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>
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<tbody>
<tr>
<td>XRT</td>
<td>• Watchful Waiting</td>
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<tr>
<td>XRT+CHEMOTHERAPY</td>
<td>• External Beam Radiation</td>
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<tr>
<td></td>
<td>• Chemotherapy</td>
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<tr>
<td></td>
<td>• Monoclonal Antibody Therapy-Rituximab</td>
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<td></td>
<td>• Stem Cell Transplant</td>
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<td></td>
<td>• Radioimmunotherapy</td>
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<tr>
<td>90Y Ibritumomab tiuxetan</td>
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<td>131I Tositumomab</td>
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<td></td>
<td>• Investigational</td>
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- **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.


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/m\(^2\) 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

- Ibritumomab: Murine monoclonal antibody parent of Rituximab
- Tiuxetan

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

Naked Antibody $^{90}$Y Zevalin

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 ($P = .002$).
  The complete response rate (including unconfirmed complete responders) was 34% in the ibritumomab tiuxetan arm and 20% in the rituximab arm ($P = .04$).

### Zevalin: ORR and Durable Remissions

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

- **Cold Ab Dose Day 1:**
  - Rituxan 250 mg/m²
  - Imaging no longer required

- **Therapeutic Dose day 7, 8, or 9:**
  - Rituxan 250 mg/m²
  - Followed by Y-90 Zevalin (0.4 or 0.3 mCi/kg; max dose: 32 mCi)

### Zevalin: Single Point Distribution System

- Biogen Idec
- Yttrium-90 Isotope Supplier
- Local Nuclear Pharmacy
- Nuclear Medicine/Radiation Oncology makes one phone call
**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**

\(^{90}\)Yttrium 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 (⁹⁰Y):**

- \(^{90}\text{Y}\) 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)
\[90^Y\] Zevalin: Minimal Exposure: Mayo Clinic Experience

- Wiseman et al measured doses to personnel during preparation and infusion of 12 doses of \[90^Y\] Zevalin
  - \[90^Y\] 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

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**Zevalin Reimbursement**

- Refer professionals to RESULTS™ 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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