

## Bexxar

Expert review by:

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### What is Bexxar?

Bexxar is a dual-action therapy that combines the tumor-targeting ability of a monoclonal antibody and the therapeutic potential of radiation. Bexxar is a radioimmunotherapy that has been shown to produce long remissions in some patients with follicular non-Hodgkin lymphoma (NHL) who have either not responded to rituximab (Rituxan) or have progressed after an initial response to rituximab. The Bexxar therapeutic regimen is given in one short course and is specifically dosed based on individualized clearance rates of radiation from the body.

### What is a Monoclonal Antibody?

Antibodies are normal components of the body's immune system that can recognize and destroy foreign invaders such as bacteria and viruses. Scientists can now produce monoclonal antibodies designed to recognize very specific targets, or antigens that are present on certain kinds of cancer cells. Rituxan was the first monoclonal antibody to receive U.S. Food and Drug Administration (FDA) approval.



Antibody targeting antigen on cell

Therapy with a monoclonal antibody is an effective way of specifically targeting certain kinds of cancer cells, with a low degree of toxicity to normal cells. Monoclonal antibody therapy is administered by intravenous infusion, generally on an outpatient basis. Once in the bloodstream, mono-

clonal antibodies travel throughout the body and attach themselves to cells that have the specific target antigen, such as cancer cells. This alerts the body's own immune system to recognize and help destroy the cancer cells. Although some normal cells that also have the specific target antigen may be affected along with the cancer cells, the body can usually replace these normal cells following treatment. The monoclonal antibody used in the Bexxar therapeutic regimen, called Tositumomab, specifically recognizes and attaches to the CD20 antigen, which is found on the surface of lymphocytes, including the cancerous B-lymphocytes in patients with B-cell non-Hodgkin lymphoma. This is the same antigen recognized by Rituxan and by Zevalin.

### What is Radioimmunotherapy?

Radioimmunotherapy is a cancer therapy involving the combination of a monoclonal antibody with a radioisotope as a source of radiation. When a monoclonal antibody is combined with a radioisotope, it is said to be 'radiolabeled.' With radioimmunotherapy, the radiolabeled antibody targets and binds to a specific antigen present on normal and cancerous B-cells, delivering a dose of radiation directly to the targeted cells. Not only does the radiation destroy the cell to which it is bound, but it also destroys the surrounding cells, a phenomenon that is called the "crossfire" effect.



Radiolabeled antibody killing off malignant cells

## **What products are currently on the market for Radioimmunotherapy?**

There are two products currently approved by the FDA for radioimmunotherapy of patients with B-cell lymphomas: Bexxar and Zevalin. Both use radiolabeled mouse monoclonal antibodies binding to the CD20 antigen.

## **What are the differences between Zevalin and Bexxar?**

Zevalin uses a monoclonal antibody called Ibritumomab tiuxetan combined with a radioisotope. Two types of radioisotopes are used with Zevalin: Indium-111 for gamma camera imaging and Yttrium-90 for therapy. Patients receiving Zevalin receive an infusion of nonradioactive rituximab shortly before administration of Indium-111 or Yttrium-90 labeled Ibritumomab tiuxetan (please see LRF's Zevalin fact sheet for more information).

Bexxar employs Iodine-131, a radiation-emitting form of iodine that has been in use for 50 years in the treatment of thyroid disease, attached to the monoclonal antibody Tositumomab. In the body, Tositumomab seeks out and selectively binds to a specific protein marker, called CD20, found on the surface of B-cells. Once it is combined with Iodine-131, Tositumomab is able to deliver its radiation to target cancer cells. Iodine-131 emits two forms of radiation. Beta radiation is responsible for most of the tumor-killing effect and gamma radiation allows gamma camera scans to be performed to evaluate the distribution and clearance of radiation from the body. Iodine-131 radiation is eliminated from the body mainly through the urine and by the natural decay of Iodine-131.

