Technical Considerations in Zevalin Radioimmunotherapy

Kathy Thomas, MHA, CNMT
City of Hope National Medical Center
Technical Considerations in Zevalin Radioimmunotherapy

Objectives:

- Explain the technical aspects of the Zevalin protocol
  - creation of the radioimmunotherapy (RIT) team
  - equipment and supplies required for RIT
  - the components and radiolabeling technique for the Zevalin cold kit
  - the safety aspects of the Zevalin cold kit
  - infusion techniques
  - acquisition parameters
  - safety techniques to achieve ALARA
Radioimmunotherapy
A Team Effort

- Oncology/Hematology
  - Referring Physician
  - Nursing staff
- Nuclear Medicine
  - Physician
  - Physicist/RSO
  - Technologist
  - Nursing staff
- Radiopharmacy
- Radiation Oncology
  - Radiation Oncologist
  - Nursing staff
- Utilization Review
- Billing/Reimbursement
Zevalin Radioimmunotherapy
Treatment Schedule

**Imaging dose**

**Rituxan® 250 mg/m²**
Followed by **In-111 Zevalin 5 mCi**

**Therapeutic dose**

**Rituxan® 250 mg/m²**
Followed by Y-90 Zevalin (0.4 or 0.3 mCi/kg*; max dose 32 mCi)
or

- Day - 5
- TUES or WED

**Day**
1 2 3 4 5 6 7 8 9

**Scans**
2–24 hours 48–72 hours 90–120 hours (optional)

*0.4 mCi/kg in patients with a platelet count ≥150,000/µL or 0.3 mCi/kg with a platelet count 100,000 - 149,000/µL.

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Equipment and Supplies

- **Equipment:**
  - Dual/Single head gamma camera system
    - Medium energy collimator(s)
  - Infusion Pump (optional)
    - Must accommodate a 10-12 cc syringe and a 10 minute infusion time for 4-10 mL
  - GM Pancake Probe – calibrated to detect beta
  - Dose Calibrator
    - Geometrically qualified to calibrate $^{90}$Y Zevalin
**Discussion:**

- Dose calibrators are designed to assay gamma emissions.
- $^{90}$Y is a pure beta emitter.
- Bremsstrahlung emitted by $^{90}$Y is the only energy that can be assayed.
- To accurately assay $^{90}$Y in the dose calibrator, it is recommended that the calibration settings for the dose calibrator be qualified using $^{90}$Y (refer to manufacturer’s recommendations, state or federal guidelines and institutional policies).
Equipment and Supplies

- **Injection Supplies:**
  - IV tubing with injection port
  - 250 mL 0.9% normal saline
  - 3-way stopcock
  - Butterfly needle or angiocath
  - Gloves
  - Alcohol prep pads
  - 2 x 2 gauze pads
  - Paper/adhesive tape
  - Band-Aids

- **Syringe Shield:**
  - Lead or tungsten – $^{111}\text{In}$
  - Plastic/acrylic or combo acrylic/lead or acrylic/tungsten – $^{90}\text{Y}$

- .22 micron filter
- Absorbent pads
- Patient dose:
  - $^{111}\text{In}$ Zevalin
  - $^{90}\text{Y}$ Zevalin
Zevalin: “Ibritumomab Tiuxetan”
Zevalin Labeled Antibodies

- **Zevalin (ibritumomab tiuxetan)**
  - **Ibritumomab (murine parent of rituximab)**
    - Binds CD20
  - **Tiuxetan**
    - Stable retention of $^{90}$Y and $^{111}$In

- **CD20 antigen**
  - Expressed only on B-lineage cells
  - Important for cell cycle initiation and differentiation
  - Does not shed or modulate
The Zevalin Cold Kit

- **Vial #1 - antibody**: in a glass septum vial containing 2 mL of *ibritumomab tiuxetan*
- **Vial #2 - sodium acetate**: in a glass septum vial containing 2 mL of sodium acetate
- **Vial #3 - formulation buffer**: is a yellow viscous solution in a 10 mL glass septum vial containing 1 x PBS, 7.5% Human Serum Albumin and 1 mM DTPA, pH of 7.2
- **Vial #4 - reaction vial**: is a clear 10 mL, glass septum, empty vial
The Zevalin Cold Kit

Sodium Acetate Buffer:

- Brings the pH of the radiopharmaceutical to approximately 4
  - Radiolabeling is pH dependent
    - pH < 4 results in decreased radiolabeling
      - Incomplete radioincorporation
    - pH > 4 results in delayed radiolabeling
      - Increased radiolysis of Zevalin
The Zevalin Cold Kit

Formulation Buffer:

- Establishes isotonicity through:
  - KCL
  - NaCl
  - HSA
  - DTPA

- Ensures safety by:
  - Chelating free $^{90}\text{YCl}_3$
  - Ensuring rapid excretion via GFR elimination
  - Excess 1 mM DTPA will chelate ALL $^{90}\text{Y}$ even if none is incorporated
The Zevalin Cold Kit

