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:

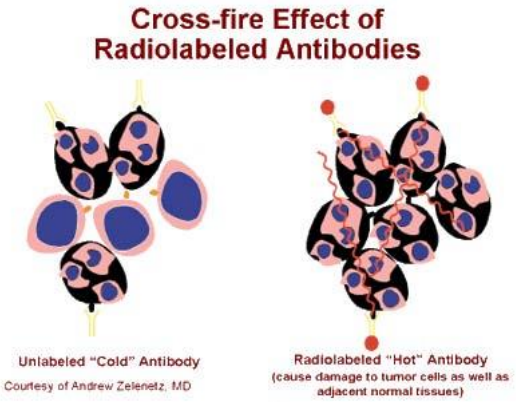
- Name the radiopharmaceutical approved by the FDA for performance of RIT Procedures
- Describe how patient- specific doses are determined and identify the typical dose for Y-90 Zevalin
- List several eligibility criteria for undergoing the RIT procedure
- Describe the pretreatment designed specifically 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

Juweid ME. J Nucl Med 2002;43:1507-1529. Kaminski MS et al. Blood 2000;96:1259-1266.

ZEVALIN: TIMELINE FOR THE ZEVALIN TREATMENT

● Treatment Options For Indolent NHL

EARLY STAGE	ADVANCED STAGE
XRT XRT+CHEMOTHERAPY	● Watchful Waiting ● External Beam Radiation ● Chemotherapy ● Monoclonal Antibody Therapy-Rituximab ● Stem Cell Transplant ● Radioimmunotherapy ^{90}Y Ibritumomab tiuxetan (ZEVALIN) ^{131}I Tositumomab (BEXXAR- No Longer Available) ● Investigational

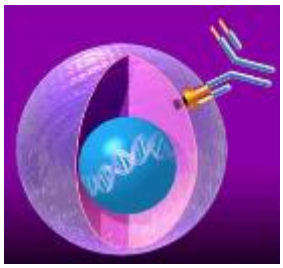
- Key Point: While external beam radiation may cure stage I or II disease, the majority of patients with indolent NHL are diagnosed with stage III or IV disease and may require alternative treatment options. The optimal management of patients with indolent lymphoma remains a challenge, and there are 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.

Ref 1. Vose JM. Classification and clinical course of low-grade non-Hodgkin's lymphomas with overview of therapy. Ann Oncol. 1996;7:S13–S19.

Ref 2. Horning SJ. Natural history of and therapy for the indolent non-Hodgkin's lymphomas. Semin Oncol. 1993; 20:75–88.

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 efractory 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]

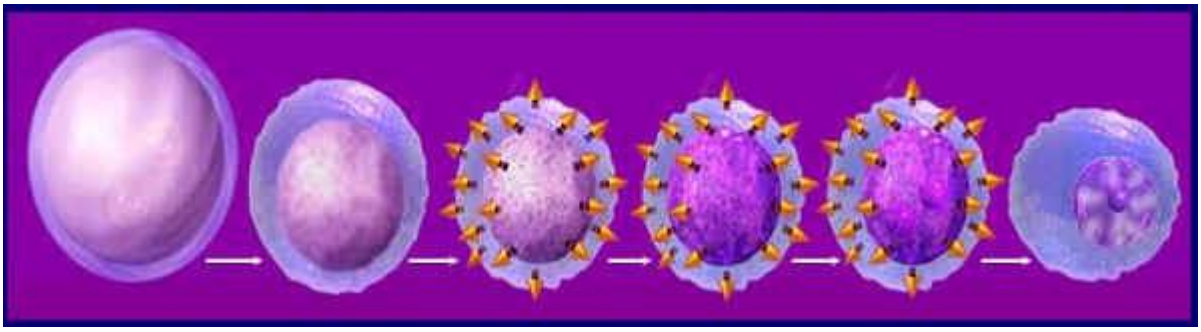


- Given the unique mechanism of action and manageable toxicity profile of rituximab, ongoing research includes its integration into standard chemotherapy regimens, use in high-grade lymphomas, and use in the front-line treatment of lymphoma.[2-4]
  McLaughlin P, Hagemeister FB, Grillo-Lopez J. Rituximab in indolent lymphoma: the single-agent pivotal trial. Semin Oncol. 1999;26(suppl 14):79–87.
- Coiffier B, Lepage E, Herbrecht R, et al. Mabthera (rituximab) plus CHOP is superior to CHOP alone in elderly patients with diffuse large B-cell lymphoma (DLCL): interim results of a randomized GELA trial. Blood. 2000;96:223a. Abstract 950.
- Czuczman MS, Fallon A, Scarpace A, et al. Phase II study of rituximab in combination with fludarabine in patients (pts) with low-grade or follicular B-cell lymphoma. Blood. 2000;96:729a. Abstract 3154.

