Radioimmunotherapy In Non Hodgkin's Lymphoma

This tutorial gives an overview of Radioimmunotherapy in Non-Hodgkin’s Lymphoma. After completing this tutorial, attendees will be able to:

- Name the radiopharmaceutical approved by the FDA for performance of RIT Procedures
- Describe how patient-specific doses are determined and identify the typical dose for Y-90 Zevalin
- List several eligibility criteria for undergoing the RIT procedure
- Describe the pretreatment designed specifically for Zevalin
- Describe the radiation safety considerations when administering Zevalin to patients
- Briefly describe the results of clinical trials in the US for the past 15 years
- List potential long-term effects that could result from this treatment

Topics to be covered for Y-90 ZEVALIN® (Spectrum Pharmaceuticals)

- Introduction to NHL & RIT of Non Hodgkin’s Lymphoma
- Patient Indications
- Timeline for the Zevalin Treatment
- Infusion Techniques for Zevalin
- Radiation Safety
- Patient Safety and Efficacy

Rationale for the Use of RIT in Follicular NHL

- High sensitivity of lymphomas to radiation
- Abundant and well-characterized surface antigens
- Multiple Monoclonal Antibodies (MAbs) available
- Promising clinical results with unconjugated antibodies (Rituximab)
Principles of Radioimmunotherapy

- Targeted delivery of radiation
- Greater exposure of tumors vs. surrounding organs by virtue of the selectivity of the carrier antibody
- Potential for continuous exposure of tumor cells
- Anti-tumor mechanisms of the antibody

### ZEVALIN: TIMELINE FOR THE ZEVALIN TREATMENT

#### Treatment Options For Indolent NHL

<table>
<thead>
<tr>
<th>EARLY STAGE</th>
<th>ADVANCED STAGE</th>
</tr>
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<tbody>
<tr>
<td>XRT</td>
<td>● Watchful Waiting</td>
</tr>
<tr>
<td>XRT+CHEMOTHERAPY</td>
<td>● External Beam Radiation</td>
</tr>
<tr>
<td></td>
<td>● Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>● Monoclonal Antibody Therapy-Rituximab</td>
</tr>
<tr>
<td></td>
<td>● Stem Cell Transplant</td>
</tr>
<tr>
<td></td>
<td>● Radioimmunotherapy</td>
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</table>

- **90Y Ibritumomab tiuxetan (ZEVALIN)**
- **131I Tositumomab (BEXXAR - No Longer Available)**
- ● Investigational

- **Key Point:** While external beam radiation may cure stage I or II disease, the majority of patients with indolent NHL are diagnosed with stage III or IV disease and may require alternative treatment options. The optimal management of patients with indolent lymphoma remains a challenge, and there are many treatment options to consider. Some patients with localized, indolent NHL (stage I or II) can be cured with external beam radiation. Unfortunately, only 10% to 20% of patients with indolent NHL are diagnosed with early-stage disease. (Ref 1)

- The remaining patients, with stage III or IV disease, may receive treatments that range from a conservative “watch and wait” approach to a more aggressive approach, such as dose-intensive chemotherapy with stem cell transplantation. (Ref 1,2)

- **Monoclonal antibodies, namely rituximab, can be used for the treatment of relapsed indolent lymphoma.** A new type of therapy is radioimmunotherapy (RIT), which combines the targeting ability of a monoclonal antibody with the strength of radiotherapy. The first drug of this class was approved by the FDA in February 2002, 90Y Ibritumomab tiuxetan (Zevalin®). Other types of RIT are currently being investigated for treating patients with NHL.


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**Monoclonal Antibodies/Clinical Requirements**
• Rituximab: First Monoclonal Antibody Approved for NHL Indication: Relapsed or refractory low-grade or follicular, CD20+, B-cell non-Hodgkin’s lymphoma

• Rituxan (rituximab) prescribing information. South San Francisco, California: Genentech Inc; 1997. Rituximab was the first monoclonal antibody approved for immunotherapy in NHL. Rituximab targets the CD20 antigen that is found on 90% of B-cell lymphomas. Specifically, rituximab is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20-positive, B-cell NHL.1

• Typically, rituximab is given at a dose of 375 mg/m2 every week for 4 weeks.1 In a pivotal trial in 166 patients, the overall response rate (ORR) with this regimen was 48%, with a 6% complete response rate.1

