Zevalin®
(Y-90 ibritumomab tiuxetan)

Overview

Zevalin (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 Yttrium-90. The approximate molecular weight of ibritumomab tiuxetan is 148 kD. The antibody moiety of Zevalin is ibritumomab, a murine IgG1 kappa monoclonal antibody directed against the CD20 antigen. The CD20 antigen is expressed on pre-B and mature B lymphocytes and on > 90% of B-cell non-Hodgkin’s lymphomas (NHL).

Ibritumomab tiuxetan is a clear, colorless, sterile, pyrogen-free, preservative-free solution that may contain translucent particles. Each single-use vial includes 3.2 mg of ibritumomab tiuxetan in 2 mL of 0.9% Sodium Chloride.

Yttrium-90 decays by emission of beta particles, with a physical half-life of 64.1 hours (2.67 days). The exposure rate for 1 mCi (37 MBq) of Y-90 is \(8.3 \times 10^3\) C/kg/hr (32 R/hr) at the mouth of an open Y-90 vial.

INDICATIONS AND USAGE

Zevalin is a CD20-directed radiotherapeutic antibody administered as part of the Zevalin therapeutic regimen indicated for the treatment of patients with:

- relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL)
- previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy.

WARNING: SERIOUS INFUSION REACTIONS, PROLONGED AND SEVERE CYTOPENIAS, and SEVERE CUTANEOUS AND MUCOCUTANEOUS REACTIONS

See full prescribing information for complete boxed warning.

- Serious Infusion Reactions, some fatal, may occur within 24 hours of rituximab infusion.
- Prolonged and Severe Cytopenias occur in most patients.
- Severe Cutaneous and Mucocutaneous Reactions, some fatal, reported with Zevalin therapeutic regimen.
- Do not exceed 32 mCi (1184 MBq) of Y-90 Zevalin.

Please see full prescribing information, including Boxed WARNINGS, for ZEVALIN. Because the ZEVALIN therapeutic regimen includes the use of rituximab, please consult prescribing information for rituximab.
CONTRAINDICATIONS

None.

EQUIPMENT AND SUPPLIES NEEDED FOR ADMINISTRATION

Required Equipment:
- Syringe Shield (acrylic/plastic for Y-90)
- 0.22 micron low protein binding filter (supplied by nuclear pharmacy)
- Absorbent paper
- 10 ml syringes
- IV tubing with injection port
- 0.9% normal saline
- Butterfly needle or angiocath
- Waterproof gloves
- Alcohol prep pads
- 2 x 2 gauze pads
- 3 way stopcock
- Infusion pump (optional)

DOSAGE AND ADMINISTRATION

Administer the Zevalin therapeutic regimen as outlined below.

Initiate the Zevalin therapeutic regimen following recovery of platelet counts to ≥150,000/mm$^3$ at least 6 weeks, but no more than 12 weeks, following the last dose of first-line chemotherapy.

For patients with relapsed or refractory, Low-grade of Follicular NHL, Zevalin may be used - Platelet count ≥ 100,000/mm$^3$ (see section on platelet counts below to appropriately adjust dose).

All patients treated with Zevalin must have < 25% lymphoma marrow involvement and appropriate bone marrow reserves.

2.1 Overview of Dosing Schedule

IV Infusion of 250 mg/m$^2$ of rituximab

Day 7, 8 or 9
IV Infusion of 250 mg/m$^2$ of rituximab

Within 4 hours

IV injection of Y-90 ZEVALIN over 10 minutes as follows:
- 0.4 mCi/kg (14.8 MBq/kg) for patients with normal platelet count
- 0.3 mCi/kg (11.1 MBq/kg) in relapsed or refractory patients with platelet count of 100,000 - 149,000 cells/mm$^3$

DO NOT TREAT PATIENTS WITH <100,000 PLATELETS/mm$^3$

THE MAXIMUM ALLOWABLE DOSE OF Y-90 ZEVALIN IS 32.0 mCi (1184) MBq
Zevalin Therapeutic Regimen Dosage and Administration