Radioimmunotherapy with Y-90 Zevalin

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

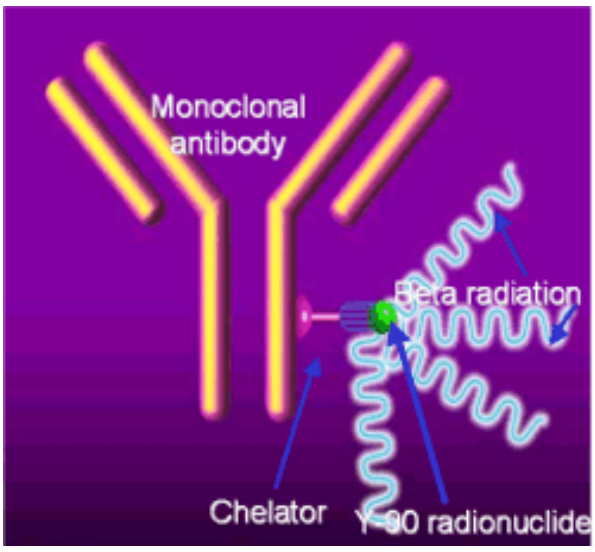
<----Bone Marrow----> <----Blood, Lymph---->



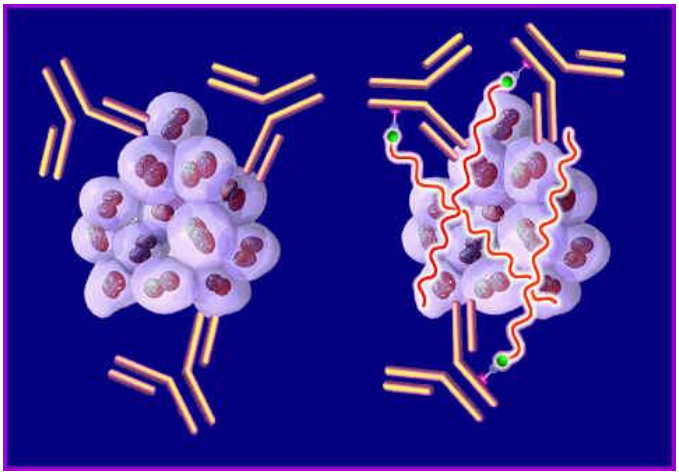
Pluripotent Stem Cell | Lymphoid Stem Cell | Pre-B Cell | B Cell | Activated B Cell | Plasma Cell

- Ibritumomab: Murine monoclonal antibody parent of Rituximab
- Tiuxetan

Conjugated to antibody, forming strong urea-type bond with stable retention of Y-90

