Radioimmunotherapy of Lymphoma

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Overview

- Lymphomas
- Therapies for lymphoma
- Radioimmunotherapy regimens
  - $^{90}\text{Y}$- ibritumomab tiuxetan
  - $^{131}\text{I}$- tositumomab
Lymphomas

- Malignancies of the lymphoid tissue
- Broadly classified into
  - Hodgkin’s lymphoma
  - Non-Hodgkin’s lymphomas
    - B-cell lymphomas: ≈ 85%
      - follicular and diffuse large B-cell lymphomas constitute ≤50 % of NHL
    - T-cell lymphomas
- Clinical patterns of disease
  - Indolent (low-grade) lymphomas: ≈ 50%
  - Aggressive lymphomas
- Ann Arbor staging is used for clinical staging
Lymphoma: Therapies *(pediatrics)*

- Chemotherapy
- Radiotherapy
  - only indicated for acute life-threatening complications refractory to initial chemotherapy or acute hemiplegia
- Hematopoietic stem cell transplantation
- Biological therapies
  - targeted therapy with monoclonal antibodies
- Surgery
  - limited role. Performed on patients in whom there is good reason to believe that total resection can be achieved without a mutilating procedure
- Combinations of above

Lymphoma: Therapies (adults)

- Chemotherapy
- Radiotherapy
- Hematopoietic stem cell transplantation
- Biological therapies
  - targeted therapy with monoclonal antibodies
    - lineage-restricted antigens
      - B-cells: CD-20 epitope
  - others: biological response modifiers, nonspecific immunotherapy, vaccination
- Radioimmunotherapy
- Combinations of above
CD20 Epitope

- CD20: 35-kd transmembrane glycoprotein
- A pan B-cell marker expressed on
  - normal B-cells
  - nearly all B-cell lymphomas (>90%)
- Initially appears in pre-B cell stage and disappears in plasma cells
- Specific function of CD20 is unknown
Radioimmunotherapy

- A unique therapeutic modality that uses an antibody carrier to target high-energy, short–path-length radionuclides to tumor sites with little effect on other solid organs
- **Components:** radioisotope combined with an anti-CD20-directed antibody
  - $^{90}$Y-ibritumomab tiuxetan: $^{90}$Y + chelator (tiuxetan) + ibritumomab
    - rituximab: chimeric (murine and human) monoclonal antibody
      - first MAb to be approved by the U.S. FDA for the treatment of cancer (1997)
  - $^{131}$I-tositumomab: $^{131}$I + tositumomab
    - tositumomab: murine monoclonal antibody
Anti-CD20 Radioimmunoconjugates

$^{90}$Y–ibritumomab tiuxetan

- FDA approved for:
  - relapsed low-grade and follicular NHL
  - consolidation after initial chemotherapy
- Regimen:
  - 2 doses of unlabeled MAb, days 1 and 8
  - a dose of labeled Mab on day 8

$^{131}$I-tositumomab

- FDA approved for:
  - relapsed low-grade and transformed NHL
- Regimen:
  - 2 two doses of unlabeled MAb, days 0 and 7-14
  - a dose of labeled Mab calculated to deliver a 75-cGy total body dose

RIT Administration Protocols

\(^{90}\text{Y- ibritumomab tiuxetan}\)
- Step A: Patient Selection and Eligibility
- Step B: Bio-distribution/Diagnostic scan
- Step C: Dose Calculation
- Step D: Therapeutic Dose Administration

\(^{131}\text{I-tositumomab}\)
- Step A: Patient Selection and Eligibility
- Step B: Thyroid protection
- Step C: Diagnostic and Dosimetry Scan
- Step D: Dose Calculation
- Step E: Therapeutic Dose Administration

**Patient Selection**

**90Y- ibritumomab tiuxetan**
- Relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL).
- Previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy.

**131I-tositumomab**
- CD20-positive relapsed or refractory, low grade, follicular, or transformed non-Hodgkin’s lymphoma who have progressed during or after rituximab therapy, including patients with rituximab-refractory non-Hodgkin’s lymphoma

http://www.zevalin.com
http://www.bexxar.com
Patient Selection & Eligibility *(adults)*

- absolute neutrophil count $\geq 1500 \times 10^6/L$
- platelet count $\geq 100,000 \times 10^6/L$
  - full dose of RIT: $\geq 150,000 \times 10^6/L$
  - reduced RIT dose: $100,000 \times 10^6/L$ and $149,000 \times 10^6/L$
- imaging: CT or PET/CT
- pretreatment bone marrow aspiration and biopsy with chromosome analysis
  - marrow $\geq 15\%$ of normal cellularity
  - percentage of marrow cellularity occupied by lymphoma cells <25%
  - in previously treated patients rule out myelodysplastic syndromes
    - fluorescence *in situ* hybridization (FISH) or
    - conventional cytogenetics for chromosomal markers
RIT Administration Protocols

