and progression-free survival rates have significantly improved since the implementation of RIT. The predominant complication of RIT is hematological toxicity that is usually manageable. There are ongoing trials to further define the expanding role of RIT as first line or concomitant therapy in the treatment of lymphoma as well as for certain antibiotic resistant infections and aggressive malignancies. There is also growing interest in the development of newer protocols for increased and more uniform dose delivery resulting in better outcomes and improved patient survival. This review will primarily focus on the role of RIT in treatment of non-Hodgkin’s lymphoma, which is of established clinical utility and FDA approved. The mechanism of RIT, available radionuclides and pharmacokinetics, therapy administration, clinical utility and toxicities, and future directions would be discussed.

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†Abbreviations: NHL, Non-Hodgkin’s Lymphoma; HD, Hodgkin’s Lymphoma; RIT, radioimmunotherapy; mAb, monoclonal antibody; HAMA, human anti-mouse antibody; HACA, human anti-chimeric antibody; ORR, overall objective response rate; CR, complete response; PR, partial response; PFS, progression-free survival; TP, time to progression; DR, duration of response; MDS, Myelodysplastic syndrome; AML, acute myeloid leukemia; RBE, relative biological effectiveness; LET, linear energy transfer.

Keywords: lymphoma, non-Hodgkin’s lymphoma, Hodgkin’s lymphoma, radioimmunotherapy, immunotherapy, Bexxar, Zevalin, Dosimetry, Y-90, Rituximab, monoclonal antibody, beta particle, alpha particle, Auger, biodistribution
INTRODUCTION

Immunotherapy utilizes the antibody-antigen mechanism to enhance or suppress the immune response for management of various disorders. Different immunomodulators that selectively modify the immune response have been used clinically with significant success, such as Rituximab (Rituxan, lymphoma), Trastuzumab (Herceptin, breast cancer), Alemtuzumab (Campath-1H, chronic lymphocytic leukemia), Cetuximab (Erbitux, colorectal cancer), and Bevacizumab (Avastin, colorectal and lung cancers).

Radioimmunotherapy (RIT) uses monoclonal antibodies (mAb) directed against specific tumor antigens labeled with a particle emitting radioisotope to deliver radiation directly to the tumor. Radioimmunotherapy combines the synergistic effects of both radiation and immunotherapy with manageable local and systemic side effects. The characteristic and complex interactions between the tumor, host, radionuclide, and the antigen-antibody complex determine the effectiveness of RIT. RIT has an established role in treatment of lymphoreticular malignancies [1], but it has not proven effective for the treatment of solid tumors due to limitations with antibody penetration within the central portions of larger tumors. However, RIT has a promising role in the treatment of bone metastases, prostate cancer, metastatic melanoma, ovarian, leukemia, high-grade brain tumors, metastatic colorectal cancer, neoplastic meningitis, and resistant fungal and viral infections through binding of radionuclides to antibodies, thereby targeting the corresponding antigens. An ideal radioimmunotherapeutic scenario offers selective targeting of a radiosensitive tumor with minimal toxicity (unique antigen expression, high affinity of the antigen-antibody binding, antigen that is not shed, internalized, or modulated, uniform distribution, similar bioprofile of the constituents, optimal tumor residence time and penetration, improved progression-free survival, minimal HAMA-human anti-mouse antibody and HAHA-human anti-chimeric antibody responses, possible repeat administration, etc.). Also, other logistics such as availability, ease of labeling process, stability of the radioimmunoconjugate, cost effectiveness, outpatient administration, minimal radiation safety precautions, etc. are important considerations during the design of an ideal radioimmunoconjugate for therapy.

Radionuclides with beta decay ($^{131}$I, $^{90}$Y, $^{177}$Lu, $^{186}$Re, $^{188}$Re, $^{67}$Cu), alpha decay ($^{211}$At, $^{212}$Bi, $^{213}$Bi, $^{225}$Ac) and low energy electrons ($^{125}$I, $^{67}$Ga ) have the potential for use in RIT. The general properties of various decay particles used in radiotherapy are outlined in Table 1 [2]. The characteristics of the radionuclide strongly influence the effectiveness and toxicity of the therapy [3]. This clinical realm of applications is rapidly expanding with a possible role in the management of several resistant and untreatable conditions. This review will primarily focus on the RIT of lymphomas, which is of established clinical utility and FDA approved.

Beta decay radionuclides have been extensively used for radionuclide treatments and offer better radiopharmaceutical characteristics for design and therapy administration. The unique characteristics of cross fire effect, adequacy of delivery to cell surface added to the ease of labeling, and availability led to widespread use of beta particle radioimmunoconjugates. The improved effectiveness of antibodies labeled with beta emitting radionuclides relates to the phenomenon of “cross fire” or “by-stander” effect [4], where in the tumor cells within close range of the targeted cell are also killed secondary to beta ionizing radiation irrespective of the antigen expression. The radiation safety precautions for beta decay radionuclides are minimal unless there is a coexisting gamma radiation.

