Indium-111 Zevalin Imaging

Background:

Most B lymphocytes (beyond the stem cell stage) contain a surface antigen called CD20. It is possible to kill these lymphocytes by injecting an antibody to CD20. Rituxan (rituximab) is such a monoclonal antibody, derived from mice. It turns out that many non-Hodgkin's lymphoma cells are B lymphocytes that contain CD20. These lymphomas can therefore be treated with Rituxan. The problem is that the antibody by itself leaves too many of the B lymphocytes alive. To help kill all these cancer cells, it is possible to tag the antibody with a radioactive isotope. Zevalin (Ibritumomab tiuxetan) is such a monoclonal mouse antibody against CD20 that can carry a radioactive isotope. For therapies, the Zevalin is tagged with Yttrium-90 (Y-90 Zevalin). Yttrium is a pure beta emitter with a half-life of 64 hours.

For most patients, the normal biodistribution of Zevalin in the body allows for the administration of a sufficient dose of Y-90 Zevalin to kill the cancer cells without causing significant toxicity in the patient. However, a small subset of patients exhibit an altered biodistribution of the Zevalin. These people have increased lung, kidney, or bowel uptake that makes the Zevalin therapy quite toxic. The problem is, how do we recognize which patients will get into trouble with Zevalin therapy? The answer is to image the biodistribution of the Zevalin prior to therapy using a safer isotope. For this pre-treatment imaging study, Indium-111 is tagged to Zevalin instead of Yttrium. This allows us to safely evaluate its biodistribution.

When interpreting In-111 Zevalin studies, we are NOT concerned about locating tumor. Although lymphoma masses may be seen on the scan, they are not always visible and for therapy purposed it is not significant whether we see them or not. The reason we are performing the In-111 Zevalin study is to DETERMINE WHETHER THE PATIENT HAS A NORMAL OR ALTERED BIODISTRIBUTION OF ZEVALIN. If the patient shows an altered biodistribution of Zevalin, they are not a candidate for Zevalin therapy.

Zevalin therapy is indicated for the treatment of relapsed or refractory low grade, follicular, or transformed B-cell non-Hodgkin's lymphoma (NHL), including patients with or without rituximab-refractory follicular NHL.

Protocol:

Immediately prior to the In-111 Zevalin imaging study (within 4 hrs), the patient is treated with Rituxan. This decreases the number of B lymphocytes in the patient and allows for a lower patient dose when treated with Zevalin. The patient is then administered 5 mCi of Indium-111 Zevalin. Anterior and posterior whole body
imaging is performed within 24 hours (Scan 1) and again between 48-72 hours (Scan 2). If imaging is not conclusive for normal vs. altered biodistribution at this time, an additional scan may optionally be performed between 90-120 hours (Scan 3).

**Interpretation:**

**Normal Expected Biodistribution - OK to Treat**

- On Scan 1 (2 to 24 hours), activity in the blood pool areas (heart, abdomen, neck, and extremities) is detectable and decreases on Scan 2 (48 to 72 hours). There is variability within patients in the visualization of the blood pool especially when images are performed late in the time window of Scan 1 and in an occasional patient, blood pool may not be visible late in the time window of Scan 1.
- Moderately high to high uptake in normal liver and spleen on Scans 1 and 2.
- Moderately low or very low uptake in normal kidneys, urinary bladder, and normal (uninvolved) bowel on Scans 1 and 2.
- Localization to lymphoid aggregates in the bowel wall has been reported.

Tumor uptake may be visualized in soft tissue as areas of increased intensity, and tumor-bearing areas in normal organs may be seen as areas of increased or decreased intensity. Tumor visualization on the In-111 ZEVALIN scan is not required for Y-90 ZEVALIN therapy.

**Expected (Normal) Biodistribution of In-111 Zevalin**

<table>
<thead>
<tr>
<th></th>
<th>Scan 1</th>
<th>Scan 2</th>
<th>Scan 3 - Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Blood Pool¹</strong></td>
<td>Present</td>
<td>Decreases</td>
<td>Decreases</td>
</tr>
<tr>
<td><strong>Normal Liver &amp; Spleen²</strong></td>
<td>Moderate to High</td>
<td>Moderate to High</td>
<td>Moderate to High</td>
</tr>
<tr>
<td><strong>Normal Kidneys, Bladder, and Bowel²</strong></td>
<td>Moderately Low to Very Low</td>
<td>Moderately Low to Very Low</td>
<td>Moderately Low to Very Low</td>
</tr>
<tr>
<td><strong>Tumor³</strong></td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
</tr>
</tbody>
</table>