Day 1:
- Premedicate with acetaminophen 650 mg orally and diphenhydramine 50 mg orally prior to rituximab infusion.
- Administer rituximab 250 mg/m² intravenously at an initial rate of 50 mg/hr. In the absence of infusion reactions, escalate the infusion rate in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. Do not mix or dilute rituximab with other drugs.
- Immediately stop the rituximab infusion for serious infusion reactions and discontinue the Zevalin therapeutic regimen.
- Temporarily slow or interrupt the rituximab infusion for less severe infusion reactions. If symptoms improve, continue the infusion at one-half the previous rate.

Day 7, 8 or 9:
- Premedicate with acetaminophen 650 mg orally and diphenhydramine 50 mg orally prior to rituximab infusion.
- Administer rituximab 250 mg/m² intravenously at an initial rate of 100 mg/hr. Increase rate by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr, as tolerated. If infusion reactions occurred during rituximab infusion on Day 1 of treatment, administer rituximab at an initial rate of 50 mg/hr and escalate the infusion rate in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
- Administer Y-90 Zevalin injection through a free flowing intravenous line within 4 hours following completion of rituximab infusion. Use a 0.22 micron low-protein-binding in-line filter between the syringe and the infusion port. After injection, flush the line with at least 10 mL of normal saline.
  - **If platelet count ≥150,000/mm³**, administer Y-90 Zevalin over 10 minutes as an intravenous injection at a dose of Y-90 0.4 mCi per kg (14.8 MBq per kg) actual body weight.
  - **If platelet count 100,000-149,000/mm³**, in relapsed or refractory patients, administer Y-90 Zevalin over 10 minutes as an intravenous injection at a dose of Y-90 0.3 mCi per kg (11.1 MBq per kg) actual body weight.
  - **Do not administer more than 32 mCi (1184 MBq) Y-90 Zevalin dose regardless of the patient’s body weight.**
- Monitor patients closely for evidence of extravasation during the injection of Y-90 Zevalin. Immediately stop infusion and restart in another limb if any signs or symptoms of extravasation occur.

Y-90 Zevalin Administration:

Syringe shields and other materials used in the preparation and administration of the Y-90 Zevalin should be made of materials with low atomic numbers such as Lucite, plastic or acrylic. Lead or leaded glass should not be utilized in order to minimize the higher energy bremsstrahlung thicker shielding requirements with lead.
HAMA/HACA

Incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparisons of the incidence of HAMA/HACA to the Zevalin therapeutic regimen with the incidence of antibodies to other products may be misleading.

HAMA and HACA response data on 446 patients from 8 clinical studies conducted over a 10-year time period are available. Overall, 11/446 (2.5%) had evidence of either HAMA formation (N=8) or HACA formation (N=4). Six of these patients developed HAMA/HACA after treatment with Zevalin and 5 were HAMA/HACA positive at baseline. Of the 6 who were HAMA/HACA positive, only one was positive for both. Furthermore, in 6 of the 11 patients, the HAMA/HACA reverted to negative within 2 weeks to 3 months. No patients had increasing levels of HAMA/HACA at the end of the studies.

WARNINGS AND PRECAUTIONS

Serious Infusion Reactions

See also prescribing information for rituximab.

Rituximab, alone or as a component of the Zevalin therapeutic regimen, can cause severe, including fatal, infusion reactions. These reactions typically occur during the first rituximab infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reactions may include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Temporarily slow or interrupt the rituximab infusion for less severe infusion reactions. Immediately stop rituximab, In-111 Zevalin, or Y-90 Zevalin administration for severe infusion reactions.

Prolonged and Severe Cytopenias

Cytopenias with delayed onset and prolonged duration, some complicated by hemorrhage and severe infection, are the most common severe adverse reactions of the Zevalin therapeutic regimen. When used according to recommended doses, the incidences of severe thrombocytopenia and neutropenia are greater in patients with mild baseline thrombocytopenia (100,000 to 149,000 /mm³) compared to those with normal retreatment platelet counts. Severe cytopenias persisting more than 12 weeks following administration can occur [see Boxed Warning and Adverse Reactions (6.1)].

