

# Treatment for Non-Hodgkin's Lymphoma

New technology links monoclonal antibodies with radioisotopes for treatment of refractory or recurrent NHL

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**N**on-Hodgkin's lymphoma is a malignancy of the lymph system that results in the abnormal production of B-lymphocytes.<sup>1</sup> There are many types of non-Hodgkin's lymphomas that range from slow-growing follicular lymphomas to intermediate and high-grade aggressive lymphomas. There are many chemotherapeutic regimens to treat these lymphomas, but almost all patients relapse, regardless of the regimens used.<sup>2</sup> Non-Hodgkin's lymphoma (NHL) is classified by severity by the Ann Arbor staging system. The system is based on the number and location of tumor sites and the presence or absence of systemic symptoms.<sup>1</sup> Stage I refers to NHL involving a single lymph node region or a single organ or site outside the lymph system. Stage II refers to two or more involved lymph node regions on the same side of the diaphragm or with localized involvement of an organ or site outside of the lymph system. Stage III refers to lymph node involvement on both sides of the diaphragm or with localized involvement of an organ or site or spleen outside the lymphatic system, or both. Stage IV refers to the presence of involvement of one or more extralymphatic organs (eg, liver, bone marrow, lung), with or without associated lymph node involvement.

Bexxar and Zevalin are two radiopharmaceuticals indicated for the treatment of CD20 positive, relapsed or refractory, follicular, non-Hodgkin's lymphoma.<sup>3,4</sup> Both pharmaceuticals are monoclonal antibodies to the CD20 receptor that is located on normal and malignant B-cells. Bexxar and Zevalin both consist of monoclonal antibodies linked to a radioisotope. When used alone, the monoclonal antibodies have the following effects: induction of antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis.<sup>5</sup> When these antibodies are linked to a radioisotope, they function not only as tumor cytotoxins, but also as a system that delivers the radioactive isotope to the malignant cells. Radioisotopes emit radiation to the tumor cells that results in increased rates of cytotoxicity. This is a result of radiation "crossfire" or "bystander" effect through malignant cells and solid tumors.<sup>4</sup> This crossfire action reaches cells that may not be reached by monoclonal antibodies alone or that may not be bound by antibodies. The type of radiation emitted and the dosimetry process is what separates the mechanisms of action of the two medications.<sup>6</sup>

The Bexxar product consists of the monoclonal antibody tositumomab, which is then linked to the radioisotope iodine-131.<sup>4,7</sup> The radioisotope is used for imaging and for treatment. Iodine-131 emits radiation of gamma particles of 0.7 mm in length. Iodine-131 tositumomab has the potential to be taken up by the



**Goal.** After reading this article, the reader should be familiar with the two new radiolabeled monoclonal antibodies indicated for the treatment of relapsed or refractory Non-Hodgkin's lymphoma.

**Objectives.** 1) Identify the two radiopharmaceuticals approved for the treatment of Non-Hodgkin's Lymphoma; 2) Identify the indications and contraindications for these pharmaceuticals; 3) Identify pre- and post-treatment monitoring parameters; 4) Compare isolation precautions and why they are necessary; 5) Explain the pre- and post-treatment regimens to patients undergoing therapy.

thyroid gland; therefore, treatment consists of saturation of the thyroid gland with iodine supplements before and after infusion. Patients who are treated with Bexxar must comply with many isolation precautions to prevent exposure of gamma radiation to family members and the general population after gamma treatment. If the patient cannot comply with these precautions, the patient must stay in the hospital until the isolation is complete.

The Zevalin product consists of the monoclonal antibody ibritumomab, which is covalently bound to the chelator, tiuxetan.<sup>3</sup> Ibritumomab tiuxetan can be labeled with two radioisotopes, indium-111 or yttrium-90. The indium-labeled antibody is used for imaging, as it emits gamma particles that may be traced by a gamma camera. Yttrium-90 emits radiation of beta particles of 5.2 mm in length, and is used in treatment. The length of radiation of yttrium is longer, giving it an advantage in treating bulky tumors. Dosing of yttrium-90 ibritumomab tiuxetan is based on body weight and platelet count. Patients treated with Zevalin must comply with minimal isolation precautions to prevent the spread of radiation after treatment.