## **How is Bexxar given?**

The Bexxar therapeutic regimen is delivered in two sets of intravenous infusions given 7-14 days apart: Nonradioactive Tositumomab is given before both the "dosimetric" infusion and the "therapeutic" infusion to improve distribution of these doses throughout the body. A trace amount of radioactive Iodine-131 Tositumomab, is initially given to evaluate the clearance of radiation from the patient's body with gamma camera scans. Calculations made on the basis of these individualized radiation clearance rates allow the therapeutic dose (given 7-14 days after the dosimetric infusion) to be tailored for each patient. The therapeutic dose contains Tositumomab labeled with the

amount of Iodine-131 tositumomab specifically calculated for the patient based on the scans performed following the dosimetric dose.

Following the infusion of the dosimetric dose, counts are taken with a gamma camera to track the elimination of radiation from the body. The patient then returns to the hospital for two more scans, approximately two days apart. These procedures are important because highly individual factors such as tumor size, bone marrow involvement and spleen size affect how long the radiation remains in the body. Dosimetry, therefore, allows the amount of Iodine-131 radiation administered in the therapeutic dose to be adjusted for each patient so that the optimal target dose of radiation is achieved for maximum effectiveness while minimizing toxicities. Starting one day before beginning the Bexxar therapeutic regimen and continuing for two weeks after receiving the therapeutic dose, patients take a medication containing non-radioactive iodine to protect their thyroid gland from Iodine-131 radiation.

Bexxar is given in either the nuclear medicine department or the radiation oncology department within the hospital or clinic. Once the therapeutic dose is successfully administered, the treatment is complete. In most cases, patients can receive Bexxar on an outpatient basis (though this varies from state to state, dependent on local laws). Following treatment, patients are provided with simple instructions to follow for a short period of time to minimize the radiation exposure to other people. If these procedures are followed, the potential exposure risk to family members is roughly equivalent to the exposure received in the course of one to two years from normal background radiation in the environment. The amount of radiation received by close contacts of patients who followed the instructions is well within the guidelines deemed acceptable by the government agency regulating radiation exposure, namely, the Nuclear Regulatory Commission (NRC).

## **Who can be treated with Bexxar?**

The FDA has approved the Bexxar therapeutic regimen for treatment of patients with follicular, non-Hodgkin lymphoma expressing the CD20 antigen whose disease is refractory to rituximab (not responding or a remission of less than six months) or who have relapsed following chemotherapy or rituximab. Patients who initially presented with follicular lymphoma but whose disease has subsequently

“transformed” to a more aggressive type of lymphoma (e.g. diffuse large B-cell lymphoma) are also approved for therapy with Bexxar. Bexxar is not indicated for the initial treatment of patients with CD20 positive non-Hodgkin lymphoma outside of the setting of research trials. Clinical trials have shown promise in a variety of other clinical settings (including front line therapy) and other B-cell lymphomas, but these have not yet been approved for treatment by the FDA. Bexxar should only be administered by physicians and other healthcare professionals qualified by training in the safe use and handling of radioactive components. Patients should not be treated with Bexxar if they have low platelet counts (<100,000), or low neutrophil counts (<1,500), more than 25 percent involvement of the bone marrow with tumor, have a known hypersensitivity to mouse proteins or any other component of the Bexxar therapeutic regimen, are pregnant or breast feeding, or have impaired kidney function.

### **How effective is Bexxar?**

The efficacy of the Bexxar therapeutic regimen was examined in a multi-center, single-arm study of 40 patients with follicular NHL whose disease had relapsed following or had not responded to rituximab. The median age of patients in the study was 57 and the median number of prior chemotherapies was four. Eighty-eight percent of patients met the definition of rituximab-refractory (defined as no response or a response of less than six months in duration). Sixty-three percent of rituximab-refractory patients responded to Bexxar, with a median duration of response of 25 months. Twenty-nine percent of patients with rituximab-refractory disease had a complete response (no clinical signs of disease) after Bexxar therapy. The results of this study were supported by demonstration of durable objective responses (long remissions) to the Bexxar therapeutic regimen in four other single-arm studies enrolling 190 patients with Rituximab-naïve, follicular NHL, with or without transformation, who had relapsed following or were refractory to chemotherapy. The overall response rates ranged from 47 percent to 64 percent in these other trials with median durations of response ranging from 12 to 18 months. Recent studies of radioimmunotherapy as frontline treatment have shown outstanding results. The overall response rates in those studies have been between 90 percent and 100 percent and the complete remission rate in those studies has been anywhere between 60 percent to

95 percent. The duration of response in the studies that are mature have all been more than five years and many of these patients have remained in continuous complete remissions without ever relapsing. Bexxar is not yet approved by the FDA for initial treatment, so reimbursement is hard to obtain at this time for the front-line setting.