Formulation Buffer:

- HSA (Human Serum Albumin)
  - Used as a radioprotectant for Zevalin using the following methods commonly found to decrease radiolysis:
    - HSA protects Zevalin by use as a surrogate
    - Enlargement of final volume
Radiopharmaceutical Characteristics

\( ^{111} \text{Indium Chloride:} \)
- **HALF-LIFE:** 67.3 hours
- **ENERGY:** 173/247 keV
- **DECAY:** Electron capture

\( ^{90} \text{Yttrium Chloride:} \)
- **HALF-LIFE:** 64.1 hours
- **ENERGY:** 2.281 MeV
- **DECAY:** beta minus emission
- **Particle pathlength (\( \chi_{90}, \text{mm} \)):** 5.3
Radiolabeling the Zevalin Cold Kit

- **Kit contents**
  - Sodium acetate
  - Zevalin antibody (ibrutinomab tiuxetan)
  - Formulation buffer
  - Empty reaction vial

- **Radiopharmaceutical starting activity**
  - 40 mCi $^{90}$Y
  - 5.5 mCi $^{111}$In

- **Required volumes**
  - Sodium acetate
    - 1.2 x volume of radiopharmaceutical
  - Antibody
    - 1.3 ml for $^{90}$Y
    - 1.0 ml for $^{111}$In
  - Formulation buffer
    - QS to 10 mL for $^{111}$In and $^{90}$Y

- **Incubation times**
  - 5 minutes – $^{90}$Y
  - 30 minutes – $^{111}$In

- **Quality control procedure**
  - Same for $^{111}$In and $^{90}$Y
Quality Control: Determination of Radiochemical Purity (RCP)

DTPA-bound $^{111}\text{In}$ or $^{90}\text{Y}$

90Y or $^{111}\text{In}$ Zevalin

One minute (cpm)

$\geq 95\%$

$$RCP = \left( \frac{(cpm \ #1)}{(cpm \ #1) + (cpm \ #2)} \right) \times 100$$
The Zevalin Cold Kit

Safety Aspects:

- In-house experiments demonstrate a very hardy cold kit:
  - Safety established via +/- 20% variation in possible operator error(s) including:
    - Activity used for radioincorporation
    - Volume of sodium acetate used to buffer the radiopharmaceutical
    - Zevalin volume used in radioincorporation
  - Few radioincorporation failures in 410 preparations:
    - $^{90}$Y 97.7% RCP
    - $^{111}$In 98.1% RCP
**Calculate Patient Dose**

- $^{111}$In Zevalin imaging dose is 5.0 mCi (in 10 mL)

- $^{90}$Y Zevalin therapy dose is based on patient’s weight and platelet levels (in 4-8 mL)
  - 0.3 mCi/kg $^{90}$Y Zevalin - platelets 100,000 - 149,000
  - 0.4 mCi/kg $^{90}$Y Zevalin - platelets > 150,000

**Note:** $^{90}$Y Zevalin dose must not exceed 32 mCi
Obtaining Radiolabeled Zevalin

- Nuclear medicine or radiation oncology places order for Zevalin from local commercial radiopharmacy:
  - Cardinal Health - Biotech - Geodax
  - Amersham Health - Independents

- Radiopharmacy places order for Zevalin components from Biogen Idec Pharmaceutical on a per-patient basis:
  - 2 Zevalin cold kits
  - $^{111}$In Chloride (supplied by radiopharmacy)
  - $^{90}$Y Chloride (supplied from MDS Nordion as part of the cold kit package)

- Delivered to nuclear medicine as a unit dose
Refrigerate Zevalin (2 - 8 °C) if not ready for immediate injection

- Shelf-life 12 hours - $^{111}$In Zevalin
- Shelf-life 8 hours - $^{90}$Y Zevalin
Zevalin
Handling and Administration
Injection Technique for Radiolabeled Zevalin

- Establish venous access with butterfly needle or angiocath attached to IV tubing and 250 mL of 0.9% sodium chloride bag or a 3-way with syringe flush
- Stop flow from IV bag
- Place a 0.22 micron (low protein binding) filter between the 10 mL syringe containing the unit dose of Zevalin
- **Note:** Pre-wet the micron filter with 0.9% sodium chloride prior to attaching to 10 mL syringe and avoid introduction of air in the filter
Injection Technique for Radiolabeled Zevalin (continued)

- SLOWLY inject Zevalin over 10 minutes
- Do not inject concomitantly with another IV solution or medication
- Do not inject as an intravenous bolus
- Slowly flush line with at least 10 mL of 0.9% sodium chloride
- Assay the residual activity in the syringe after injection to determine the total injected activity
Zevalin Radioimmunotherapy - Adverse Events -