The major adverse effects of both products include neutropenia, thrombocytopenia, and anemia.<sup>3,4</sup> Both products also carry the risk of causing formation of human anti-mouse antibodies (HAMA) or human-anti chimeric antibodies (HACA). Both products are murine antibodies which are produced from either "hybridomas" of mouse B-cell lymphocytes and human myeloma cells or from human genes.<sup>6</sup> Patients who receive these products in high amounts may produce antibodies against the foreign proteins found on the products. This usually occurs within 2-3 weeks after the first administration of the monoclonal antibody. If the patients are ever re-challenged with monoclonal antibodies, the patients may experience flu-like symptoms or mild anaphylactic reactions. More

importantly, the HAMA or HACA can alter the pharmacokinetics of monoclonal antibodies that are given. HAMA and HACA can bind to monoclonal antibodies, reducing the quantity of circulating free monoclonal antibodies, and thus, reducing the effectiveness of the medication.

### PHASE II CLINICAL TRIALS

Primary and secondary endpoints evaluated for all trials studying the effectiveness of Bexxar and Zevalin include the following terms: overall response rate (ORR), complete response (CR), partial response (PR), time to progression (TTP), and duration of response (DR).<sup>8</sup> Overall response is defined as the percentage of patients with complete response, complete clinical response, or partial response. Complete response is achieved when there is no evidence of disease, and when all lesions regress to a size of under 1.5 cm x 1.5 cm for 28 days. Partial response is defined as 50% or more decrease from baseline of a sum of the products of the greatest perpendicular diameter (SPD) of measured lesions and no progression of the disease for at least 28 days. Time to progression is measured from the date of the first dose to the earlier of the following two dates: date of disease progression or last date of contact. Progression of disease is a 50% or more increase in the SPD of measured lesions compared to baseline. Duration of response (DR) is the date of the first observation of 50% or more shrinkage of tumor response to the earlier of the following two dates: date of progression of disease or date of last contact. Duration of response is only followed in patients who have a CR or PR.

### BEXXAR PHASE II CLINICAL TRIALS

Bexxar was tested for safety and efficacy in a single arm, single-center, open-label trial. Fifty-nine patients were enrolled in the study.<sup>9</sup> Patients were required to be 18 years of age with CD20 positive B-cell NHL, and to have relapsed or failed to respond to at least one chemotherapy regimen. Patients were required to have less than 25% of their bone marrow space affected by lymphoma. Of the 59 patients, 83% were 60 years old or younger and 63% were male. Eighty-eight percent of patients were stage III/IV at study entry, and 31% had bone marrow involvement. Twenty-four percent of patients had received a bone marrow transplant prior to the study. Patients in the study had a median of 3 prior chemotherapy treatments and a median of 4 prior therapeutic treatments (chemotherapy, radiation, and immunotherapy). Forty-eight percent of patients had no response to the last (most recent) therapy for NHL. The overall response rate was 71%, with a complete response rate of 34%. The median progression-free survival (PFS) for all patients was 12 months for all responders and 20.3 months for patients who achieved a CR. The mean duration of response was 11.7 months.

### ZEVALIN PHASE II CLINICAL TRIALS

Zevalin was tested for safety and efficacy in 30 patients in a single arm, multi-center, open-label trial.<sup>10</sup> Of the patients enrolled in the study, the median age was 61 years, and 60% were male. Patients were required to be 18 years old and to have relapsed or refractory low-grade, follicular, or transformed CD20-positive non-Hodgkin's

lymphoma. Patients were excluded if they had received prior myeloablative therapy with autologous bone marrow transplantation or peripheral blood stem cell support. Ninety percent of patients were stage III/IV at study entry, and 67% had bone marrow involvement, and all patients had less than 25% of their marrow space affected by lymphoma. Patients in the study had a median of 2 therapy regimens (radiotherapy, chemotherapy or bioimmunotherapy). Sixty-three percent of patients had either no response (complete or partial) to their last chemotherapy or progressed within 6 months after one or more chemotherapy regimens. Forty-seven percent of patients were resistant (no complete or partial response) to their last chemotherapy regimen prior to enrollment. Patients were excluded if they had received prior bone marrow transplants or peripheral stem cell support or prior treatment with radioimmunotherapy or anti-CD20 therapy.

The overall response rate was 67%, with a complete response rate of 33%, and partial response rate of 40%. The median time to progression was 9.4 months in intent-to-treat patients. Responders had a median TTP of 12.6 months. The median duration of response was 11.7 months.

### BEXXAR PHASE III CLINICAL TRIALS

Bexxar was tested for safety and efficacy in patients with chemotherapy-refractory, low-grade or transformed low-grade non-Hodgkin's lymphoma and to compare its efficacy to the patient's last qualifying chemotherapy.<sup>2</sup> Sixty patients were enrolled who had been treated with at least two chemotherapy regimens and had not responded or progressed within 6 months after their last qualifying chemotherapy regimen. The primary endpoint of the study was to assess the comparison of the number of patients who had a longer duration of response (more than 30 days difference) on Iodine 131 Bexxar with the number of patients who had a longer response to their last chemotherapy. A masked panel comprised of one radiologist and one medical oncologist assessed the endpoints of the trial. Seventeen patients (28%) had equivalent durations of response, and eleven patients (26%) had a longer duration of response on their last chemotherapy. Thirty-two patients (74%) had a longer duration of response after Bexxar treatment ( $P < 0.001$ ).