Alpha decay results in denser ionizations with much higher linear energy transfer (LET) and relative biological effectiveness (RBE) and also can be employed in hypoxic conditions. However, the range is only microns, and thus, it requires actual binding of the therapeutic agent to the cancer cell itself.
for the therapy to be effective (i.e., there is no cross fire effect with alpha decay, which is one of the advantages of beta particles). Also, the alpha emitting radionuclides are usually either short-lived (that limits the duration of their biological effectiveness) or decay to a beta emitting daughter product with long half-life (for example, $^{207}$Bi is the daughter radionuclide of $^{211}$At and has a half-life of ~30 years). Alpha emitting radionuclides pose a significant challenge for the design of RIT compound due to short half-life and in vivo metabolic instability. However, due to significant sparing of healthy tissues with alpha emitting agents, there is growing interest in the application of alpha therapy as adjunctive treatment for patients with residual disease.

Low energy electrons have relatively dense ionizations with high toxicity, but they need to be incorporated into the nucleus of the target cell due to their extremely short range of nanometers. The success of Auger electron therapy depends on selective delivery and stable bio-localization of the radioimmuno conjugate into the nucleus of all the tumor cells, and this poses a significant challenge for radiopharmaceutical design.

**RIT OF LYMPHOMAS**

Lymphomas are malignancies of the lymphoid tissue and are broadly classified into Hodgkin’s lymphoma (HD) and non-Hodgkin’s lymphomas (NHL, 85 percent).

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**Table 1: Therapeutic Radionuclides [2]**

|                         | Beta decay                                                                 | Alpha decay                                                                 | Low energy electron decay |
|-------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------------|
| **Emission**            | Negative charged electron                                                 | Helium nucleus                                                             | Auger electrons           |
| **Energy**              | 0.05 – 2.5 MeV                                                            | 2-10 MeV                                                                  | 10 eV-10 keV              |
| **Range**               | 0.2 – 15 mm                                                               | 10-500 μm                                                                 | nanometers                |
| **Path track**          | Tortuous                                                                  | Straight                                                                  | contorted                 |
| **Ionizations**         | Less dense                                                                | Dense                                                                     | Relatively dense but only in immediate vicinity |
| **Linear Energy Transfer** | 0.2 keV/μm                                                               | 80 – 300 keV/μm                                                           | 4 – 26 keV/μm             |
| **Mechanism**           | Cross fire effect, half-life and radioactivity dependent, Oxygen dependent | Traversed path length in the cell nuclei, Oxygen independent            | Breaks in DNA strands     |
| **Relative Biological Effectiveness** | Low                                                                      | High                                                                      | Low                       |
| **Requisite**           | Close to target/cell surface                                              | Binding to cancer cell                                                    | Incorporation into nucleus |
| **Clinical application** | FDA approved                                                              | Experimental                                                              | Experimental              |
| **Cross fire effect**   | Yes                                                                       | No                                                                        | No                        |
| **Radiation safety**    | Minimal; other precautions if coexisting gamma decay                      | Minimal, avoid inhalation/ingestion                                       | Minimal                   |
Non-Hodgkin’s lymphomas are a heterogeneous group of lymphoreticular malignancies with a wide range of aggressiveness. The majority of NHL are B-cell lymphomas, with the follicular and diffuse large B-cell lymphomas constituting up to 50 percent of NHL. NHL can also be classified as indolent (40 percent) or aggressive lymphomas (60 percent). B-cell CLL/small lymphocytic lymphoma, marginal zone lymphoma, lymphoplasmacytoid and follicle center lymphoma constitute the indolent types, whereas diffuse large B-cell, mantle cell, Burkitt’s and precursor B-cell leukemia constitute the aggressive types. NHL accounts for 4 percent of all malignancies and 4 percent of all cancer relate deaths [5]. The TNM staging cannot be applied for lymphomas and a pathological WHO/REAL classification [6] integrating the cytological, molecular, and immunological information is in current use. The Ann Arbor staging is used for clinical staging of both HD and NHL [7]. Various prognostic scores and classifications have been developed to risk stratify the patients [8]. The initial staging and histological grade are important factors that determine the patient’s prognosis.

Pressman et al. [9] reported the initial localization of $^{131}$I polyclonal antibodies to tumor cells in rabbits, and Bierwaltes et al. [10] reported their therapeutic potential in human metastatic melanoma. Subsequently, monoclonal antibody technology (mAb) was developed by Kohler and Milstein in 1975 [11], thereby opening doors for selective targeting. DeNardo et al. [12] first described the successful use of RIT with Lym-1 ($^{131}$I labeled anti B-cell lymphoma mAb) in NHL. The use of anti CD-20+ mAbs was described by Nadler et al. [13], and subsequently, the use of $^{131}$I and $^{90}$Y anti CD-20+ mAbs was described [14]. Since then, several modifications and new protocols were reported.