### **What side effects are associated with Bexxar?**

Bexxar is generally very well tolerated. The most common side effects occurring in clinical trials of the Bexxar therapeutic regimen included predictable suppression of the bone marrow, which occurs somewhere between four and eight weeks after treatment. This results in low blood counts, including low white blood cells (leukopenia), low platelets (thrombocytopenia) and low red blood cells (anemia) that could be both prolonged and severe but were generally reversible.

The most common side effects other than low blood counts included weakness, fever, nausea, infection and cough. Bexxar was associated with a risk of hypothyroidism and human anti-murine antibody (HAMA) formation. Certain chemotherapy agents and ionizing radiation have been associated with the development of myelodysplasia (MDS), secondary leukemia and solid tumors. MDS, secondary leukemia and solid tumors have also been observed in patients receiving the Bexxar therapeutic regimen. Bexxar carries a warning about infusion-related reactions that may be induced by the administration of foreign proteins. Hypersensitivity reactions occurred in six percent of patients. Adjustments of the rate of infusion to control adverse reactions occurred in seven percent of patients.

### **What radiation safety precautions are recommended after Bexxar therapy?**

The radiation risks to family members or healthcare workers appear minimal based on two studies in which radiation monitoring was performed. The nuclear medicine physician or radiation safety officer will give patients specific written instructions concerning how long to follow these guidelines; for most patients it is for 1-2 weeks after the therapeutic infusion of Bexxar.

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## Is Bexxar an option when Rituxan stops working?

As noted above, approximately two thirds of patients who fail to respond to Rituxan will achieve a partial or complete remission when treated with Bexxar, and these remissions lasted an average of two years.

## Can a patient who has been treated previously with radiation therapy receive Bexxar?

Yes, provided that the prior radiation treatment did not cause impairment of bone marrow reserve by encompassing large areas of the bone marrow-bearing bones, which could increase the risk of a serious drop in the blood counts.

## Can Bexxar be combined with other treatments for lymphoma?

The FDA has not approved combination therapies with Bexxar; research studies suggest that treatment regimens such as CHOP or CVP chemotherapy followed by Bexxar, Fludarabine followed by Bexxar and high dose Bexxar followed by stem cell transplantation are well tolerated and effective. At the current time, though, such therapies should only be conducted on approved research protocols.

## Can a patient who has received Bexxar in the past be treated again with Bexxar?

Bexxar has only been approved as a single course of treatment. However, on a research trial 32 patients who responded to Bexxar have been retreated with Bexxar following recurrence of their disease and 18 achieved remissions, with tolerable side effects. Seven of these 18 patients achieved complete remissions (Kaminski, Journal of Clinical Oncology, 2005).

## Does Bexxar therapy "burn bridges" for future treatments with other products?

There is a theoretical concern that radioimmunotherapy may damage bone marrow stem cells making it more difficult to administer future chemotherapy regimens or collect stem cells for transplantation. However, data available to date indicate that treatment with Bexxar does not preclude subsequent treatments. In one report, 44 patients successfully received combination chemotherapy after Bexxar, with regimens containing potent drugs such as doxorubicin, fludarabine, and cisplatin and 13 patients successfully underwent stem cell transplantation (Dosik, Cancer 2006).

## Bexxar Information Resources

To learn more about lymphoma, treatments and ongoing clinical trials, contact LRF's *Lymphoma Helpline* at 800-500-9976, [helpline@lymphoma.org](mailto:helpline@lymphoma.org) or visit [www.lymphoma.org](http://www.lymphoma.org). For more information about Bexxar, please consult Bexxar Prescribing Information, call 1-877-4-BEXXAR, visit [www.bexxar.com](http://www.bexxar.com) or speak with your physician.