### ZEVALIN PHASE III CLINICAL TRIALS

Zevalin was tested for safety and effectiveness in patients with relapsed or refractory low-grade, follicular, or transformed NHL.<sup>8</sup> Patients included in the study were to be at least 18 years of age and with disease in less than 25% of the bone marrow. Patients who were rituximab naïve were to have bi-dimensionally-measured disease of greater than or equal to 3 cm by CT or MRI scans. Patients were excluded if they had a life expectancy of under three months, and if they had received external-beam radiation to more than 25% of their bone marrow. The primary endpoint of the study was to compare the overall response rate of Zevalin versus the unlabeled antibody, rituximab. One hundred and forty-three patients were enrolled in the study. An independent, blinded panel comprised of one radiologist and one oncologist assessed the effectiveness of the two drugs. Seventy-three patients were randomized to receive Zevalin and seventy patients were randomized

to receive rituximab alone. The overall response rate was 80% for the Zevalin group versus 56% in the rituximab group ( $P = 0.002$ ). The complete response rate was 30% in the Zevalin group versus 16% in the rituximab group ( $P = 0.040$ ). The Kaplan-Meier-estimated median time to progress was 11.2 months for the Zevalin group compared to the 10.1 months for the rituximab treated group ( $P = 0.173$ ).

### ADVERSE EFFECTS

Adverse effects are summarized in Table 1. The most common adverse effects observed in Bexxar treated patients were hematologic, including neutropenia, thrombocytopenia, and anemia.<sup>3,4</sup> Adverse events in Table 1 were obtained from 230 patients enrolled in five clinical trials using the package insert recommended dose and schedule. Nineteen patients (8%) experienced infections for which they were hospitalized. Delayed reactions include hypothyroidism, secondary leukemia, myelodysplastic syndrome, and immunogenicity. The overall incidence of hypothyroidism in the patients was 14% of 230 patients. Among 994 patients, there were 32 (3.2%) patients who presented with new cases of myelodysplastic syndrome or secondary leukemia with a median follow-up of 21 months. Twenty-three (11%) of the patients were positive for HAMA or HACA after 6 months.

The most common adverse reactions for Zevalin treated patients were neutropenia, thrombocytopenia, and anemia. Three percent of patients developed "serious infections," although this term was not defined in the package insert. Only six patients (2%) developed secondary malignancies following treatment with Zevalin. The onset of a cancer was 8-34 months following treatment with Zevalin. Of 211 patients who received Zevalin, there were 8 (3.8%) patients with positive HAMA or HACA after 90 days.

Percentages of patients who experienced hematologic effects with Bexxar and Zevalin, including thrombocytopenia (25% and

30%) and anemia (53% and 51%), were similar in duration (32 and 24 days respectively) and severity with both agents.

### DOSING REGIMENS

Treatment with Zevalin or Bexxar consists of many steps.<sup>3,4</sup> Both medications require a dosimetric dose and a therapeutic dose to be given. Before each of these steps, unlabeled antibody is given in order to bind all CD20 positive cells that are easily accessible.<sup>6</sup> This is to ensure that the radioactive isotopes reach less accessible binding sites so that cytotoxicity is optimized. The unlabeled antibody used in the Bexxar regimen is tositomomab,<sup>4</sup> whereas the unlabeled antibody used in the Zevalin regimen is rituximab.<sup>3</sup> After unlabeled antibody is given, the dosimetric dose is given. The dosimetric dose is a small dose of antibody that is labeled with a gamma-emitting radioisotope which is given to assess the therapeutic index of the drug by measuring its biodistribution.<sup>3,4,6</sup> Therapeutic index is defined as the ratio of the radiation absorbed dose delivered to cancer cells and the dose delivered to normal tissues. This index is measured to ensure that the radiation absorbed into normal tissues is safe. Biodistribution is determined by whole body gamma camera scans that produce an image of the radiation given off by the drug within the body. Gamma camera scans will only image gamma radiation; therefore, the antibody must be labeled with an isotope that emits gamma radiation. The therapeutic radioisotope used with Bexxar is Iodine-131, which emits gamma radiation. Iodine-131 Bexxar may be used for both the dosimetric dose and the therapeutic dose. The therapeutic radioisotope used with Zevalin is Yttrium-90, which emits beta radiation. Since beta radiation will not be traced by gamma cameras, an alternate radioisotope must be used for dosimetry of Zevalin. Therefore, for imaging purposes, Indium-111, a gamma-emitter, is linked to Zevalin to determine its biodistribution. After biodistribution is determined to be acceptable, the therapeutic dose may be given. It is important to note that administration of iodine (Lugol's solution, SSKI drops or potassium iodide tablets) is required for 24 hours before and 2 weeks after administration of Bexxar. No iodine supplementation is required with Zevalin.