More than 90 percent of the lymphoma B-cells demonstrate cell surface CD-20+ antigen (a human B-lymphocyte restricted differentiation antigen), which is expressed only on mature B-cell lineage and not found on stem or plasma cells. The CD-20+ antigen serves the function of cell cycle initiation and differentiation and is not shed, internalized, or modulated [15,16,17]. Rituximab (Rituxan) is a chimeric (murine and human) monoclonal antibody targeting CD-20+ antigen on both malignant and normal mature B-cells. Binding of Rituximab with CD-20+ antigen triggers various cellular pathways that result in apoptosis, antibody dependent cytotoxicity, and complement dependent toxicity with an overall improvement in treatment response rates [18].

**ZEVALIN AND BEXXAR**

The two currently FDA-approved therapeutic agents for management of lymphoma are $^{90}$Y ibritumomab tiuxetan (Zevalin, Cell Therapeutics Inc, Seattle, WA, and Schering AG, Berlin, Germany; 2002) and $^{131}$I tositumomab (Bexxar, GlaxoSmithKline, Research Triangle Parks, NC; 2003). The indications and contraindications for RIT in the treatment of lymphoma are detailed below. The properties of Zevalin and Bexxar are compared in Table 2.

**Radio-immunoconjugates**

Zevalin is $^{90}$yttrium labeled ibritumomab tiuxetan. $^{90}$Y ($^{90}$yttrium) is produced from decay of Strontium-90. $^{90}$Y is a pure beta emitter that decays to non-radioactive stable Zirconium-90 with a half-life of 64 h (2.7 d). The max energy of the beta emission is 2.29 MeV, and it has an effective path length of 5.3 mm (meaning 90 percent of its energy is absorbed within a sphere with a 5.3 mm radius or about 100-200 cell diameters). The beta emission from $^{90}$Y has a longer path length than that of $^{131}$I, which is advantageous in tumors with heterogeneous antibody distribution as it permits radiation to a larger area. Ibritumomab is a murine IgG-1 kappa anti-CD20+ antibody genetically engineered from a Chinese hamster ovary (CHO) line that is conjugated to Y90 in the presence of a chelate tiuxetan (Mx-DTPA). The median biological half-life of Zevalin in blood is 48 hours with clearance primarily through the genitourinary system. Approximately, 7 percent of the administered dose is
Table 2: Comparison of Zevalin and Bexxar

| Components                      | Zevalin                                                      | Bexxar                                                      |
|--------------------------------|--------------------------------------------------------------|--------------------------------------------------------------|
| Antibody                       | $^{90}$Y ibritumomab tiuxetan                                 | $^{131}$I tositumomab                                         |
| Ease of Labeling               | More complex                                                 | Ease                                                         |
| Availability                   | Available in US, Canada, and Europe                           | Not available in Europe                                       |
| Radionuclide                   | $^{90}$Y                                                     | $^{131}$I                                                    |
| Max beta energy (mean)         | 2.29 MeV (0.9 MeV)                                           | 0.6 MeV (0.19 MeV)                                          |
| Principal gamma emissions      | None                                                         | 364 keV                                                      |
| Effective mean path length     | 5.3 mm                                                       | 0.8 mm                                                       |
| Half life                      | 2.7 d                                                        | 8.04 d                                                       |
| Clearance                      | Urinary                                                      | Urinary, faster                                              |
| Critical organ                 | Spleen, testes                                               | Thyroid                                                      |
| Cold antibody                  | Rituximab                                                    | Tositumomab                                                  |
| Diagnostic scan purpose        | Bio-distribution                                             | Dosimetry and bio-distribution                               |
| Dose determination             | Fixed based on weight and platelets (0.4 or 0.3 mCi/kg)     | Clearance rate/dosimetry based to deliver 75cGy or 65cGy total body dose |
| Pre-therapy preparation        | Antihistamines/NSAID                                         | Additional thyroid blocking                                  |
| Hematological toxicity         | Predominant toxicity                                         | Predominant toxicity, less severe than Zevalin               |
| Other unique toxicities        | Dehalogenation in liver, and effect on marrow                | Hypothyroidism                                               |
| HAMA                           | 2%                                                          | 20% or more                                                  |
| Myelodysplastic syndromes (MDS/AML) | 1.4 – 5.2%                                           | 10%                                                          |
| Radiation precautions          | Universal for 1 week                                         | Additional precautions for gamma radiation                   |
| Therapy setting                | Outpatient                                                   | Majority outpatient                                          |
Table 3a: Zevalin therapy administration protocol [19]

**Step A: Patient Selection and Eligibility**

**Step B: Bio-distribution/ Diagnostic scan**

**Day 1:**
- Acetaminophen 650 mg and diphenhydramine 50 mg, 30 minutes prior to infusion
- Unlabeled rituximab infusion (250 mg/m²) at a rate of 400 mg/hr, incremental to 500 mg/hr
- 5 mCi or 185 MBq/1.6 mg antibody (10 mL) of ¹¹¹In-Zevalin slow intravenous injection over 10 minutes; administered within 4 hours of the cold antibody infusion

