Radiation Safety in Radioimmunotherapy

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## Common Radionuclide Therapy Procedures

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Agent</th>
<th>Indication</th>
<th>AA (MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{32}$P</td>
<td>Phosphate</td>
<td>Polycythemia Vera</td>
<td>148</td>
</tr>
<tr>
<td></td>
<td>Chromic Phosphate</td>
<td>Neoplastic Effusions and Radiation Synovectomy</td>
<td>111-185</td>
</tr>
<tr>
<td>$^{89}$Sr</td>
<td>Chloride</td>
<td>Bone pain</td>
<td>148</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>Ibritumomab Tiuxetan</td>
<td>NHL</td>
<td>1184 (max)</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>Sodium iodide</td>
<td>Hyperthyroidism</td>
<td>370-1110</td>
</tr>
<tr>
<td></td>
<td>Sodium iodide</td>
<td>Thyroid Cancer</td>
<td>3700-14800</td>
</tr>
<tr>
<td></td>
<td>Tositumomab</td>
<td>NHL</td>
<td>3108 (av)</td>
</tr>
<tr>
<td>$^{153}$Sm</td>
<td>EDTMP</td>
<td>Bone pain</td>
<td>2590</td>
</tr>
</tbody>
</table>

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Nuclear Medicine Therapy

Use of radioactive materials in radionuclide therapy (radioimmunotherapy) governed in US by Nuclear Regulatory Commission and Agreement States

Outpatient v Inpatient Treatment?
NHL and RIT

RIT is a treatment modality in which cytotoxic radiation from therapeutic radionuclides is delivered to tumors via antibodies that bind to tumor-specific or tumor-associated antigens

$^{131}$I and $^{90}$Y → most widely investigated for RIT

Both have demonstrated efficacy in treating NHL
NHL and RIT

- Lymphomas particularly radiosensitive making them attractive targets for RIT
- Most studied cellular target in NHL has been CD20
  - $^{90}$Y ibritumomab tiuxetan
  - $^{131}$I tositumomab
  - Both agents are FDA-approved

Abs directed against
  - CD22
    - $^{90}$Y, $^{131}$I, and $^{186}$Re epratuzumab
  - HLA-DR
    - $^{67}$Cu, $^{90}$Y and $^{131}$I Lym-1
RIT and Crossfire Effect

Unlabeled “Cold” Antibody

Radiolabeled Antibody
RIT Advantages over XRT for Low-Grade NHL

Majority of low-grade NHL patients have disseminated disease; not amenable to local radiation fields.

External beam

RIT

Targets radiation to tumor
**90Y Ibritumomab Tiuxetan**

**Ibritumomab**

Parent murine MAb from which widely used human chimeric Ab rituximab developed

**Tiuxetan**

Linker-chelator: covalently links Ab & chelates

$^{111}$In for imaging and $^{90}$Y for therapy
RIT with $^{90}$Y Ibritumomab Tiuxetan

Monoclonal antibody

Chelator

Beta radiation

$^{90}$Y
BEXXAR™ (Tositumomab and \(^{131}I\) Tositumomab)

- **Tositumomab**
  - Murine IgG2a anti-CD20 MAb
  - B-cell specific
  - Induction of apoptosis
  - Complement-dependent cytotoxicity (CDC)
  - Antibody-dependent cellular cytotoxicity (ADCC)

- **Iodine-131**
  - Cytotoxic beta emission
  - Physical half-life of 8 days
  - Short path length
  - Gamma emission allows dosimetry
**131I vs 90Y**

**131Iodine**
- $T_{1/2} = 8.04$ d
- 1 mm $\beta$ range (max: 2.4 mm)
  - Av Energy = 192 keV
- Efficacious for Nonuniform Distribution in Tumors
- Better for Small Tumors/ Micromets
- Gamma for Imaging
- Thyroid (can be blocked)

**90Yttrium**
- $T_{1/2} = 2.7$ d
- 5 mm $\beta$ range (max: 11.9 mm)
  - Av Energy = 935 keV
- Efficacious for Nonuniform Distribution in Tumors
- Better for large tumors
- No gamma, surrogate ($^{111}$In) for imaging
- Bone (cannot be blocked)
Shielding Requirements