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- Step A: Patient Selection and Eligibility
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- Step A: Patient Selection and Eligibility
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A bio-distribution scan was obtained as an outpatient for exclusion of abnormal antibody tracer distribution (0.6 to 1.3 percent of patients) that would preclude treatment.
RIT Administration: FDA removed Bioscan requirement in November 2011

$^{90}$Y- ibritumomab tiuxetan (simplified protocol)

- Step A: Patient Selection and Eligibility
- Step B: Unlabeled Rituximab Infusion
- Step C: Dose Calculation
- Step D: Therapeutic Dose Administration

Cold MAB infusion, followed within 4 hrs by radiolabelled MAb
• **Antigen sinking effect**: administered labeled MAb predominantly targets and accumulates within the normal reticuloendothelial system (liver & spleen) and circulating lymphocytes

• **Preloading**: infusion of unlabeled Mab is performed for both biodistribution and treatment studies, in an effort to minimize the *antigen sinking effect*
90Y-ibritumomab tiuxetan

**Step C: Dose Calculation**
- Platelet counts > 150,000: 0.4 mCi/kg (14.8 MBq/kg)
- Platelet counts between 100 and 150,000: 0.3 mCi/kg (11.1 MBq/kg)
- Platelets < 100,000: therapy contraindicated
- Maximum administered activity is 32 mCi

131I-tositumomab

**Step D: Dose Calculation**
- Tolerated maximum whole body radiation dose is 75cGy (65cGy, if platelets are 100,000-150,000)
A bio-distribution scan for the $^{90}\text{Y}$ ibritumomab tiuxetan radioimmunotherapy regimen is shown. Which choice is FALSE?

A. This regimen was FDA approved for the treatment of relapsed low-grade and follicular NHL in 2002
B. Rituximab is a murine monoclonal antibody (MAb)
C. $^{111}$Indium is the radiotracer used for imaging
D. Prior to the injection of the radiolabelled MAb, preloading is performed with unlabeled MAb to minimize the antigen sinking effect

E. $^{90}\text{Y}$ttrium is a beta emitter
Yttrium-90–ibritumomab tiuxetan therapy administration protocol

Step A: Patient Selection and Eligibility

Step B: Bio-distribution/ Diagnostic scan
Day 1:
Acetaminophen 650 mg and diphenhydramine 50 mg, 30 minutes prior to infusion
Unlabeled rituximab infusion (250 mg/m2) at a rate of at a rate of 50mg/hr, incremental to 400mg/hr
5 mCi or 185 MBq/1.6 mg antibody (10 mL) of $^{111}$In-Zevalin slow intravenous injection over 10 minutes; administered within 4 hours of the cold antibody infusion
Days 2-6:
Whole body planar images obtained at 48-72 hours (subsequent scanning optional)
Previously, images at 2-24, 48-72, and 90-120 hours

Step C: Dose Calculation
Assess the bio-distribution and if acceptable, determine the dose (0.4 or 0.3 mCi/kg based on platelet counts)

Step D: Therapeutic Dose Administration
Day 7/8/9: (exact timing depends on dose arrival and logistics)
Acetaminophen 650 mg and diphenhydramine 50 mg, 30 minutes prior to infusion
Unlabeled rituximab infusion (250 mg/m2) at a rate of 50mg/hr
Calculated dose of Zevalin slow IV infusion over 10 minutes through a low protein binding millipore filter (maximum dose 32 mCi or 1184 MBq); administered within 4 hours of the cold antibody infusion
Flush the catheter post infusion to administer complete dose
Assay the administration tubing set
Yttrium-90 –ibritumomab tiuxetan therapy administration protocol

Step A: Patient Selection and Eligibility

Step B: Bio-distribution/ Diagnostic scan
Day 1:
Acetaminophen 650 mg and diphenhydramine 50 mg, 30 minutes prior to infusion
Unlabeled rituximab infusion (250 mg/m2) at a rate of at a rate of 50mg/hr, incremental to 400mg/hr

Premedications are used to help reduce the side effects of monoclonal antibody (Mab)

Step C: Dose Calculation
Assess the bio-distribution and if acceptable, determine the dose (0.4 or 0.3 mCi/kg based on platelet counts)

Step D: Therapeutic Dose Administration
Day 7/8/9: (exact timing depends on dose arrival and logistics)
Acetaminophen 650 mg and diphenhydramine 50 mg, 30 minutes prior to infusion
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Calculated dose of Zevalin slow IV infusion over 10 minutes through a low protein binding millipore filter (maximum dose 32 mCi or 1184 MBq); administered within 4 hours of the cold antibody infusion
Flush the catheter post infusion to administer complete dose
Assay the administration tubing set
Yttrium-90–ibritumomab tiuxetan therapy administration protocol