1 activity should decrease with time
2 areas not involved by tumor
3 Diagnosis of tumor is NOT the purpose

**Altered Biodistribution – Do Not Treat**

The criteria for altered biodistribution is met if any one of the following is detected on visual inspection of gamma images:

- Rapid clearance of the radioimmunoconjugate from the blood pool with liver, spleen, and/or bone marrow uptake in Scan 1.
- Increased uptake in normal organs (not involved by tumor) such as:
  + Diffuse uptake in normal lung more intense than the cardiac blood pool on Scan 1, or more intense than the liver Scan 2.
  + Kidneys with greater intensity than the liver on the posterior view on Scan 2. Fixed areas (unchanged with time) of uptake in the normal bowel greater than uptake in the liver on Scan 2.
  + In <0.5% of patients receiving In-111 ZEVALIN, prominent bone marrow uptake was observed, characterized by clear visualization of the long bones and ribs on Scan 1.
**Altered Biodistribution of In-111 Zevalin**

<table>
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<th>Scan 2</th>
<th>Scan 3 - Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(2-24 hrs)</td>
<td>(48-72 hrs)</td>
<td>(90-120 hrs)</td>
</tr>
<tr>
<td><strong>Cardiac Blood Pool</strong></td>
<td>Not Visualized</td>
<td>Not Visualized</td>
<td>Not Visualized</td>
</tr>
<tr>
<td><strong>Diffuse Uptake in</strong></td>
<td>&gt; cardiac blood pool</td>
<td>&gt; liver</td>
<td>&gt; liver</td>
</tr>
<tr>
<td><strong>Normal Lungs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Normal Kidneys</strong></td>
<td>-</td>
<td>&gt; liver in posterior view</td>
<td>&gt; liver in posterior view</td>
</tr>
<tr>
<td><strong>Normal Bowel</strong></td>
<td>-</td>
<td>&gt; liver</td>
<td>&gt; liver</td>
</tr>
</tbody>
</table>

4 Rapid clearance by the liver, spleen, and/or marrow  
5 Predicts possible excessive radiation to nontarget organ  
Normal = uninvolved by tumor

Prepared on 2/12/05 by D. Parker

References:
Case Study 1

Patient History
51-year-old man with follicular lymphoma of predominantly small cleaved-cell histology. The ZEVALIN therapeutic regimen was initiated approximately 18 years after diagnosis, following a course of cyclophosphamide, vincristine, and prednisone (CVP) (complete response, 14-year duration), another course of CVP (no response), and then Rituxan (stable disease, 2-month duration). Pretreatment disease status was stage III/IV and lesions 7-10 cm.

Imaging Findings
The expected biodistribution is observed, with the radiopharmaceutical easily detectable in the blood pool areas on the later images. Moderately high to high uptake in normal liver and spleen is seen on the first day and later images, while moderately low or very low uptake is seen in normal kidneys, urinary bladder, and normal bowel on the first-day and later images. Tumor uptake is seen in the mediastinal lymph nodes.
Case Study 2

Patient History

54-year-old man with follicular lymphoma of a predominantly small cleaved-cell histology. The ZEVALIN therapeutic regimen was initiated approximately 9 years after diagnosis, following a course of chlorambucil (stable disease, 4-year duration) and a course of Rituxan (stable disease for 99 days). Pretreatment disease status was stage III/IV and lesions 5-7 cm.

Imaging Findings

The expected biodistribution is observed, with the radiopharmaceutical easily detectable in the blood pool areas on the first-day images and less activity seen in the blood pool areas on the later images. Moderately high to high uptake in normal liver and spleen is seen on the first day and later images, while moderately low or very low uptake is seen in normal kidneys, urinary bladder, and normal bowel on the first-day and later images. Tumor uptake is seen in the bilateral pelvis, right axilla, and right inguinal nodes.
Case Study 3

Patient History

59-year-old woman with follicular lymphoma of predominantly large-cell histology. Patient was initially treated with single-agent Rituxan, with a complete response that lasted 5 months. The ZEVALIN therapeutic regimen was initiated approximately 4 years after diagnosis, following a course of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus Rituxan (no response) and then Rituxan (no response). Pretreatment disease status was stage III/IV and lesions ≥10 cm.