• Given the unique mechanism of action and manageable toxicity profile of rituximab, ongoing research includes its integration into standard chemotherapy regimens, use in high-grade lymphomas, and use in the front-line treatment of lymphoma.2-4


Radioimmunotherapy with Y-90 Zevalin

CD20: Normal B Cells and 90% of B cell NHL but NOT on Stem Cells or Plasma Cells

<table>
<thead>
<tr>
<th>Pluripotent Stem Cell</th>
<th>Lymphoid Stem Cell</th>
<th>Pre-B Cell</th>
<th>B Cell</th>
<th>Activated B Cell</th>
<th>Plasma Cell</th>
</tr>
</thead>
</table>

- Ibritumomab: Murine monoclonal antibody parent of Rituximab
- Tiuxetan

Conjugated to antibody, forming strong urea-type bond with stable retention of Y-90
\( ^{90} \text{Y Zevalin} \) Produces a Crossfire Effect

Zevalin® and Rituximab®

- The ORR based on the International Workshop NHL response criteria was 80% in the ibritumomab tiuxetan arm and 56% in the rituximab arm (\( P = .002 \)).\(^1 \) The complete response rate (including unconfirmed complete responders) was 34% in the ibritumomab tiuxetan arm and 20% in the rituximab arm (\( P = .04 \)).

<table>
<thead>
<tr>
<th>Study N</th>
<th>Overall Responders</th>
<th>CR/CRu</th>
<th>Ongoing CR/CRu Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Med %</td>
<td>Median DR (mo)</td>
</tr>
<tr>
<td>Phase 1/2 (51)</td>
<td>73</td>
<td>29</td>
<td>11.7</td>
</tr>
<tr>
<td>Phase 2 (30)</td>
<td>83</td>
<td>47</td>
<td>11.5</td>
</tr>
<tr>
<td>Phase 3 (73)</td>
<td>80</td>
<td>34</td>
<td>13.9</td>
</tr>
</tbody>
</table>

Zevalin: ORR and Durable Remissions

Zevalin: Treatment Schema

Zevalin: Single Point Distribution System
Scheduling/Availability Concerns

- Zevalin Dose Calibrator Calibration
- Zevalin PI states:
  - Unit dose(s) should be assayed immediately before use
  - Dose calibrator(s) should be operated via manufacturer’s specifications
  - Some method of verification or instrument calibration may be necessary
- Dose Calibrator Contacts: Manufacturers
  - Biodex 800-224-6339, Ext. 2143
  - Cardinal Health 888-466-8257
  - Capintec, Inc. 800-631-3826
- Use with standards or accuracy questions: NIST 301-975-5539
- Getting started
  - Y-90 Zevalin therapy dose is based on patient’s actual baseline weight and platelet levels
    - 0.3 mCi/kg Y-90 Zevalin if platelets 100,000 - 149,000
    - 0.4 mCi/kg Y-90 Zevalin if platelets > 150,000

NOTE: Y-90 Zevalin dose must not exceed 32 mCi

Radiopharmaceutical Characteristics

90Yttrium Chloride

- Y-90 is available for calibration / use any day of the week
- same day delivery
- half-life: 64.1 hours
- energy: 2.281 mev
- decay: Beta minus
Zevalin Administration Equipment

- 10 mL syringe for 0.9% NS
- Low protein binding 0.22 micron filter
- Syringe shield
- 0.9% Normal Saline
Zevalin Administration

- Patient preparation: In order to minimize the likelihood of an allergic reaction to a foreign protein, the patient receives 650 mg of Tylenol and 50 mg of Benadryl orally at least 30 min before administration of the cold non-radioactive antibody (Rituxan) used to block non-specific binding sites.

- Establish venous access with butterfly needle or angiocath attached to IV tubing and 250 mL of 0.9% normal saline bag
  - Flush venous line with 10 mL of 0.9% NaCl to reconfirm patency
  - Stop flow from IV bag
  - Pre wet 0.22 micron filter with NaCl 0.9%
  - Place a 0.22 micron (low protein binding) filter between the stopcock and injection port
  - Slowly inject Y-90 over ten minutes
  - Slowly flush line with at least 10 mL of 0.9% NaCl after injection is completed
  - DO NOT Bolus
Zevalin Radioimmunotherapy: Typical Schedule