- The most common severe adverse events are primarily hematological and reversible
  - Monitored with weekly blood counts by the oncologist/hematologist

- Most non-hematological toxicities are mild in severity and include gastrointestinal symptoms (nausea, vomiting, abdominal pain and diarrhea), increased cough, dyspnea, dizziness, arthralgia, anorexia, anxiety and ecchymosis
  - Monitored by physician at the time of infusion and followed, as necessary by nursing staff
Zevalin Imaging Protocol
Data Acquisition for $^{111}$In Zevalin

- Dual or single head gamma camera system
- Medium energy collimator(s)
- 172 and 247 keV with 15-20% window
- 256 x 1024 matrix
- Speed (dependent on time after injection)
  - 10 cm/min (20 minute scan) at 2 - 24 hours
  - 7 - 10 cm/min (30 minute scan) at 48 - 72 hours
  - 5 - 7 cm/min (40 minute scan) at 90 - 120 hours

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Whole Body Gamma Camera Images

24 hours

72 hours

144 hours
Expected Biodistribution

- Radioactivity in the blood pool on first image, less on second image
- High uptake in normal liver and spleen
- Low uptake in kidneys, urinary bladder, and bowel
- Tumor uptake visualized as areas of increased intensity
- Decision: administer $^{90}$Y Zevalin
Altered Biodistribution

- Blood pool not visualized on first image
- Lung uptake more intense than liver uptake on second image
- Kidney uptake greater than liver uptake on second image
- Diffuse intense uptake in bowel comparable to uptake in liver on second image
- Altered biodistribution is rare—one patient identified in the clinical trials
Altered Biodistribution Image

4 hours

Anterior

Posterior

67 hours

Anterior

Posterior

Abnormal
Injected Activity - $^{90}$Y Zevalin

- Same injection procedure as $^{111}$In-Zevalin
- Just prior to injection, assay the dose in the dose calibrator
  - Dial in the appropriate calibration setting determined for your dose calibrator
  - For most dose calibrators, once the reading has stabilized, multiply the reading by a factor of 10 to determine the dose
- Assay the residual activity in the syringe after injection to determine the total activity injected
Zevalin Radiation Safety
Exposure to health care workers can be low for multiple therapies each year providing that the basic principals for handling radioactive materials are adhered to including:

- Minimize Time
- Increase Distance
- Maximize Shielding
Examples of shielding for Zevalin infusion:

- Lead, aluminum/lead, or tungsten for $^{111}\text{In}$
- 1 cm Plexiglas or Lucite/acrylic - stops $^{90}\text{Y}$ beta particles
- Lead, tungsten aluminum/lead or acrylic/lead - absorbs attenuate Bremsstrahlung emissions
- Lead/acrylic, aluminum/lead/acrylic, or tungsten/acrylic stops $^{90}\text{Y}$ beta particles and absorbs attenuates from Bremsstrahlung emissions

With proper handling and shielding, exposure to personnel can be ALARA
90Y Zevalin: Minimal Exposure to Healthcare Workers/Family

- Median effective half-life in blood = 27 hours
- Most activity is retained; urinary excretion = 7.3% ± 3.2% over 7 days
- Assuming maximum 32 mCi dose and excretion of 7.3% over a week, the total urinary excretion over one week is approximately 2.3 mCi
  - Activity per urination = Microcuries
- Conclusion: Universal precautions are adequate for patients receiving 90Y Zevalin
Patient Release Instructions

● 7 days following administration:
  – Wash hands carefully after using the toilet
  – Avoid transfer of bodily fluids (saliva, blood, urine, stool)
  – Use condoms for sexual relations
  – Clean up spilled urine and dispose of blood contaminated material so that others will not inadvertently handle it

● Up to 12 months following treatment:
  – Use effective contraceptive methods
Zevalin Resources

● Information for Zevalin Therapy:
  1-877-433-4332

● Reimbursement questions:
  1-800-386-9997

● The Zevalin Website:
  www.Zevalin.com
Zevalin Summary:

- Successful administration of the therapy protocol requires a multidisciplinary team effort
- Zevalin is a hardy cold kit that when radiolabeled with $^{90}$Y or $^{111}$In demonstrates an average radioincorporation of 97.7% and 98.1% respectively.
- The Formulation Buffer, containing DTPA ensures safety by chelating free $^{90}$YCl$_3$ and ensuring rapid excretion via GFR elimination.
- Imaging performed:
  - As an additional safety measure
  - To verify the expected biodistribution
- Dosing based on clinical parameters and patient weight
Zevalin Summary (continued):

- Short treatment course performed over 7-9 days without the need for hospitalization, isolation, or shielding
- \(^{90}\)Y - Pure beta emitter
  - Exposure to health care workers can be ALARA when appropriate time, distance and shielding guidelines are followed
  - Makes therapy procedures a routine outpatient procedure
  - Results in minimal disruption to patient’s daily routine; thus, improving quality of life