$^{90}\text{Y} \& \; ^{131}\text{I}$

- Alpha emission
- Beta emission
- Gamma emission

Lead

Plastic

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Shielding Requirements
\(^{90}\text{Y}\) Ibritumomab Tiuxetan

Plastic and acrylic materials (\(\beta\)s absorbed with 1 cm)

Lead should be avoided due to potential exposure risk from bremsstrahlung

Use of gloves
Acrylic Syringe and Vial Shield
Bremsstrahlung

- Electron (β-particle) mode of interaction involving nucleus
- Rapid deceleration/deflection/scatter of β by nucleus; involves loss of β kinetic energy emitted as photons
- Brems → braking Strahlung → radiation (brake: die Bremse; to brake: bremsen)
- Bremsstrahlung radiation ranges in energy from 0 to maximum β energy (2.28 MeV for $^{90}\text{Y}$)

Minimal external radiation exposure

$< 0.6 \, \mu\text{R/h/mCi at 1 m}$
Dose Calibrator Activity Measurement of $^{90}$Y Ibritumomab Tiuxetan

Activity supplied in 10 cc BD syringe in volumes ranging from 3 - 9 cc, dependent upon activity prescription.

Commercial reentrant ionization chamber (dose calibrator)

*De facto* standard instrument to measure radioactivity in nuclear medicine.

Usually used to measure activity of photon-emitting radionuclides but increasingly used for beta-emitters.

Measurement of beta-emitting radionuclides ($^{90}$Y) in dose calibrator dependent upon bremsstrahlung radiation produced from beta interaction with source matrix, its container and calibrator chamber wall.
Dose Calibrator Activity Measurement of $^{90}\text{Y}$ Ibritumomab Tiuxetan

Use of single dose calibrator dial setting (user defined) with no correction required for varying volume

Capintec, Inc.

National Institute of Standards and Technology

Sun Nuclear Corporation

Cardinal Health Nuclear Pharmacy Services

Dose calibrators - Atomlab, Capintec, Nuclear Associates

Siegel et al. JNM 2004; 45:450-454
$^{90}$Y Calibration Standard (NIST Traceable)

30 mCi $^{90}$Sr/$^{90}$Y: simulates 10 ml BD syringe geometry
Available April 2003
Treatment Regimen

$^{111}$In and $^{90}$Y Ibritumomab Tiuxetan

Day 1

**Imaging dose**
250 mg/m$^2$ rituximab, 5 mCi $^{111}$In Zevalin

Whole body images $\times$ 2-3

- Imaging dose used to determine if altered biodistribution

Day 7, 8, or 9

**Therapeutic dose**
250 mg/m$^2$ rituximab, 0.4 or 0.3 mCi/kg dose of $^{90}$Y Zevalin

- 0.4 mCi/kg if platelets $\geq$ 150k;
- 0.3 mCi/kg if 100-149k
- Max activity = 32 mCi

Day 0-6

- 2-24 h
- 48-72 h
- 90-120 h (optional)
Treatment Regimen
Tositumomab & Iodine I-131 Tositumomab

Thyroprotection: 24 hours prior to Day 0 and continuing for 14 days following the Therapeutic dose

Day 0

Dosimetric dose

450 mg tositumomab, 5 mCi iodine I\(^{131}\) tositumomab (35 mg)]

Whole body counts \(\times 3\)

Therapeutic dose

[450 mg tositumomab, mCi dose of iodine I\(^{131}\) tositumomab (35 mg) to deliver individualized cGy TBD]

• Unlabeled predose infused over 1 hour
• Dosimetric dose used to determine individual TB clearance

• Day 0
• Day 2, 3, or 4
• Day 6 or 7

• Unlabeled predose infused over 1 hour
• Administered mCi activity based on TB clearance
• 75 cGy TBD; if platelets 100-150K cells/mm\(^3\), 65 cGy


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Critical Role of Dosimetry
Achieve Equal Area Under Curve (AUC)

Iodine I 131 tositumomab effective half-life varies widely.