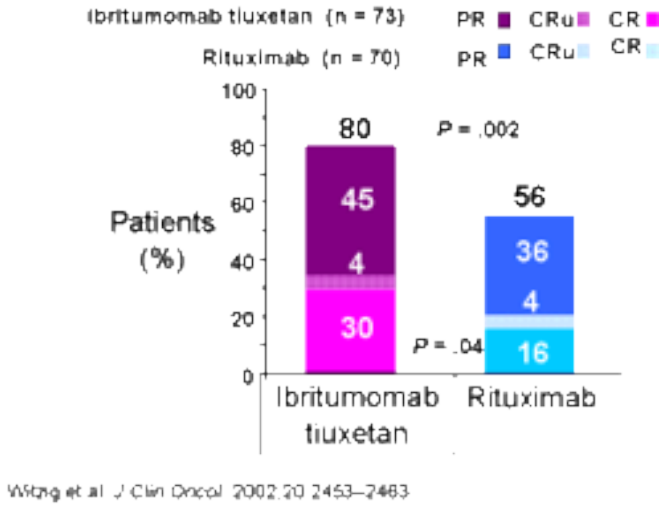


^{90} Y Zevalin Produces a Crossfire Effect



Naked Antibody **^{90}Y Zevalin**

Zevalin® and Rituximab®

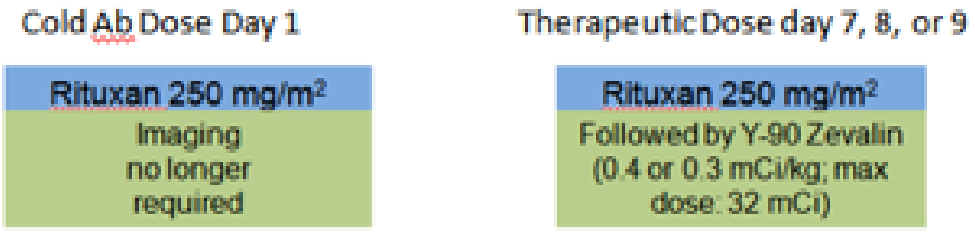


Witzig et al. J Clin Oncol 2002;20:2453–2463

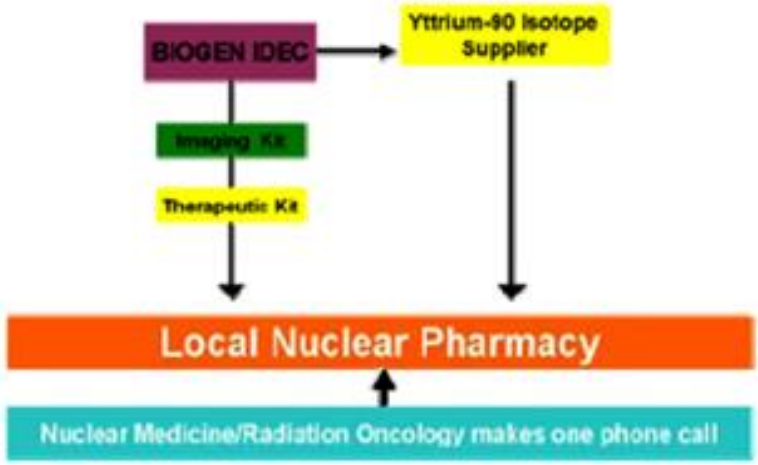
- The ORR based on the International Workshop NHL response criteria was 80% in the ibritumomab tiuxetan arm and 56% in the rituximab arm (P = .002).[1]
  The complete response rate (including unconfirmed complete responders) was 34% in the ibritumomab tiuxetan arm and 20% in the rituximab arm (P = .04).
- (Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol. 2002:20:2453–2463.)

Zevalin: ORR and Durable Remissions							
	Overall Responders		CR/CRu		Ongoing CR/CRu Responders		
Study N	%	Median DR (mo)	%	Median DR (mo)	%	Median DR (mo)	Range (mo)
Phase 1/2 (51)	73	11.7	29	23	19	62.1	60+ to 66+
Phase 2 (30)	83	11.5	47	23	41.2	41.2	40+ to 42+
Phase 3 (73)	80	13.9	34	23	42.2	42.2	33+ to 48+