Imaging Findings

The expected biodistribution is observed, with the radiopharmaceutical easily detectable in the blood pool areas on the first day images and less activity seen in the blood pool areas on the later images. Moderately high to high uptake in normal liver and spleen is seen on the first-day and later images, while moderately low or very low uptake is seen in normal kidney, urinary bladder, and normal bowel on the first-day and later images. Tumor uptake is seen in the mediastinal lymph nodes, with bulky disease seen in the right pelvis.
Case Study 4

Patient History

38-year-old man with follicular lymphoma of a predominantly small cleaved-cell histology. The ZEVALIN therapeutic regimen was initiated approximately 3.5 years after diagnosis, following, most recently, a course of dexamethasone, cytarabine, and cisplatin (DHAP) (partial response, 8-month duration) and then Rituxan (partial response, 3-month duration). Pretreatment disease status was stage III/IV and lesions 5-7cm.

Imaging Findings

The expected biodistribution is observed, with the radiopharmaceutical easily detectable in the blood pool areas on the first day images and less activity seen in the blood pool areas on the later images. Moderately high to high uptake in normal liver and spleen is seen on the first-day and later images, while moderately low or very low uptake is seen in normal kidney, urinary bladder, and normal bowel on the first-day and later images. Tumor uptake is seen in disease in the left axilla, mesenteric lymph nodes, and bilateral pelvis. Uptake is also seen in the testicular region.
Case Study 5

Patient History

49-year-old man with follicular lymphoma of mixed small cleaved and large-cell histology. The ZEVALIN therapeutic regimen was initiated approximately 1 year after diagnosis, following a course of CHOP (partial response, 4-month duration) and then Rituxan (stable disease, 3-month duration). Pretreatment disease status was stage III/IV and lesions <5 cm.

Imaging Findings

The expected biodistribution is observed, with the radiopharmaceutical easily detectable in the blood pool areas on the first day images and less activity seen in the blood pool areas on the later images. Moderately high to high uptake in normal liver and spleen is seen on the first-day and later images, while moderately low or very low uptake is seen in normal kidney, urinary bladder, and normal bowel on the first-day and later images. Tumor uptake is seen in the mesenteric lymph nodes. Uptake is also seen in the testicular region.
Case Study 6

Patient History

54-year-old man with follicular lymphoma of a predominantly small cleaved-cell histology. The ZEVALIN therapeutic regimen was initiated approximately 9 years after diagnosis, following a course of chlorambucil (stable disease, 46 days) and a course of Rituxan (stable disease, 3 month-duration). Pretreatment disease status was stage III/IV and lesions 5–<7 cm.

Imaging Findings

The expected biodistribution is observed, with the radiopharmaceutical easily detectable in the blood pool areas on the first day images and less activity seen in the blood pool areas on the later images. Moderately high to high uptake in normal liver and spleen is seen on the first day and later images, while moderately low or very low uptake is seen in normal kidney, urinary bladder, and normal bowel on the first-day and later images. Subtle evidence of tumor uptake is seen in the pelvic lymph nodes.
Case Study 7

Patient History

56-year-old woman with diffuse lymphoma of mixed, small, and large cell histology. The ZEVALIN therapeutic regimen was initiated approximately 5 years after diagnosis, following 4 years of stable disease after a course of cyclophosphamide, mitoxantrone, vincristine, and prednisone (CNOP) and partial responses to many other myelosuppressive chemotherapeutics, including bleomycin, cyclophosphamide, and mitoxantrone, as well as a course of Rituxan. Pretreatment disease status was stage III/IV and lesions 5-7cm.

Imaging Findings

The expected biodistribution is observed, with the radiopharmaceutical easily detectable in the blood pool areas on the first day images and less activity seen in the blood pool areas on the later images. Moderately high to high uptake in normal liver and spleen is seen on the first day and later images, while moderately low or very low uptake is seen in normal kidney, urinary bladder, and normal bowel on the first day and later images. Tumor uptake is seen in the mesenteric lymph nodes.
Case Study 8

Patient History
54-year-old woman with follicular lymphoma of a predominantly small cleaved histology. The ZEVALIN therapeutic regimen was initiated approximately 7 years after diagnosis, following several cycles of chemotherapy. The patient had a complete response to her second regimen, which consisted of cyclophosphamide, dexamethasone, prednisone, and vinblastine for more than 4 years. She also had a partial response for 5 months after her third regimen, which consisted of cyclophosphamide, dexamethasone, and vinblastine. Pretreatment disease status was stage III/IV and lesions 5-<7 cm.

Imaging Findings
The expected biodistribution is observed, with the radiopharmaceutical easily detectable in the blood pool areas on the first day images and less activity seen in the blood pool areas on the later images. Moderately high to high uptake in normal liver and spleen is seen on the first-day and later images, while moderately low or very low uptake is seen in normal kidney, urinary bladder, and normal bowel on the first-day and later images. Tumor uptake is seen in the mediastinal lymph nodes, paraaortic lymph nodes, and left pelvic lymph nodes.