**Days 2-6:**
- Whole body planar images obtained at 48-72 hours (subsequent scanning optional)
- Previously, images at 2-24, 48-72, and 90-120 hours

**Step C: Dose Calculation**

Assess the bio-distribution and if acceptable, determine the dose (0.4 or 0.3 mCi/kg based on platelet counts)

**Step D: Therapeutic Dose Administration**

**Day 7/8/9: (exact timing depends on dose arrival and logistics)**
- Acetaminophen 650 mg and diphenhydramine 50 mg, 30 minutes prior to infusion
- Unlabeled rituximab infusion (250 mg/m²) at a rate of at a rate of 50 mg/hr
- Calculated dose of Zevalin slow IV infusion over 10 minutes through a low protein binding millipore filter (maximum dose 32 mCi or 1184 MBq); administered within 4 hours of the cold antibody infusion
- Flush the catheter post infusion to administer complete dose
- Assay the administration tubing set

Eliminated through urine within the first 7 days. The estimated tumor absorbed radiation dose is 15 Gy (1500 rad), with a tumor-to-normal organ ratio of 7:1.

Bexxar is ¹³¹I covalently linked to tositumomab, a murine IgG2a lambda monoclonal antibody also directed to CD-20+ antigen. ¹³¹I is a beta and gamma emitter with a physical half-life of 193 h (8.04 days). The max beta energy is 606 keV (mean 191.6 keV), and the principal gamma emission has energy of 364.5 keV (82 percent). The mean path length is 0.4 to 0.8 mm. The median total body effective half-life for Bexxar is 67 hours (28-115 hours), and elimination occurs predominantly through urine (67 percent is cleared within 5 days).

**Indications and Contraindications**

Zevalin therapy is indicated for relapsed or refractory, low grade or follicular B-cell NHL lymphoma. It was approved in 2009 for previously untreated follicular NHL patients who achieve a partial or complete response to first-line chemotherapy. Bexxar therapy is indicated for treatment of patients with CD20+ antigen-expressing relapsed or refractory, low-grade, follicular, or transformed NHL, including patients with rituximab refractory NHL.

Both Zevalin and Bexxar are contraindicated in the following conditions: pregnancy or ongoing breast feeding, known allergy or hypersensitivity to the murine antibodies, or components of the therapy; absolute Neutrophil Count <1500 cells/cu mm, platelet count <100,000; bone marrow involvement of more than 25 percent involvement; effective beam radiation therapy of >25 percent of active marrow; prior autologous stem cell transplant; and elevated HAMA titers with altered biodistribution. Additional contraindications for Bexxar therapy include iodine allergy, urinary incontinence (relative contraindication), non-compliant patients, and a reduced renal function with creatinine >1.5.

**Treatment Administration**

Once the patient is referred for RIT therapy, a determination needs to be made if patient is eligible for treatment.
For Zevalin therapy, a bio-distribution scan is obtained as an outpatient for exclusion of abnormal antibody tracer distribution (0.6 to 1.3 percent of patients) that would preclude treatment. Given that $^{90}$Y is a pure beta emitter and has no gamma decay, $^{111}$In is used as a surrogate. During the bio-distribution or pre therapy planning stage, $^{111}$In-Zevalin is injected intravenously, and whole body planar images are obtained at 48 hours following administration of the agent. Prior to dosing, patients receive a dose of unlabeled rituximab to block CD-20+ binding sites on B-cells in the circulation and in the spleen. Upon confirmation of the normal expected bio-distribution, a dose of Zevalin is calculated based on patient’s weight and platelet count. The dose of Zevalin is 0.4 mCi/kg (14.8 MBq/kg) in patients with platelet counts greater than 150,000. If the platelet counts are between 100 and 150,000, the dose is decreased to 0.3 mCi/kg (11.1 MBq/kg). If platelets are fewer than 100,000, therapy is contraindicated. The maximum administered activity of Zevalin is 32 mCi. Zevalin does not have any gamma emissions, and the activity is measured indirectly through Bremsstrahlung radiation. The standardization and calibrations factors are set up at the time of the initial site inspection. Table 3a details the protocol for administration of Zevalin therapy [19].

For Bexxar therapy, the therapeutic dose is calculated from pre-therapy dosimetric studies after administration of a small dose (5mCi) of $^{131}$I-tositumomab. Similar to the Zevalin protocol, prior to tracer administration, the patient is given an infusion of unlabeled tositumomab to bind non-tumor B-cells
in the circulation and spleen. Additionally, SSKI is administered to block thyroid uptake of $^{131}$I. Initial studies reported at least a four-fold normal variation in the clearance of the administered activity depending on tumor burden, presence of splenomegaly, and extent of bone marrow involvement. The tolerated maximum whole body radiation dose for Bexxar therapy is 75cGy or 75 rad (65cGy or 65 rad, if platelets are 100,000-150,000). The geometric whole body counts are plotted on a semi-log paper, and a residence time is calculated (time to reach 0.37 from the initial activity, 8-24 days). The expected activity hours from the provided data are compared to the residence time derived from semi log graph, and the resulting activity is adjusted for platelet count to calculate the administered activity. Refer to Table 3b for Bexxar administration protocol [20].

