# RADIOIMMUNOCONJUGATES

## TOSITUMOMAB
## (BEXXAR®)

### I. MECHANISM OF ACTION

Tositumomab and Iodine I $^{131}$ tositumomab is an antineoplastic radioimmunotherapeutic monoclonal antibody-based regimen composed of the monoclonal antibody tositumomab, and the radiolabeled monoclonal antibody, Iodine I $^{131}$ tositumomab. Tositumomab is a murine IgG2a lambda monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes.

Iodine I $^{131}$ tositumomab is a radio-iodinated derivative of tositumomab that has been covalently bonded to I $^{131}$.

This radioimmunocomjugate targets CD20 and is thought to cause cell death by induction of apoptosis or antibody dependent cell cytotoxicity mediated by the antibody. Cell death also occurs through local ionizing radiation. The high energy beta particles emitted by I $^{131}$ are cytotoxic over distances of approximately 1-2 mm thus permitting eradication of antigen-negative tumor cells by cross-fire from neighboring antibody-coated cells.

### II. PHARMACOKINETICS

A) The median blood clearance following administration of 485 mg tositumomab in 110 patients with NHL was 68.2 mg/h. Patients with high tumor burden, splenomegaly, or bone marrow involvement were noted to have a faster clearance, shorter terminal half-life, and larger volume of distribution. The total body clearance, as measured by total body gamma camera counts, was dependent on the same factors noted for blood clearance.

B) $^{131}$I decays with beta and gamma emissions with a physical half-life of 8.04 days. Elimination of$^{131}$I occurs by decay and excretion in the urine. Urine was collected for 49 dosimetric doses. After 5 days, the whole body clearance was 67% of the injected dose. Ninety-eight percent of the clearance was accounted for in the urine.

C) In clinical studies, administration of the therapeutic regimen resulted in sustained depletion of circulating CD20 positive cells. One of them was conducted in chemotherapy-naïve patients and 1 in heavily pretreated patients. At 7 weeks, the median number of circulating CD20 positive cells was 0. Lymphocyte recovery began at approximately 12 weeks following treatment. Among patients who had CD20 positive cell counts recorded at baseline and at 6 months, 14% chemotherapy naïve patients had CD20 positive cell counts below normal limits at 6 months, and 32% of heavily pretreated patients had CD20 positive cell counts below normal limits at 6 months. There was no consistent effect of the therapeutic regimen on posttreatment serum IgG, IgA, or IgM levels.

## III. DOSAGE AND ADMINISTRATION

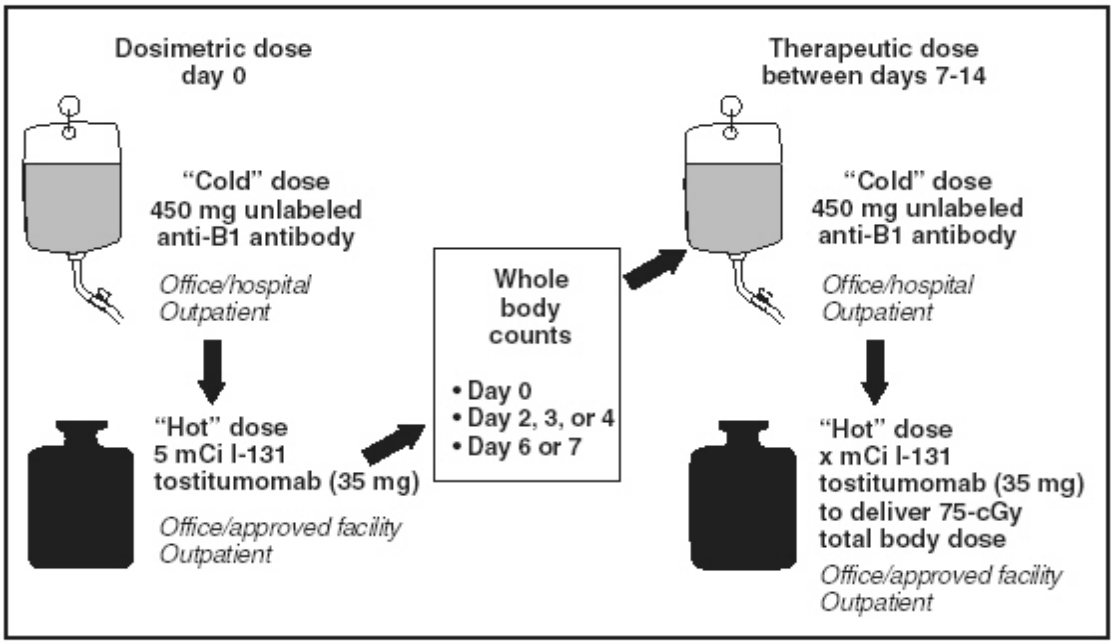


***Figure 4. Treatment regimen for therapy with Bexxar.*** *X = patient-specific dose. Reprinted with permission from* Hohenstein et al. *[50].*