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

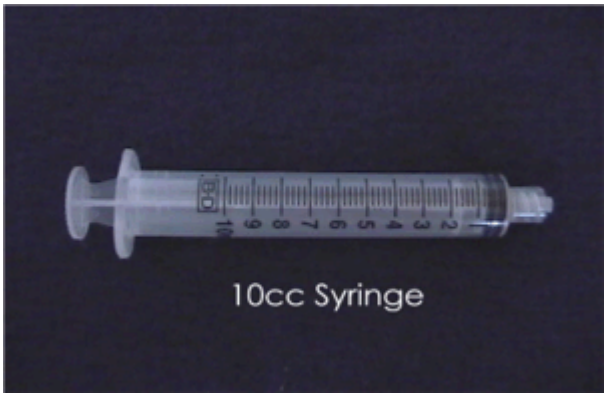
^{90}Yttrium Chloride

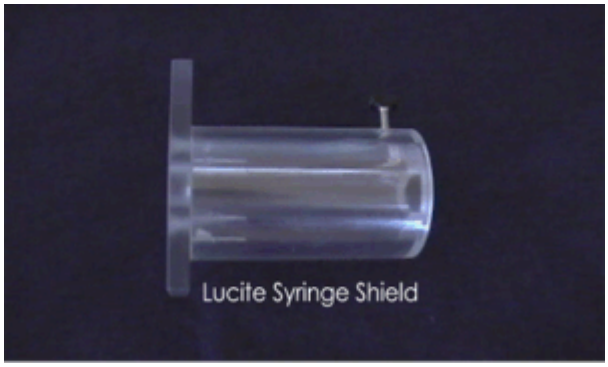
• Y-90 is available for calibration / use any day of the week
• same day delivery
• half-life: 64.1 hours
• energy: 2.281 mev
• decay: Beta minus

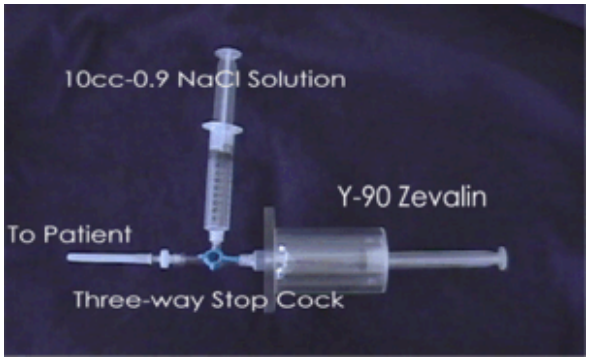
ZEVALIN: INFUSION TECHNIQUES

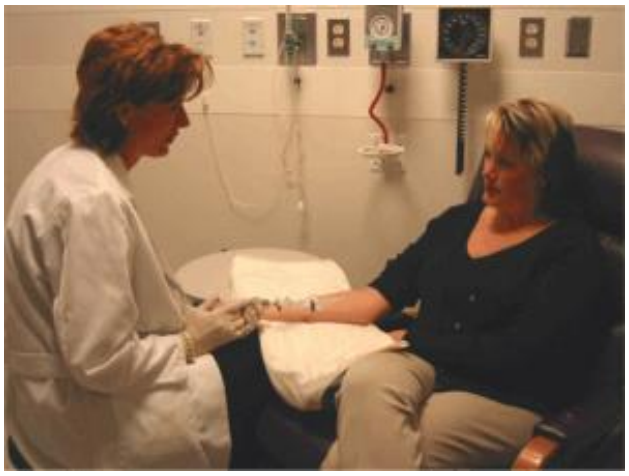
Zevalin Administration Equipment

- 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 with10 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

Day Minus 5	Thursday	Place Order
Day 1	Tuesday	Administer Rituxan 250 mg/m^2
Day 8	Tuesday	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

Zevalin Unit-Dose Storage & Shelf-life

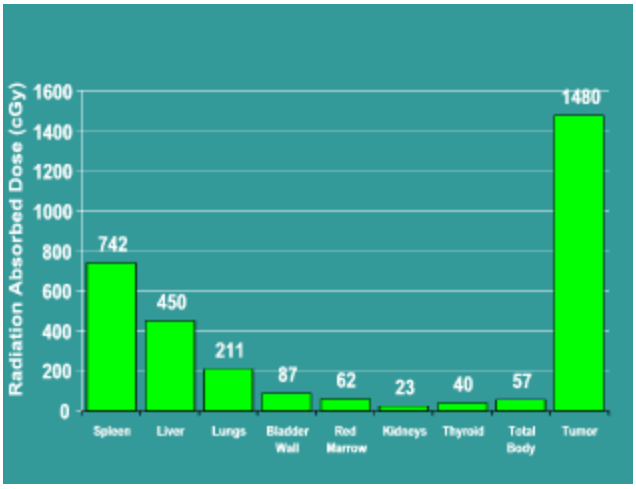
Refrigerate Zevalin unit-dose (2 - 8 °C) if not ready for immediate injection