**Scintigraphic Imaging and Findings**

The variations in the bio-distribution of the antibody scan images provide clues to their recognition. The whole body antibody scan image reflects a blood pool scan. A fragment antibody scan results in rather intense renal activity due to faster clearance. $^{111}$In images demonstrate better image resolution (Figures 1 and 2) compared to $^{131}$I-Bexxar images. Pre-loading is performed with an unlabeled antibody infusion for both bio-distribution and treatment studies, in an effort to minimize the antigen sinking effect, wherein the administered activity predominantly targets and accumulates within the normal reticuloendothelial system and circulating lymphocytes [21]. If a scan is performed without administration of a pre-dosing unlabeled antibody, this would result in intense spleen and marrow uptake.

On a normal pre-therapy $^{111}$In-Zevalin scan, there is good uptake in the blood pool areas that decreases over time, moderately high to high uptake in the normal liver and spleen, and moderately low to low uptake in the lungs, kidneys, and urinary bladder. Tumor uptake may be visualized but is not required. Altered bio-distribution is suggested when blood-pool activity is not visualized, lung uptake exceeds liver activity, renal activity exceeds hepatic activity on posterior images, and if there is more uptake in the bowel than the liver. Increased bone marrow accumulation of the tracer can be seen in patients with HAMA response, tumor involving marrow, or related to use of marrow stimulating factors. Figure 1 demonstrates a di-
agnostic $^{111}\text{In}$-Zevalin obtained at 48 hours, with normal bio-distribution and tumoral uptake.

Normal bio-distribution of Bexxar includes blood pool activity that decreases over time and liver and splenic activity less than heart, which decreases over time. There may be mild uptake within the thyroid, kidney, and urinary bladder and minimal uptake within the lungs. Lymphomatous tissues can demonstrate concentration of the radionuclide with increasing activity. An abnormal bio-distribution includes absent blood pool activity, intense liver or spleen activity, increased lung uptake greater than blood pool activity, findings indicative of urinary obstruction, or an abnormal calculated total body residence time (normal 50-150 hrs). Figure 2 demonstrates initial dosimetric Bexxar images obtained at three different time points as per the imaging protocol.

**Clinical Utility**

The CD-20+ antigen is densely expressed on nearly all (more than 90 percent) of B-cell lymphomas, and these tumors are amenable for treatment with immunomodulators. Unlabeled Rituximab treatment directed against the cell surface antigen CD20+ has proven effective in the treatment of B-cell non-Hodgkin’s lymphoma [22,23]. However, lymphomas are generally radiosensitive tumors, and this feature offers a unique opportunity for even more effective treatment with radiolabeled immunomodulators that are also directed against the CD-20+ antigen.

In a randomized pivotal trial of patients with relapsed or refractory low-grade follicular NHL, Zevalin treatment resulted in significantly higher ORR (overall objective response rate) and CR (complete response) compared to unlabeled rituximab therapy alone [24]. A multicenter randomized study demonstrated prolonged median progression free survival (PFS) with conversion of 77 percent of partial responders to complete response with Zevalin for consolidation after chemotherapeutic induction compared to a control group [25]. These results suggest that Zevalin may have an important role in eliminating minimal residual disease following induction chemotherapy. In a pivotal
## Table 4: Important studies signifying the role of RIT in lymphoma

| Immuno or radioimmunon conjugate | Population and N | Results | Reference |
|----------------------------------|------------------|---------|-----------|
| Rituximab                        | Relapsed low grade or follicular NHL, N=166 | ORR: 48%; CRR: 6%; Projected median TTP for responders: 13m | McLaughlin et al., 1998 [22] |
| Rituximab + CHOP vs. CHOP         | Aggressive NHL, N=399; randomized study | 76% vs. 63% Higher event free and overall survival rate, reduced risk of treatment failure and death | Coiffer et al., 2000 [23] |
| Zevalin                          | Rituximab refractory follicular NHL, N=54 | ORR: 74%; CR: 15%; Overall TTP: 6.8m | Witzig et al., 2002 [30] |
| Zevalin vs. Rituximab             | Relapsed or refractory follicular, low-grade, or transformed NHL, N=143; randomized multicenter study | ORR: 80% vs. 56%; CR: 30% vs. 16%; TTP and median DR: no significant difference | Witzig et al., 2002 [24] |
| Zevalin after chemotherapy induction of a CR or PR vs. control group | Advanced stage follicular lymphoma in first remission, N=414; multicenter randomized study | Median PFS of 36.5m vs. 13.3m; 77% of PR cases converted to CR with Zevalin | Morschauer et al., 2008 [25] |
| Bexxar vs. tositumomab           | Relapsed or refractory NHL, N=78; randomized trial | ORR: 55% vs. 19%; CR: 33% vs. 8% | Davis et al., 2003 [27] |
| Bexxar vs. salvage chemotherapy  | Low grade or transformed low-grade NHL, N=60 | ORR: 65% vs. 28%; CR: 17% vs. 3% | Kaminski et al., 2001 [26] |
| Bexxar                           | Relapsed or refractory low-grade, follicular, or transformed low-grade NHL, N=250; integrated efficacy analysis of the previous five clinical trials | ORR: 47% - 68%; CR: 20% - 38%; 5-year PFS: 17% | Fischer et al., 2005 [31] |
| Bexxar                           | Stage III or IV follicular lymphoma, N=76 | ORR: 95%; CR: 75%; 5-yr PFS: 59% | Kaminski et al., 2005 [28] |
| Bexxar after short course of Fludarabine | Early stage, N=35 | ORR: 98%; Median PFS > 48m | Leonard et al., 2005 [29] |