The complete course of Bexxar® is carried out in 2 phases and is performed by nuclear medicine:

First, patients received a trace-labeled dosimetric dose, and dosimetry studies are conducted to establish the patient specific dose. Patients first receive infusion of an unlabeled antibody followed by a trace-labeled dosimetric dose of antibody, and total-body camera gamma camera counts are then obtained 3 times over the next 6 – 7 days (day 0; on day 2, 3, or 4; and on day 6 or 7). The therapeutic dose is calculated on the effective half-life of the antibody to ensure that they patient receive a dose calculated to deliver a 75 cGy TBD (for patients with platelet counts ≥ 150 x $10^9$/L). Patients who have platelet counts of 100 – 149 x $10^9$/L receive a TBD of 65 cGy. The actual amount of radioactivity administered to each patient varies from 45 – 239 mCi. A 60-minute infusion of 450 mg (in 50 mL NS) unlabeled (i.e. cold) tositumomab is administered before administering the dosimetric dose on day 0 to improve biodistribution of the radiolabeled antibody. The dosimetric dose of iodine I $^{131}$ labeled tositumomab (5 mCi) is then administered as a 20-minute infusion (in 30 mL NS) followed by a 10-minute flush. Based on the calculated residence time of the antibody, a patient-specific dose is calculated.

Second, a single therapeutic dose is administered. From days 7 – 14, the patient receives a 60-minute infusion of 450mg cold tositumomab followed by the therapeutic dose of iodine I $^{131}$ tositumomab via a 20-minute infusion plus a 10-minute flush. The administered dose of Bexxar® is calculated based on patient specific variables. Dosimetry ensures that each patient receives the maximum tolerated TBD, which will maximize therapeutic benefit and ensure that organ toxicity is minimal. The "therapeutic" dose that is administered is based on total body clearance of the radiolabeled antibody from each patient, which is affected by lean body mass and tumor burden.

Oral iodine supplements to block I $^{131}$ uptake by the thyroid gland are administered 1 day prior to administration of the dosimetric infusion and continuing for 2 weeks following the therapeutic dose. Patients should also be premedicated with APAP 650 mg PO, and either diphenhydramine 50 mg or chlorpheniramine 4 mg 1 hour prior to each infusion of tositumomab

NOTE: Iodine I $^{131}$ tositumomab and iodine$^{131}$are excreted primarily by the kidneys. Impaired renal function may decrease the rate of excretion of the radiolabeled iodine and increase patient exposure to the radioactive component of the Bexxar® regimen. There are no data in patients with impaired renal function.

## IV. TOXICITY

A) Hematological toxicity: Grade III/IV thrombocytopenia in 53% patients; Grade III/IV neutropenia in 63% patients. The time to nadir is 3 – 7 weeks, and the duration of cytopenias is approximately 30 days.
B) Hypersensitivity: including anaphylaxis reported. Emergency medications used in anaphylaxis should be readily available during administration. Patients who have received murine proteins should be screened for HAMA. Patients who are positive for HAMA are at increased risk of anaphylaxis and severe hypersensitivity reactions. The rate of infusion of the tositumomab may be reduced by 50% for mild to moderate infusional toxicity. Interrupt the infusion for severe infusional toxicity.
C) Secondary malignancies: MDS and/or AML reported in 8% of patients enrolled in the clinical studies. The median time to development of MDS/AML is 27 months.
D) Hypothyroidism: administer thyroid-blocking medications as listed above.

## V. CLINICAL MONITORING

Due to the variable nature of in the onset of cytopenias, complete blood counts should be obtained weekly for 10 – 12 weeks.

Patients should be given a list of instructions once released from hospital advising patients how close they can come to others and how they should conduct themselves and dispose of bodily wastes to minimize radiation exposure to others. For example patients are to sleep in a separate bed (≥ 6 feet from others), not take a long trip (≥ 4 hours) during which they will be sitting near to others, to maintain a safe distance (≥ 6 feet) from others, and to avoid contact with children and pregnant women. The duration of these restrictions is dependent upon a patient's residence time and dose rate at 1m.

TSH should be monitored before treatment and annually thereafter.

## VI. DRUG INTERACTIONS:

No formal studies have been performed.