### SAFETY AND PRECAUTIONS

As with most radiopharmaceuticals, specific precautions are necessary to avoid exposing others to radiation. Patients who are treated with Bexxar must take extensive precautions including:<sup>4</sup>

- Sleep alone for 3 nights;
- Stay away from work (if others are in close proximity) for 1 day;
- Maintain a prudent distance (>9 ft) from others for 4 days ;
- Avoid prolonged contact with children and pregnant women for 10 days;
- Maintain sole use of a bathroom for 2 days. If not possible, then flush the toilet 3 times after use. Men should sit during urination;
- Refrain from traveling by airplane or mass transportation for 4 days;
- Refrain from traveling on a prolonged automobile trip (>6 hours) with others for 7 days;
- Drink plenty of fluids for 2 days;

**TABLE 1. ADVERSE EFFECTS FROM POOLED TRIALS**

Adverse Effects	Bexxar (n = 230)%	Zevalin (n = 349)%
Asthenia	46	43
Fever	37	17
Nausea	36	31
Infection	21	29
Pain	19	13
Chills	18	24
Headache	16	12
Abdominal Pain	15	16
Vomiting	15	12
Anorexia	14	<10
Diarrhea	12	<10
Myalgia	13	<10
Cough increased	21	10
Pharyngitis	12	<10
Dyspnea	11	14
Rash	17	<10
Pruritis	10	<10
Throat irritation	N/A	10

- Wash clothing and eating utensils separately for 2 days.

Patients who are treated with Zevalin require less stringent precautions including:<sup>3</sup>

- Clean up spilled urine and dispose of any body fluid (blood, saliva, stool) or contaminated material (e.g., flush it down the toilet or place it in a household trash) to prevent its being handled by any family members for 3 days;
- Wash their hands thoroughly after urination for 3 days;
- Use a condom during sexual intercourse to prevent the transfer of body fluids for 1 week.

### COST AND HOW SUPPLIED

Both Bexxar and Zevalin are extremely expensive. Bexxar is distributed as a two-part kit, one part for dosimetry and one for therapy.<sup>4</sup> Both of these parts include radiolabeled and unlabeled antibodies. The cost of one Bexxar kit, sufficient to treat one patient, is approximately \$26,000.

Zevalin is currently supplied as two separate kits that contain all of the non-radioactive ingredients needed to produce a single dosing step of Zevalin.<sup>3</sup> Included in each kit are two doses of unlabeled ibritumomab (one to be given unlabeled and the other to be labeled with the appropriate isotope). The yttrium-90 is also included in the kit. Indium-11 chloride must currently be ordered separately from a manufacturer-specified radiopharmacy, and rituximab must be purchased separately from a wholesaler. The cost of all ingredients necessary to produce a single treatment with Zevalin is approximately \$24,000.

### PHARMACY PRACTICE PEARLS

Bexxar and Zevalin are products that are only administered in highly specialized practice sites.<sup>3,4</sup> As the use of these products expand, it will become critical for all pharmacists to have a practical knowledge of many issues related to the care of patients who undergo this type of therapy. Important points to remember include:

- Bexxar emits gamma radiation, which means longer and stricter isolation precautions to family members;
- Bexxar requires 24 hours of pre-treatment and 2 weeks of post-treatment with iodine supplements to prevent radiation damage to the thyroid gland;
- Bexxar carries the risk of causing hypothyroidism, whereas Zevalin does not;
- Zevalin emits beta radiation, which means fewer and less strict isolation precautions to family members;
- Zevalin has a five times greater path length, which gives it an advantage in treating bulky tumors;
- The preparation of both products require two steps, a dosimetric step and a therapeutic step, separated by 6 or 7 days;
- Both products require several gamma camera scans to ensure that the amount of radiation delivered to normal tissues is safe;
- Bexxar uses the same radioisotope, Iodine-131, for both steps of treatment;
- Zevalin uses Indium-11 for the dosimetric step and Yttrium-90 for the therapeutic step;
- Both products are contraindicated in pregnancy;

- Women should be advised to discontinue breast-feeding before treatment;
- Both products can cause thrombocytopenia and anemia, so it is important that patients get platelet counts drawn every week for 10 weeks after treatment.