**Legend:**
- ORR: Overall objective response rate
- CR: Complete response
- PR: Partial response
- PFS: Progression free survival
- TP: Time to progression
- DR: Duration of response
- m: months
trial, treatment with Bexxar resulted in significantly better ORR and CR compared to the last chemotherapy in refractory and relapsed cases [26]. Also, another randomized trial reported significantly better overall and complete response rates with Bexxar as compared to unlabeled tositumomab alone [27]. Subsequent studies demonstrated the utility of Bexxar alone in stage III or IV follicular lymphoma and Bexxar after a short course of Fludarabine in early stage with better ORR and PFS rates [28,29]. Other trials also reported the utility of RIT with better ORR, CR and increased PFS, and some of them are detailed in Table 4.

**Toxicity Profile**

The primary and dose-limiting side effect from RIT is hematologic toxicity.

The primary adverse effects of Zevalin therapy are hematological toxicity with anemia, thrombocytopenia and neutropenia [32]. There is a delayed nadir for the hematological toxicity that reaches a peak at 7 to 9 weeks following treatment (which is slightly delayed compared to standard chemotherapy), and the duration can last 7 to 35 days. Other side effects are flu-like symptoms, including infection, chills, fever, abdominal pain, and allergic reactions. Reduced renal function and toxic skin reactions have rarely been reported with Zevalin administration. There is a reported small risk of developing AML (acute myeloid leukemia) in 1.4 percent of the patients between 8 and 34 months after therapy, although myelodysplastic syndrome (MDS)/AML has been reported in up to 5.2 percent of the cases. HAMA response can develop in up to 2 percent of Zevalin therapy patients.

The toxicities of Bexxar are similar to Zevalin with the predominant adverse effect being hematological toxicity resulting in anemia, neutropenia, and thrombocytopenia [33]. However, these are reported to be less severe compared to Zevalin. The median absorbed dose is highest in the thyroid (2.7 mGy or 270 mrad/MBq), and there is a risk of hypothyroidism (6 percent) from any free I^{131} following Bexxar administration. The incidence of hypothyroidism increases with the time period after therapy [34]. This emphasizes the significance of administering thyroid blocking agents before and during the therapy. HAMA response can develop in 10 percent to 50 percent of patients treated with Bexxar (more in patients without prior chemotherapy) and is higher compared to Zevalin [35]. However, conversion to HAMA positivity has not been shown to be associated with altered therapeutic efficacy. MDS/acute leukemias were reported in up to 10 percent of patients during a median follow-up of 27 to 39 months, with a higher increased incidence over time following therapy.

**Radiation Safety**

Plastic and acrylic shielding is used for Y^{90}, and lead and tungsten are not appropriate due to the concern for bremsstrahlung radiation. Written radiation safety instructions are not mandated, but helpful for the patients. Administration of Zevalin therapy can be performed with minimal risk to close contacts [32,36,37]. Universal radiation precautions should be observed post Zevalin therapy, and emphasis should be maintained to prevent contact from body fluids and urine for up to 1 week. Usually, Bexxar can be administered as an outpatient, and the patient can be released with appropriate precautions for I^{131} as per the 10 CFR 35.75 regulations that require a determination of total effective dose equivalent to other exposed individuals to be less than 5mSv (500 mrem). This determination involves a dose-specific calculation based on individual occupancy and social factors with appropriate written safety instructions. Previous studies have demonstrated the feasibility of Bexxar outpatient treatment and safe release of the patients without exceeding the regulatory limits to general public, family members, or health care personnel [38].

**DISCUSSION**

The staging and treatment of lymphomas have witnessed significant changes in the last few decades with newer technologies (PET-CT, tracers) and newer treatment modalities
including new chemotherapeutic agents and monoclonal antibodies. The management of NHL includes radiation therapy, chemotherapy, immunotherapy, combination therapy, and stem cell transplant depending on the histology, grade, and disease extent. The advantage of RIT is the selective delivery of an individualized radiation dose to the tumor cells throughout the body with relative sparing of normal tissues. The radiation induced killing of the tumor, and cross fire effect is felt to be advantageous compared to the conventional/combinational chemotherapy. Local or extended field radiation therapy is an option; however, its effectiveness is often limited due to the disseminated nature of the disease, as well as the inability to treat clinically silent disease sites. Moreover, there is often significant clinical toxicity from external radiation. Both Zevalin and Bexxar are of proven clinical utility and can be safely administered to outpatients for the treatment of low-grade refractory or relapsing CD-20+ B-cell lymphomas. Additionally, Zevalin has been approved for consolidation therapy in previously untreated follicular NHL patients who achieve a partial or complete response to first-line chemotherapy. The contraindications are similar for both the available radionuclide treatments.