Resulting in a wide range of administered Iodine-131 (mCi) dose to deliver 75 cGy.

Zelenetz et al., ASCO 2001.

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RIT Requires Multidisciplinary Team

- Hematology Oncology
- Nursing
- Nuclear Medicine or Radiation Oncology
- Radiopharmacy
- Radiation Safety

PATIENT
NRC changed patient release rule 10 CFR 35.75 (11/29/97)

FROM: Activity-based limit (<30 mCi) or Dose rate-based limit (<5 mrem/h @ 1m)

TO: Dose-based limit (<0.5 rem)
Licensees can now release patients regardless of how much administered activity they received, as long as the radiation dose to any individual from exposure to the released patient< 0.5 rem
Origin of NRC 30-mCi Rule?
Siegel JA. Tracking the origin of the NRC 30-mCi rule. JNM 2000; 41:10N-16N

- Patients hospitalized, radioactivity content <30 mCi
  Applied to All radionuclide treatments (1946 - 1997)
  Recommendation not regulation → License condition until 1987

- Isotopes Division & The Subcommittee on Human Applications (1946-1955)
  30 mCi of most radioisotopes → no significant hazard
  AEC 30 mCi limit lacked evidence of hazard to PH&S
  Inappropriately low administered activity for cancer treatments, unnecessary patient hospitalizations, increased health care costs
5 mSv Dose Level

Deterministic or stochastic effects have not been demonstrated

Based on LNT model $\rightarrow$ 0.025% risk of fatal CAs

A 5 mSv dose will result from all of the following:

- Living 1.7 y in typical natural background area (~ 3 mSv/y)
- Living 0.6 y in some portions of Colorado
- Flying 625 h in an airplane (dose due to cosmic radiation ~270x higher than at sea level; 8 µSv/h)
- Smoking 12 cigarettes/day for one year
NRC Patient Release Rule

† THE RULE

10 CFR 35.75

† GUIDANCE FOR THE RULE


Appendix U, Model Procedure for Release of Patients or Human Research Subjects Administered Radioactive Materials
35.75 Release of individuals containing unsealed byproduct material or implants containing byproduct material

(a) A licensee may authorize the release from its control of any individual who has been administered unsealed byproduct material or implants containing byproduct material if the total effective dose equivalent to any other individual from exposure to the released individual IS NOT LIKELY TO exceed 0.5 rem
NRC Patient Release Rule

- **35.75** Release of individuals containing unsealed byproduct material or implants containing byproduct material

(b) *A licensee shall provide the released individual, or the individual’s parent or guardian, with instructions, including written instructions…*

NRC does not intend to enforce patient compliance with the instructions nor is it the licensee’s responsibility to do so (NUREG-1556, Vol. 9, footnote 1, U.2.1)
Instructions Requirements
10 CFR 35.75

- Written instructions must be provided to released individual, or individual’s parent or guardian, on actions to maintain doses to others ALARA if TEDE likely to exceed 100 mrem

- If dose to breast-feeding infant or child could exceed 100 mrem assuming no interruption of breast-feeding, instructions must also include:
  
  Guidance on interruption or discontinuation of breast-feeding
  
  Information on potential consequences, if any, of failure to follow guidance
Lastly, records must be maintained of

✓ Basis for authorizing release if TEDE calculated by
  Using retained activity rather than AA
  Using OF < 0.25 at 1 m
  Using biological or effective half-time
  Considering shielding by tissue

✓ Instructions provided to breast-feeding female
GUIDANCE FOR THE RULE
NUREG-1556, Vol. 9

- Describes methods for release of patients administered radioactive material

  Radiation doses calculated to other individuals to demonstrate compliance with 10 CFR 35.75

1. “Default” tables (Appendix U)
   - Activity and dose rate at 1 m release limits

2. Patient-specific dose calculation (Appendix U, Supplement B)
   - Patients can be released with higher values
Activity and dose rate limits not given for pure beta emitters ($^{32}$P, $^{89}$Sr, $^{90}$Y)

Activity limit for Zevalin = 32 mCi

**NOT** applicable “because of the minimal exposures to members of the public resulting from activities normally administered for diagnostic and therapeutic purposes.”