- 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

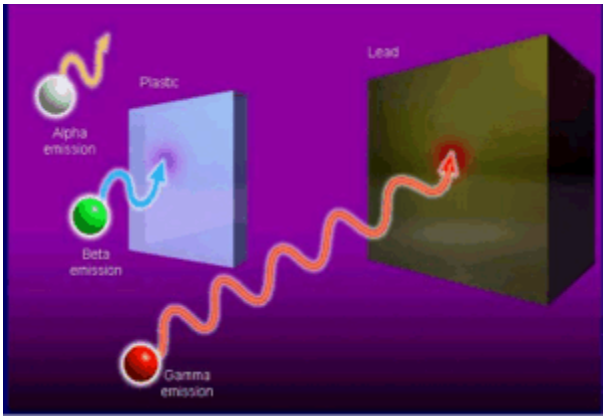
Zevalin: Radiation Safety

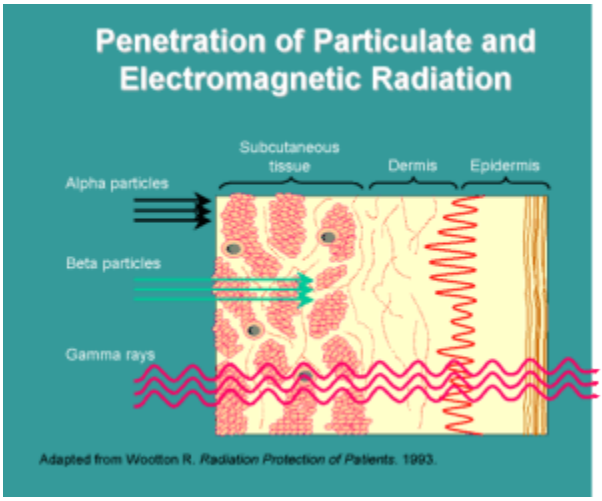
- Zevalin should be administered by physicians and other professionals qualified by training and experienced in the safe use and handling of radiopharmaceuticals (e.g., nuclear medicine physicians or radiation oncologists)
  *Wagner et al. J Nucl Med.2002:43:267-272

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

- ^{90}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}Y, a plastic shield is sufficient to absorb the beta particles. With gamma emitters like ^{131}I, thick lead shielding is required to absorb the longer gamma rays.

Penetration of Particulate and Electromagnetic Radiation

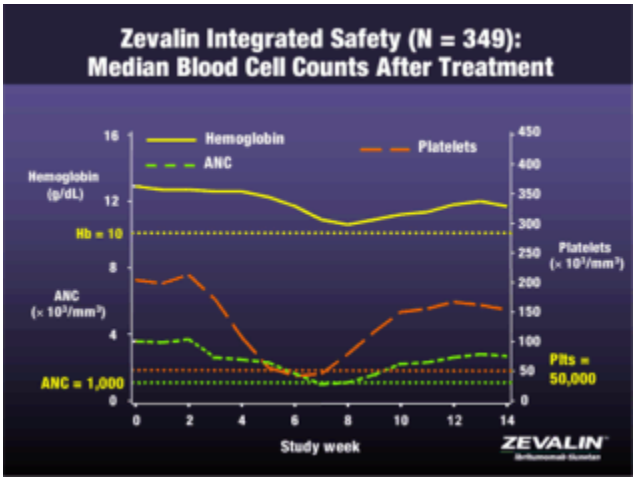




Zevalin®: Risk of Radiation Exposure to Others Is Negligible*

*Wiseman et al. Eur J Nucl Med.200:28: Abstract PS479

- 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

  G.A. Wiseman and D.N. Gansen (abstract submitted to Soc. Nuc. Med. 2002)