There are no randomized clinical studies comparing Zevalin and Bexxar, and the choice of radio-immunotherapeutic agent depends on the tumor, institutional preferences, and the ability of the patient to conform/implement the required radiation safety precautions. RIT can be only performed by an authorized user, and a written directive is needed. Therapy administration requires safe handling and radiation safety precautions, with additional precautions for $^{131}$I following Bexxar therapy. Zevalin, and most cases of Bexxar therapy, can be performed on an outpatient basis. In some countries other than the United States, in-patient therapy may be preferred. Planning, treatment, and post-treatment follow-up require a multidisciplinary approach and interdepartmental coordination.

Both Zevalin and Bexxar require an initial diagnostic/bio-distribution exam, followed by the therapeutic dose administration. The purpose of the initial diagnostic scan for Zevalin is to confirm a normal bio-distribution, whereas the diagnostic exam also provides dosimetric information for Bexxar dosing. For both therapies, the predominant toxicity is hematological with a delayed nadir at 7-9 weeks. Serial blood counts and supportive treatment is performed as needed. The systemic side effects typically observed in association with standard chemotherapy are not seen with RIT. Following RIT, a slightly increased risk for developing myelodysplastic/AML disorders has been reported. An increased risk for developing a HAMA response has been reported with Bexxar therapy (and the risk appears to be higher without prior chemo- or immunotherapy). HAMA can result in falsely elevated biomarkers, but does not cause an increased risk for infusion reactions. In most of cases, the HAMA titers resolve spontaneously. However, the presence of HAMA may alter the bio-distribution and is a contraindication to future immunotherapy [34]. Follow up imaging after RIT can be performed as per the recommended guidelines [39]. RIT with Zevalin and Bexxar does not preclude further treatment with other modalities [40,41].

**ONGOING CONCERNS AND FUTURE DIRECTIONS IN RIT**

**Radionuclide of choice for lymphoma**

Different properties such as mean energy, effective path length, clearance, and slightly differing toxicity profile may affect the choice of radio-immunotherapeutic agent. However, there is currently no clear clinical consensus as to which agent would be superior in a specific clinical scenario, and there are no direct randomized clinical trials comparing efficacy of Zevalin and Bexxar [42]. The reported studies significantly differ in patient selection, prior and concurrent treatments, treatment length, response evaluation, follow-up criteria, etc., and it is difficult to draw an accurate comparison. Zevalin may be effective for bulkier tumors given its higher energy and relatively larger effective path length. The reported risk of antibody re-
actions and incidence of secondary malignancies are relatively less for Zevalin. Overall, the Bexxar labeling process is easier; however, the administration requires individualized dosimetric calculations and appropriate radiation safety precautions for the concomitant gamma emission. Hematological toxicity has been reported to be less severe for Bexxar therapy, and it may be the preferred agent in patients with more limited marrow reserve. Though both Zevalin and Bexxar target the B-cell CD-20+ antigen, there is a subtle difference in the predominant binding to the amino versus carboxy terminal of the motif respectively [43,44]. Though this theoretically results in slightly different functional activity and therapeutic mechanisms, the clinical significance of this is uncertain. For all practical purposes, based on the current knowledge, both Zevalin and Bexxar share similar clinical utility with comparable ORR and CR rates.

Dosimetry scans

There is consensus on utilizing a dosimetric approach for Bexxar therapy with an individualized dose determination based upon the variation in patient clearance rates in an attempt to increase the therapeutic effectiveness of the therapy, while minimizing possible toxicity.

In Europe, the 111In-Zevalin administration and scanning prior to Zevalin therapy administration may be omitted. However, a previous study reports possibility of altered distribution and the need for the initial biodistribution scan [45].

Expanded role

There is a concern in the lymphoma community regarding underutilization of RIT, despite FDA approval for specific indications. The utility of these agents has been recognized, but their use is not widespread due to various barriers with only a very small population of eligible patients receiving the RIT treatment [46]. Some of these barriers include regulatory and reimbursement challenges, complex referral and coordination efforts, self-referral office based practices for non-radioactive alternate therapies, and a perception of increased health care costs. These obstacles necessitate appropriate changes to streamline the RIT process and provide evidence based cost-effective health care to patients [47]. The current ongoing research and recent clinical trials are likely to expand the utility of RIT as a concomitant and/or first-line therapeutic agent for lymphoma treatment [48]. The predominant and dose limiting adverse effect for RIT is hematological toxicity. Therefore, RIT therapy in cases with more than 25 percent marrow involvement is contraindicated at the current time. However, newer protocols such as fractionation and concomitant stem cell transplant (SCT) with decreased hematological toxicity and improved dose delivery might lead to a change in these indications and contraindications.