Embryo-Fetal Toxicity

Based on its radioactivity, Y-90 Zevalin may cause fetal harm when administered to a pregnant woman. If the Zevalin therapeutic regimen is administered during pregnancy, the patient should be apprised of the potential hazard to a fetus [see Use in Specific Populations (8.1)].

Extravasation

Monitor patients closely for evidence of extravasation during Zevalin infusion. Immediately terminate the infusion if signs or symptoms of extravasation occur and restart in another limb.

Immunization

The safety of immunization with live viral vaccines following the Zevalin therapeutic regimen has not been studied. Do not administer live viral vaccines to patients who have recently received Zevalin. The ability to generate an immune response to any vaccine following the Zevalin therapeutic regimen has not been studied.
Laboratory Monitoring
Monitor complete blood counts (CBC) and platelet counts following the Zevalin therapeutic regimen weekly until levels recover or as clinically indicated.

Radionuclide Precautions
During and after radiolabeling Zevalin with In-111 or Y-90, minimize radiation exposure to patients and to medical personnel, consistent with institutional good radiation safety practices and patient management procedures.

POST-TREATMENT PRECAUTIONS

Advise patients:
• To contact a healthcare professional for severe signs and symptoms of infusion reactions.
• To take premedications as prescribed [see Dosage and Administration (2.2) and Warnings and Precautions (5.1)].
• To report any signs or symptoms of cytopenias (bleeding, easy bruising, petechiae or purpura, pallor, weakness or fatigue).
• To avoid medications that interfere with platelet function, except as directed by a healthcare professional [see Warnings and Precautions (5.2)].
• To seek prompt medical evaluation for diffuse rash, bullae, or desquamation of the skin or oral mucosa.
• To immediately report symptoms of infection (e.g. pyrexia) [see Adverse Reactions (6.3)].
• That immunization with live viral vaccines is not recommended for 12 months following the Zevalin therapeutic regimen [see Warnings and Precautions (5.8)].
• To use effective contraceptive methods during treatment and for a minimum of 12 months following Zevalin therapy.
• To discontinue nursing during and after Zevalin treatment [see Use In Special Populations (8.3)].

PATIENT FOLLOW-UP

The patient will be followed by Medical Oncology. In general, complete CBC and platelet count are obtained weekly until levels recover or as clinically indicated.

REFERENCES

Table 1. Estimated Radiation Absorbed Doses from Y-90 Zevalin

<table>
<thead>
<tr>
<th>Organ</th>
<th>Y-90 Zevalin cGy/mCi (mGy/MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Spleen&lt;sup&gt;a&lt;/sup&gt;</td>
<td>34.78 (9.4)</td>
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<tr>
<td>Liver&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17.76 (4.8)</td>
</tr>
<tr>
<td>Lower Large Intestinal Wall&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17.39 (4.7)</td>
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<tr>
<td>Upper Large Intestinal Wall&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.32 (3.6)</td>
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<tr>
<td>Heart Wall&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.73 (2.9)</td>
</tr>
<tr>
<td>Lungs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.4 (2)</td>
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<tr>
<td>Testes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.55 (1.5)</td>
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<tr>
<td>Small Intestine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.18 (1.4)</td>
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<tr>
<td>Red Marrow&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.81 (1.3)</td>
</tr>
<tr>
<td>Urinary Bladder Wall&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Bone Surfaces&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.33 (0.9)</td>
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<tr>
<td>Total Body&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.85 (0.5)</td>
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<tr>
<td>Ovaries&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.48 (0.4)</td>
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<tr>
<td>Uterus&lt;sup&gt;e&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Organ</td>
<td>Dose (cGy)</td>
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<tr>
<td>------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Adrenals&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Kidneys&lt;sup&gt;a&lt;/sup&gt;</td>
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a) Organ region of interest  
b) Sacrum region of interest  
c) Whole body region of interest