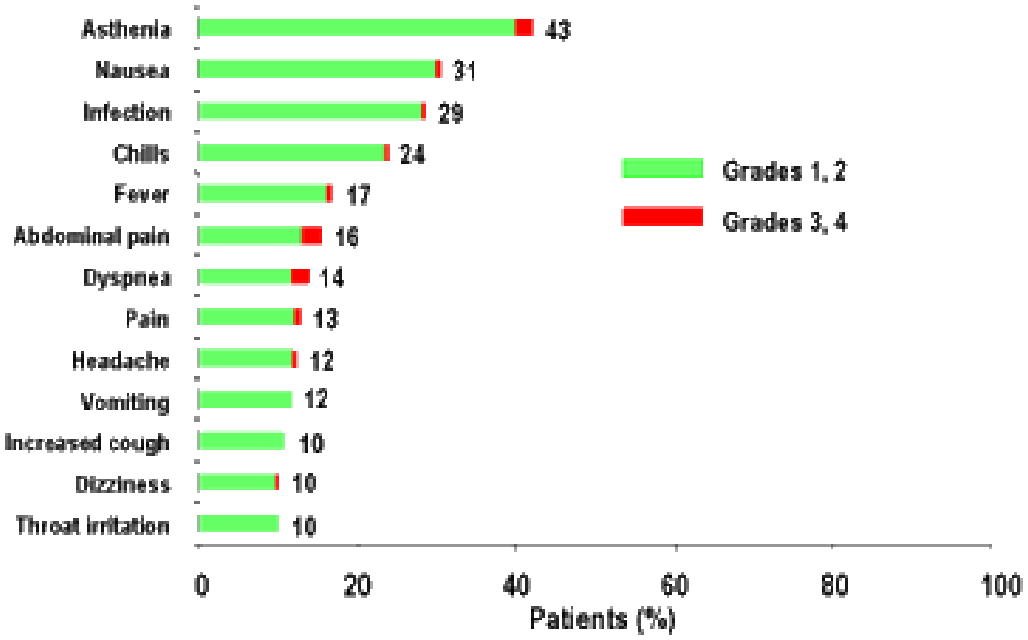
Zevalin® Patient Release Instructions*

- 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

  *Wagner et al. J Nucl Med.2002:43:267-272

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

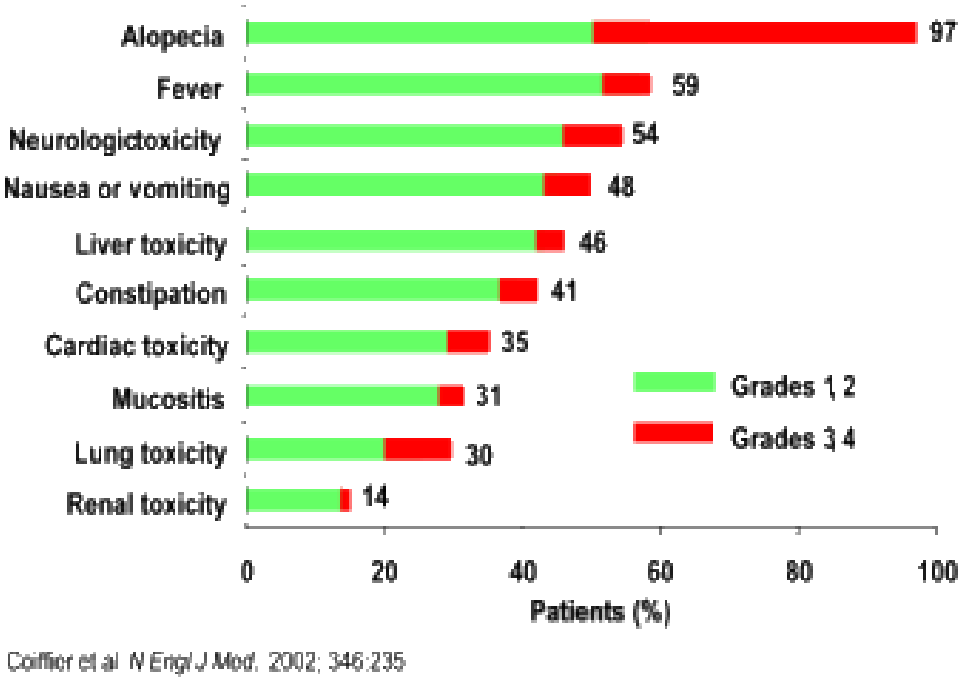


Zevalin (Ibritumomab tiuxetan) prescribing information. San Diego, Calif: IDEC Pharmaceuticals; 2002.

Zevalin: Most Common Non-hematologic Adverse Events

Coiffier et al. N Engl J Med. 2002; 346:235

CHOP: Most Common Non-hematologic Adverse Events



Coiffier et al. N Engl J Med. 2002; 346:235

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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