Dosing Strategies

Dose intensification can be achieved through different methods and protocols [49]. A higher myeloablative dose can be given along with stem cell transplant, thereby potentially achieving higher remission rates [50,51]. The toxicity in such an approach is higher compared to the current approved non-ablative treatments; however, it would still be better than the conventional chemotherapy. Fractionated strategy involves use of multiple fractions of the radiation dose in comparison to the current approved single dose [52,53]. It has been demonstrated in radiation oncology that fractionated radiation treatments result in higher, uniform dose delivery and lesser toxicity. The exact role of this strategy in RIT is not yet defined, but in concept could result in more effective treatment. Pre-targeting involves separation of the therapeutic radionuclide delivery process (90Y-DOTA-biotin) subsequent to a separate delivery of the target molecule (anti-CD20+ mAbs, conjugated to streptavidin) and can be performed as a two- or three-step process. This approach provides higher tumor to background ratios, dose escalation, and better outcomes [54,55].

Subsequent therapy in cases of failed RIT

Subsequent to a failed RIT, other therapies (chemotherapy, immunotherapy, stem
cell transplant etc.) can be performed and are not contraindicated. The side effects of additional conventional therapy are not significantly different in the post-RIT group compared to a similar cohort without RIT [35,40,41]. There are no studies that support repeat RIT administration, although this is feasible. Patients who develop a HAMA response after RIT (with elevated titers) are not candidates for future immunotherapy and radio-immunotherapy due to the potential for altered bio-distribution of the agents.

**Radionuclides, antigens, antibodies and carriers**

Though most of these radionuclide agents are still investigational and not FDA approved, several beta, alpha [56,57], and low energy electron [58,59] emitting radionuclides are being investigated and demonstrate a promising role for RIT. Each class of the above agents offers distinct advantages for RIT due to their physical decay and pharmacokinetic characteristics [60], and these are detailed in Table 1. These agents have been used with variable clinical success in the clinical trials for various tumors [61]. There is also growing interest in the application of this technology for certain resistant infections such as fungal or HIV, which are not easily cured by conventional treatments [62].

Several phase I and phase II studies are being conducted with beta-emitting radionuclides labeled with anti CEA mAbs for colorectal cancer, anti PMSA mAbs targeting the external domain for prostate cancer, intraperitoneal administration of MUC1 antibody for ovarian cancer, and antitenascin antibodies for brain tumors [56-61]. RIT with beta and alpha emitters appears promising for adjunctive treatment of hematological malignancies such as acute leukemia. Unlike hematological malignancies, application of RIT to solid tumors has been limited for several reasons such as lesser radiosensitivity, low tumor vascularity, and lower dose accretion resulting in failure to deliver an adequate and effective tolerable radiation dose. However, newer dosing strategies and protocols detailed in the above section provide dose escalation and intensification that may overcome some of the inherent limitations in administration of RIT to solid tumors [56,63,64]. Pre-clinical studies have shown that alpha-targeted RIT might be of benefit in low tumor burden or micro-metastatic disease due to the high LET and RBE associated with alpha particles. Alpha particle therapy is also being investigated for conditions such as leukemias, lymphomas, gliomas, melanoma, and peritoneal carcinomatosis. The Auger electrons are low-energy electrons that should be deposited only in the immediate nuclear vicinity and have potential for adjunctive treatments [65]. A recent study reported utility of Auger electrons from $^{125}$I labeled 35A7, an anti-CEA antibody for small volume peritoneal carcinomatosis after cytoreductive surgery, as opposed to chemotherapy, which has rather non-uniform dose distribution [66]. Recently, $^{111}$In-NLS-7G3, an auger electron-emitting radionuclide targeting CD-123 was reported to be promising for leukemia in animal studies [59].

There is an ongoing search for newer antigens representing ideal antibody targets. For example, a recent study reported use of $^{90}$Y-epratuzumab tetraxetan (a radiolabeled mAb to CD-22 antigen) in NHL patients with a higher dose delivery and better objective response [53,67]. A smaller radionuclide carrier results in more uniform distribution and better clearance with an opportunity for dose escalation. The ultimate role of humanized antibodies, fragments, diabodies, minibodies in comparison to the conventional murine mAbs is unclear. Newer antibody mimics such as small molecular constructs and selective high affinity ligands targeting HLA-DR10 receptor may offer a novel approach for RIT in hematological malignancies [68,69]. RIT may find a role in early and concomitant/cocktail treatment of lymphoma.

**CONCLUSIONS**

There have been significant developments in RIT since Paul Ehrlich’s Seitenkette-Tentheorie of selective targeting with “magic bullets” to the current day of “radioactive magic bullets.” Although the current role of RIT is primarily focused on lymphoma, future advances will serve to expand its role with in-
dividualized treatment options for multiple tumors that will hopefully result in greater cure rates with decreased systemic toxicity.

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