Good practice

Example: Activity release limit for $^{90}$Y would be 38,500 mCi


**NO record or instructions required** for $^{90}$Y ibritumomab tiuxetan patient release
Internal Contamination Risk

$^{90}\text{Y}$ Ibritumomab Tiuxetan

- Almost entire therapeutic dose retained in the body
  - Urinary excretion is primary clearance mechanism
    - $7.3\% \pm 3.2\%$ of AA excreted over 7 d
- Rapid blood pharmacokinetics
  - Median $T_e = 27$ h (14-44 h)
  - Therefore, small amount of activity in urine and blood
  - Minimal internal contamination risk

Radiation Dose to Others

$^{90}$Y Ibritumomab Tiuxetan

Measurement of radiation exposure to 13 family members

Family members of patients treated with $^{90}$Y ibritumomab tiuxetan wore electronic dosimeter 1 week

Family members allowed unrestricted contact with patient. Only recommendation was to avoid contamination from body fluids

Median family member dose 3.5 mrem
(range: 1.4 - 7.9 mrem)


In the range of background radiation (5.8 mrem/week)
# Release Instructions for Patients Treated with $^{90}$Y Ibritumomab Tiuxetan

<table>
<thead>
<tr>
<th>Time period</th>
<th>Recommended Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 d</td>
<td>Clean up spilled urine and dispose of any body fluid-contaminated material to prevent its being handled (e.g., flush down toilet)</td>
</tr>
<tr>
<td></td>
<td>Wash hands thoroughly after using toilet</td>
</tr>
<tr>
<td>7 d</td>
<td>Use condoms for sexual relations</td>
</tr>
</tbody>
</table>

NUREG-1556, Vol. 9
Default Values ($^{131}\text{I}$)

- Activity & dose rate limits based on $T_p$
  
  *Equation used in 1970 by NRCP (Report No. 37)*

  \[ TEDE = 34.6 \times \Gamma \times Q_0 \times T_p \times OF / r^2 \]

- Default values for $^{131}\text{I}$ (20 other radionuclides)
  
  **Activity:** 33 mCi (range for others: 2-790 mCi)
  
  **Dose rate @ 1 m:** 7 mrem/h (range for others: 0.5-58)

- NRC acknowledges conservatism ($T_p$ & OF = 0.25)
  
  Predicted dose will be overestimated

  $^{131}\text{I}$ therapy patients do not retain radioactivity for $T_p$
Patient Release

$^{131}$I

- $^{131}$I activity and dose rate limits given in **GUIDANCE** insufficient for adequate dose estimation & issuance of patient instructions

  Today, only reason to maintain activity or dose-rate based release limits is to preclude performing patient-specific dose calculation (recommended by NCRP in 1970)

- Dose to others governed by radionuclide distribution & rate of clearance

  Patient-specific approach provides more appropriate dose estimate
Patient-Specific Dose Calculation
ala NUREG-1556, Vol. 9

Bexxar: Activity → 33 - 161 mCi
TBRT → 50 - 129 h
DR$_{1m}$ → 4 - 24 mrem/h

Licensee may release patients with higher activity values (> 33 mCi and/or > 7 mrem/h) if use patient-specific factors:

1. Retained activity
2. OF < 0.25 at 1 m
3. Biological or effective half-life
4. Shielding by tissue (i.e., measured dose rate)
Steps to $^{131}$I Tositumomab Outpatient Use

1. Evaluate the patient’s living and working conditions
2. Determine dose to others and establish duration of precautions
3. Provide written instructions to the patient

Siegel et al. JNM 2002; 43:354-363
Step 1: Evaluate the patient’s living and working conditions

• Interview the patient to determine whether the patient’s living and working conditions are appropriate to permit patient release

• Factors to be considered for patient release include:
  - Patient’s ability and willingness to follow instructions
  - Patient’s ability to perform self-care and delay returning to work
  - Patient’s living arrangements
STEP 2A: Determine Dose to Others