Step A: Patient Selection and Eligibility

Step B: Bio-distribution/ Diagnostic scan
Day 1:
Acetaminophen 650 mg and diphenhydramine 50 mg, 30 minutes prior to infusion
Unlabeled rituximab infusion (250 mg/m2) at a rate of at a rate of 50mg/hr, incremental to 400mg/hr

The removal of the biodistribution scan requirement approved by the FDA in November 2011 simplified ZEVALIN administration

Step C: Dose Calculation
Assess the bio-distribution and if acceptable, determine the dose (0.4 or 0.3 mCi/kg based on platelet counts)

Step D: Therapeutic Dose Administration
Day 7/8/9: (exact timing depends on dose arrival and logistics)
Acetaminophen 650 mg and diphenhydramine 50 mg, 30 minutes prior to infusion
Unlabeled rituximab infusion (250 mg/m2) at a rate of 50mg/hr
Calculated dose of Zevalin slow IV infusion over 10 minutes through a low protein binding millipore filter (maximum dose 32 mCi or 1184 MBq); administered within 4 hours of the cold antibody infusion
Flush the catheter post infusion to administer complete dose
Assay the administration tubing set
Iodine-131–tositumomab therapy administration protocol

Step A: Patient Selection and Eligibility
Step B: Thyroid protection
Day -1:
Saturated solution of potassium iodide (SSKI) - 4 drops orally 3 times/day or Lugol's solution 20 drops orally 3 times/day or KI tablets 130 mg orally once/day; Administered from the day before until 14 days following therapy

Step C: Diagnostic and Dosimetry Scan
Day 0:
Acetaminophen 650 mg and diphenhydramine 50 mg, 30 minutes prior to infusion
Unlabeled tositumomab 450 mg intravenously in 50 ml saline over 1 hour
Small dosimetric amount of $^{131}$I-tositumomab (5 mCi or 185 MBq of $^{131}$I and 35 mg Tositumomab) in 30 ml saline over 20 minutes
Whole body dosimetry and bio-distribution immediately following injection within one hour, pre-void
Day 2, 3 or 4:
Whole body dosimetry and bio-distribution, post void
Day 6 or 7:
Whole body dosimetry and bio-distribution, post void (to maintain consistency, the same camera, collimator, and set up are utilized on all the dosimetric scans)

Step D: Dose Calculation
Assess the bio-distribution and if acceptable, determine the dose
Calculate the dose to deliver 75cGy total body dose (65 cGy, if platelets are 100-150,000)

Step E: Therapeutic Dose Administration
Day 7 up to 14: (exact timing depends on dose arrival and logistics):
Acetaminophen 650 mg and diphenhydramine 50 mg, 30 minutes prior to infusion
450 mg infusion of unlabeled Tositumomab in 50 mL of saline over 1 hour
20 minute infusion of Bexxar in a volume of 30 mL given through a millipore micron filter
Flush the catheter post infusion to administer complete dose
Assay the administration tubing set
Evaluation for Antitumor Response

- Recommended at week 12
- Subsequent reevaluation as per standard of care
- The first reevaluation often does not reflect the maximal response. Improvement in response without further therapy can occur commonly
- In the setting of normal blood counts, repeat bone marrow evaluation is needed only to confirm CR when it was involved prior to treatment
Contraindications to RIT (both agents)

- Pregnancy or ongoing breast feeding
- Known allergy or hypersensitivity to the murine antibodies, or components of the therapy
- Absolute Neutrophil Count <1500 cells/cu mm
- Platelet count <100,000
- Bone marrow involvement of more than 25 percent involvement
- Effective beam radiation therapy of >25 percent of active marrow
- Prior autologous stem cell transplant
- Elevated HAMA titers with altered biodistribution
Contraindications to RIT (I131-tositumomab)

- Iodine allergy
- Urinary incontinence (relative contraindication)
- Non-compliant patients
- Reduced renal function with creatinine > 1.5
Adverse event for RIT

• Myelosuppression most common
  • Predictable, generally transient, and reversible
  • Hematologic nadirs begin to appear at week 4, bottoming out at 6–8 weeks, with subsequent recovery
  • Recommended supportive care: weekly complete blood counts, assessed beginning at week 4 until the nadir is complete and blood cell counts are rising. Aspirin or coumadin is stopped once platelets are below 75,000/mm$^3$ or at the sign of any bleeding tendency. Granulocyte growth factors may be administered if clinically indicated
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