<table>
<thead>
<tr>
<th>Day Minus 5</th>
<th>Thursday</th>
<th>Place Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Tuesday</td>
<td>Administer Rituxan 250 mg/m²</td>
</tr>
<tr>
<td>Day 8</td>
<td>Tuesday</td>
<td>Administer Rituxan 250 mg/m² followed by Y-90 Zevalin infusion of 0.4 mCi/kg or 0.3 mCi/kg based on platelet counts. Max dose = 32 mCi</td>
</tr>
</tbody>
</table>

Zevalin Unit-Dose Storage & Shelf-life

Refrigerate Zevalin unit-dose (2 - 8 °C) if not ready for immediate injection
• Shelf-life 8 hours for Y-90 Zevalin after preparation

ZEVALIN: SAFETY ISSUES

Radiation Safety

Zevalin®: Risk of Radiation Exposure to Others Is Negligible *

- Most activity is retained in the body; urinary excretion = 7.3% ± 3.2% over 7 days
  Assuming maximum 32-mCi dose and excretion of 7% over a week, total urinary excretion over a week = 2.3 mCi
- Activity per urination = microcuries
- Ordinary amounts of blood (e.g., menstruation, bad cuts, hemorrhoids) will not contain appreciable levels of radioactivity
Zevalin Precautions = Universal Precautions

- Isolation room not required
- Outpatient administration without restrictions
- No need to determine activity limits or dose rate limits prior to patient release
- Patients can be released immediately after treatment

Zevalin: Radiation Safety

- Zevalin should be administered by physicians and other professionals qualified by training and experienced in the safe use and handling of radiopharmaceuticals (e.g., nuclear medicine physicians or radiation oncologists)

Radiation Safety Issues Are Fewer With Pure Beta Decay (\(^{90}\text{Y}\)):

- \(^{90}\text{Y}\) is a pure beta emitter. Risk of exposure to personnel from treated patient is minimal
- The risks of radiation exposure can be minimized by limiting the duration of exposure, maximizing the distance from the radiation source, and using shielding.
- Doses, exposure, and the likelihood of being exposed should be kept as low as reasonably achievable (ALARA). In preparing and transporting a radioactive chemical, precautions must be taken to minimize exposure.
- With pure beta emitters like \(^{90}\text{Y}\), a plastic shield is sufficient to absorb the beta particles. With gamma emitters like \(^{131}\text{I}\), thick lead shielding is required to absorb the longer gamma rays.

Penetration of Particulate and Electromagnetic Radiation
Zevalin®: Risk of Radiation Exposure to Others Is Negligible*

• Prospective study in 13 family members of patients treated with Zevalin
  • Family members with closest contact wore DoseGUARD Plus personal dosimeter for 7 days
  • Family was instructed to avoid body wastes, but no other precautions were given
  • Median deep dose equivalent over 7 days = 3.5 mrem (range, 1.4–7.9 mrem)
  • Conclusion: Exposure to others is negligible, in the range of background radiation (300 mrem/year)
90Y Zevalin: Minimal Exposure: Mayo Clinic Experience

• Wiseman et al measured doses to personnel during preparation and infusion of 12 doses of
  90Y Zevalin
  • 90Y hand dose (plastic shields used)
  • Median 50 mrem
  • Range 30-80 mrem
  • Conclusion: Exposures to healthcare workers can be low even when giving multiple
    therapies each year

Zevalin® Patient Release Instructions*

• For 3 days after treatment
  • Clean up spilled urine and dispose of body-fluid- contaminated material so that others will
    not inadvertently handle it (ie, flush down toilet or place in plastic bag in household trash)
  • Wash hands thoroughly after using the toilet
  • For 1 week after treatment, use condoms for sexual relations
  • Use good contraceptive method for 1 year following Zevalin Therapy
**Patient Safety and Efficacy: Summary**

- High ORR and CR in relapsed or refractory LG,F, T NHL
- Efficacy in Rituxan® nonresponders
- Well tolerated; hematologic toxicity is dose limiting

Patient selection is important to ensure safety
Regimen completed in 7 to 9 days in an OP setting
Universal Precautions = Zevalin Precautions
- Team approach to therapy
Zevalin: Most Common Non-hematologic Adverse Events


CHOP: Most Common Non-hematologic Adverse Events

Zevalin Reimbursement
• Refer professionals to RESULTSTM hotline for questions on current billing or reimbursement and to pre-qualify patients

• RESULT (Reimbursement Support Line-Trained Specialists)
• 1-800-386-9997
• Mon - Fri, 0900 - 2000 ET
Zevalin Concierge Program

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