For each patient,
- Total body clearance, RT (measured after dosimetric dose)
- Dose rate at 1 m, $\text{DR}_{1\text{m}}$ (measured after therapeutic dose)

Estimated Dose to Others

$\text{TEDE} = \text{Occupancy Factor} \times \text{Measured DR}_{1\text{m}} \times (8.95 + 0.99 \times \text{RT})$

If $\text{TEDE} < 5\text{mSv}$, patient can be released
STEP 2B: Establish Duration of Precautions

Use patient-specific measurements of RT and DR to determine precaution durations necessary to maintain dose to others below regulatory limit.
Step 3: Provide Instructions to Patient

Patients provided with written instructions regarding radiation safety guidelines to maintain dose to others as low as reasonably achievable; instructions specify how long precautions must be followed:

- Maintain appropriate distance from others
- Separate sleeping arrangements
- Discontinue breast-feeding

*Nuclear Medicine physician/RSO must be professionally satisfied that patient compliance with instructions highly likely*
Internal Contamination Risk

$^{131}$I Tositumomab

- Dose to other persons predominantly result of external exposure
- Contamination risk low with radioiodine

$10^{-6}$ intake ($7400 \text{ MBq} \rightarrow 0.1 \text{ mSv}$)

Even lower for $^{131}$I attached to antibody

$7400 \text{ MBq} \rightarrow$ factor of 5 less

Siegel and Rutar. RSO Mag. 2001; 6:19-23

- If patients and caregivers able to follow radiation precautions, doses rarely approach or exceed recommended dose limit
Radiation Dose to Others

$^{131}$I Tositumomab

- **Study Objective:** To determine the radiation doses received by maximally exposed members of public from patients who received Bexxar™

- **Method:** 26 family members of the 22 patients were provided with radiation monitoring devices (worn for 2 to 17 days). Patients received Bexxar™ 30-75 cGy (25-129 mCi).

- **Results:** The measured dose values ranged from 0.17 to 4.09 mSv (17 to 409 mrem)

- **Conclusion:** Patients can be released immediately with confidence that doses to other individuals should be below the 5 mSv (caregiver) limit

## Release Instructions for Patients Treated with $^{131}$I Tositumomab

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Mean time (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleeping in common bed (d=0.3 m)</td>
<td>7.8 (2.8 -14.6)</td>
</tr>
<tr>
<td>Travel for 4 h (d= 0.3 m)</td>
<td>0.3 (0 - 2.4)</td>
</tr>
<tr>
<td>Close contact with infant or pregnant woman (d=0.1m to limit exposure to 1 mSv)</td>
<td>8.1 (3.5 - 12.9)</td>
</tr>
<tr>
<td>Contact with others (&gt; 6 h @ 1m to limit exposure to 1 mSv)</td>
<td>4.3 (1.5 – 7.2)</td>
</tr>
</tbody>
</table>

Siegel et al. JNM 2002; 43:354-363
Radiation Doses to Health Care Workers: $^{131}$I Tositumomab

- Multicenter study conducted over 4.5 y at 4 institutions monitored a multidisciplinary group of 20 health care workers
  
  481 GBq of BEXXAR™ to 147 patients

- Workers received additional whole-body dose per month: 0 - 0.038 mSv attributable to scanning and 0.04 - 0.1 mSv during compounding and/or admin.

- Conclusion: BEXXAR™ can be prepared and administered safely, with little or no risk to health care personnel

Harwood JNM 2003; 44:327P
Conclusions

- Zevalin and Bexxar should be administered by physicians and other professionals qualified by training and experienced in the safe use and handling of radiopharmaceuticals

- Standard universal precautions for handling body fluids are recommended for health care workers, patients, and their family members

  **Zevalin precautions = Universal precautions**

- All Zevalin patients can be treated as outpatients

  Minimal paperwork; no records/instructions

Conclusions

- Essentially all Bexxar patients can be treated as outpatients
  - Simple to perform, less involved than for inpatient
  - Emotional benefits to patients and their families
  - Hospital personnel receive much lower dose
  - Lower health care costs

Disadvantage: certain individuals receive higher dose than if patient hospitalized longer; if patient given appropriate instructions, dose modest