# IBRITUMOMAB TIUEXETAN
## (ZEVALIN®)

## I. MECHANISM OF ACTION

Ibritumomab tiuxetan is the immunoconjugate resulting from a stable thiourea covalent bond between the monoclonal antibody ibritumomab and the linker-chelator tiuxetan. This linker-chelator provides a high affinity, conformationally restricted chelation site for Indium-111 or Yttrium-90. The approximate molecular weight of ibritumomab tiuxetan is 148 kD. The antibody moiety of ibritumomab tiuxetan is ibritumomab, a murine IgG1 kappa monoclonal antibody directed against the CD20 antigen, which is found on the surface of normal and malignant B lymphocytes. Ibritumomab is produced in Chinese hamster ovary cells and is composed of 2 murine gamma 1 heavy chains of 445 amino acids each and 2 kappa light chains of 213 amino acids each.

Ibritumomab, like rituximab, induces apoptosis in CD20+ B-cell lines in vitro. The chelate tiuxetan, which tightly binds In-111 or Y-90, is covalently linked to the amino groups of exposed lysines and arginines contained within the antibody. The beta emission from Y-90 induces cellular damage by the formation of free radicals in the target and neighboring cells. Ibritumomab tiuxetan binding was observed in vitro on lymphoid cells of the bone marrow, lymph node, thymus, red and white pulp of the spleen, and lymphoid follicles of the tonsil, as well as lymphoid nodules of other organs such as the large and small intestines. Binding was not observed on the nonlymphoid tissues or gonadal tissues.

## II. PHARMACOKINETICS

In pharmacokinetic studies of patients receiving the ibritumomab tiuxetan therapeutic regimen, the mean effective half-life of Y-90 activity in blood was 30 hours, and the mean area under the fraction of injected activity (FIA) vs. time curve in blood was 39 hours. Over 7 days, a median of 7.2% of the injected activity was excreted in urine.

In clinical studies, administration of the ibritumomab tiuxetan therapeutic regimen resulted in sustained depletion of circulating B cells. At 4 weeks, the median number of circulating B cells was 0 (range, 0 to 1084 cells/$mm^3$). B-cell recovery began at 12 weeks following treatment, and the median level of B cells was within the normal range (32 to 341 cells/$mm^3$) by 9 months after treatment. Median serum levels of IgG and IgA remained within the normal range throughout the period of B-cell depletion. Median IgM serum levels dropped below normal (median, 49 mg/dL; range, 13 to 3990 mg/dL) after treatment and recovered to normal values by 6 month post-therapy.

## III. DOSAGE AND ADMINISTRATION

Radionuclides:

Two separate and distinctly labeled kits are ordered for the preparation of a single dose each of In-111 ibritumomab tiuxetan and Y-90 ibritumomab tiuxetan.

In-111 ibritumomab tiuxetan and Y-90 ibritumomab tiuxetan are radiopharmaceuticals and should be used only by physicians and other professionals qualified by training and experienced in the safe use and handling of radionuclides. Changing the ratio of any of the reactants in the radiolabeling process may adversely impact therapeutic results. In-111 ibritumomab tiuxetan and Y-90 ibritumomab tiuxetan should not be used in the absence of the rituximab predose.

Ibritumomab tiuxetan therapeutic regimen administration:

Step 1:
First rituximab infusion:
Administer rituximab at a dose of 250 mg/$m^2$ IV at an initial rate of 50 mg/hr. Do not mix or dilute rituximab with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If hypersensitivity or an infusion-related event develops, temporarily slow or interrupt the infusion (see Warnings). The infusion can continue at 50% the previous rate upon improvement of patient symptoms.

In-111 ibritumomab tiuxetan injection:
Within 4 hours following completion of the rituximab dose, 5 mCi (1.6 mg total antibody dose) of In-111 ibritumomab tiuxetan is injected IV over a period of 10 minutes.

Assess biodistribution:
First image 2 to 24 hours after In-111 ibritumomab tiuxetan;
Second image 48 to 72 hours after In-111 ibritumomab tiuxetan.
Optional: Third image 90 to 120 hours after In-111 ibritumomab tiuxetan.
If biodistribution is not acceptable, do not proceed.

Step 2:
Step 2 of the ibritumomab tiuxetan therapeutic regimen is initiated 7 to 9 days following Step 1 instructions.
Second rituximab infusion:
Rituximab at a dose of 250 mg/$m^2$ is administered IV at an initial rate of 100 mg/hr (50 mg/hr if infusion-related events were documented during the first rituximab administration) and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr, as tolerated.
Y-90 ibritumomab tiuxetan injection:
Within 4 hours following completion of the rituximab dose, Y-90 ibritumomab tiuxetan at a dose of 0.4 mCi/kg (14.8 MBq/kg) actual body weight for patients with a platelet count greater than 150 x $10^9$/L, and 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with a platelet count of 100 - 149 x $10^9$/L is injected IV over a period of 10 minutes. Take precautions to avoid extravasation. Establish a free-flowing IV line prior to Y-90 ibritumomab tiuxetan injection. Close monitoring for evidence of extravasation during the injection of Y-90 ibritumomab tiuxetan is required. If any signs or symptoms of extravasation have occurred, immediately terminate the infusion and restart in another vein. The prescribed, measured, and administered dose of Y-90 ibritumomab tiuxetan must not exceed the absolute maximum allowable dose of 32 mCi (1184 MBq), regardless of the patient's body weight. Do not give Y-90 ibritumomab tiuxetan to patients with a platelet count < 100 x $10^9$/L (see Warnings).
See manufacturer's product labeling for product preparation instructions.