### CONCLUSION

Bexxar and Zevalin are two radiopharmaceuticals indicated for the treatment of patients with relapsed or refractory, low grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. In clinical trials, patients were similar in severity of disease and median number of chemotherapy regimens before the trials. Overall response rates, complete response rates, and time to progression were all similar as well. Zevalin emits beta radiation that has a longer path length that may be an advantage when treating bulky tumors. Both radiopharmaceuticals appear to be equally safe and effective. Zevalin is currently the less expensive of the two regimens. Bexxar has a disadvantage of a higher rate of hypothyroidism than that of Zevalin (14% vs. 0%), as well as a greater incidence of HAMA (11% vs. 0%) and greater incidence of myelodysplastic syndromes (5-8% vs 1-2%) as compared to Zevalin. However, the clinical implications of these are modest (hypothyroidism) or are yet unknown (HAMA and myelodysplastic syndromes). In summary, both Bexxar and Zevalin show increased overall response rates versus conventional therapy, so there is an advantage in using these radiolabeled pharmaceuticals for relapsed or refractory disease. While expensive, these products represent novel and exciting therapies for Non-Hodgkin's lymphoma. ●

Caitlin Curtis is a pharmacy practice resident at the University of Wisconsin Hospital and Clinics, Department of Pharmacy. The contributions of Richard Hammes and Dr. Brad Kahl are gratefully acknowledged.

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**SELF ASSESSMENT QUESTIONS**

# Treatment for Non-Hodgkin's Lymphoma

New technology links monoclonal antibodies with radioisotopes for treatment of refractory or recurrent NHL

- |  |  |
|--|--|
| <p>1. <b>T F</b> Bexxar and Zevalin are considered to be first-line treatment for patients with Non-Hodgkin's lymphoma.</p> <p>2. <b>T F</b> Bexxar uses the radioisotope Iodine-131 that can be used for both the dosimetric and therapeutic steps of treatment.</p> <p>3. <b>T F</b> Bexxar requires pre- and post-treatment with iodine-saturation regimens to prevent radiation damage to the thyroid gland.</p> <p>4. <b>T F</b> Zevalin emits gamma radiation, and therefore requires stricter isolation precautions.</p> <p>5. <b>T F</b> Bexxar and Zevalin consist of unlabeled and radiolabeled monoclonal antibodies that bind to the CD20 receptor of malignant and non-malignant B-lymphocytes.</p> <p>6. <b>T F</b> Only Bexxar requires weekly platelet counts for 10 weeks following treatment, since the gamma radiation causes more severe hematologic adverse effects.</p> <p>7. <b>T F</b> Zevalin may be used in pregnancy as it emits beta radiation that is not harmful to the fetus.</p> <p>8. <b>T F</b> Patients treated with Bexxar must maintain a prudent distance (&gt;9 feet) from others for 4 days.</p> | <p>9. <b>T F</b> Gamma-camera scans are only needed for Bexxar therapy, as it emits gamma radiation and Zevalin emits beta radiation.</p> <p>10. <b>T F</b> Both products carry the risk of causing the patient to produce HAMA and HACA.</p> <p>11. <b>T F</b> Both products carry the risk of causing hypothyroidism.</p> <p>12. <b>T F</b> Bexxar has a longer radiation path length.</p> <p>13. <b>T F</b> Bexxar emits gamma radiation and therefore has the advantage in treating bulky tumors.</p> <p>14. <b>T F</b> Both products require a dosimetric step in order to ensure that the amount of radiation delivered to normal tissues is within safe limits.</p> <p>15. <b>T F</b> Iodine saturation regimens are required for 24 hours before and after treatment with Bexxar because the radioisotope Iodine-131 can be taken up by the thyroid gland and cause damage to this organ.</p> <p>16. How do you rate this lesson?<br/> <b>a. Very Good    b. Good    c. Poor</b></p> <p>17. <b>Y N</b> Did it meet the learning objectives?</p> <p>18. How long did it take to complete this lesson?</p> |
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**QUIZ ANSWER FORM** *circle one answer per question*

- |        |         |           |
|--------|---------|-----------|
| 1) T F | 7) T F  | 13) T F   |
| 2) T F | 8) T F  | 14) T F   |
| 3) T F | 9) T F  | 15) T F   |
| 4) T F | 10) T F | 16) a b c |
| 5) T F | 11) T F | 17) Y N   |
| 6) T F | 12) T F | 18) _____ |

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