## IV. TOXICITY

A) Fatal infusion reactions: Deaths have occurred within 24 hours of rituximab infusion, an essential component of the ibritumomab tiuxetan therapeutic regimen. These fatalities were associated with an infusion reaction symptom complex that included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, MI, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first rituximab infusion (see Warnings and Adverse Reactions). Discontinue rituximab, In-111 ibritumomab tiuxetan, and Y-90 ibritumomab tiuxetan infusions in patients who develop severe infusion reactions and give medical treatment.

B) Prolonged and severe cytopenia: Y-90 ibritumomab tiuxetan administration results in severe and prolonged cytopenias in most patients. Do not administer the ibritumomab tiuxetan therapeutic regimen to patients with 25% lymphoma marrow involvement or impaired bone marrow reserve.

C) Hematologic toxicity: The most common severe adverse reactions reported with the ibritumomab tiuxetan therapeutic regimen were thrombocytopenia (61% of patients with platelet counts $< 50 \times 10^9$/L) and neutropenia (57% of patients with absolute neutrophil count [ANC] $< 1 \times 10^9$/L) in patients with $150 \times 10^9$/L platelets prior to treatment. Both incidences of severe thrombocytopenia and neutropenia increased to 78% and 74% for patients with mild thrombocytopenia at baseline (platelet count of 100 – 149 $\times 10^9$/L). For all patients, the median time to nadir was 7 to 9 weeks and the median duration of cytopenias was 22 to 35 days. In < 5% of cases, patients experienced severe cytopenia that extended beyond the prospectively defined protocol treatment period of 12 weeks following administration of the ibritumomab tiuxetan therapeutic regimen. Some of these patients eventually recovered from cytopenia, while others experienced progressive disease, received further anticancer therapy, or died of their lymphoma without having recovered from cytopenia. The cytopenias may have influenced subsequent treatment decisions.

D) Hemorrhage, including fatal cerebral hemorrhage, and severe infections have occurred in a minority of patients in clinical studies. Careful monitoring for and management of cytopenias and their complications (eg, febrile neutropenia, hemorrhage) for up to 3 months after use of the ibritumomab tiuxetan therapeutic regimen are necessary. Exercise caution in treating patients with drugs that interfere with platelet function or coagulation following the ibritumomab tiuxetan therapeutic regimen and closely monitor patients receiving such agents.
Do not administer the ibritumomab tiuxetan therapeutic regimen to patients with 25% lymphoma marrow involvement or impaired bone marrow reserve (e.g., prior myeloablative therapies; platelet count $< 100 \times 10^9$/L; neutrophil count $< 1.5 \times 10^9$/L; hypocellular bone marrow [15% cellularity or marked reduction in bone marrow precursors])or to patients with a history of failed stem cell collection.

E) Secondary malignancies: a total of 2% of patients developed secondary malignancies following the ibritumomab tiuxetan therapeutic regimen. One patient developed a Grade 1 meningioma, 3 developed acute myelogenous leukemia, and 2 developed a myelodysplastic syndrome. The onset of a second cancer was 8 to 34 months following the ibritumomab tiuxetan therapeutic regimen and 4 to 14 years following the patients' diagnosis of NHL.

F) Mucocutaneous reactions – some reports of severe and fatal reactions. See FDA Safety Warnings.

## V. CLINICAL MONITORING

Obtain CBC and platelet counts weekly following the ibritumomab tiuxetan therapeutic regimen and until levels recover. Monitor CBC and platelet counts more frequently in patients who develop severe cytopenia, or as clinically indicated.

Patients with known Type I hypersensitivity or anaphylactic reactions to murine proteins or to any component of this product, including rituximab, yttrium chloride, and indium chloride.

## VI. DRUG INTERACTIONS

No formal drug interaction studies have been performed with ibritumomab tiuxetan. Patients receiving medications that interfere with platelet function or coagulation should have more frequent laboratory monitoring for thrombocytopenia. In addition, the transfusion practices for such patients may need to be modified given the increased risk of bleeding.