Radioimmunotherapy in Non-Hodgkin’s Lymphoma with Tositumomab & I-131 Tositumomab

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Manager Medical Affairs
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The speaker has no conflict of interest which would affect this presentation.

Slides and Data Contributed by
Kathy Thomas
GlaxoSmithKline
Learning Objectives

Upon completion of this program, participants will be able to:

- Explain the benefits of establishing a comprehensive RIT program
- Describe the procedure for determining dosing for the Bexxar® therapeutic regimen using dosimetry calculations
- Describe the procedure for injection of the therapeutic dose of Bexxar®
- List three clinical safety considerations for the patient undergoing therapy
- List three technical safety considerations for the technologist administering therapy
Benefits of Establishing a Comprehensive RIT Program

A radioimmunotherapy program that offers the referring clinician a choice of approved protocols including:

- **Bexxar® Therapeutic Regimen**
  (Tositumomab & $^{131}$I Tositumomab)

- **Zevalin® Therapeutic Regimen**
  (Rituximab & $^{111}$In Ibritumomab Tiuxetan & $^{90}$Y Ibritumomab Tiuxetan)
Benefits of Establishing a Comprehensive RIT Program

Referral physician preference/requirements:

- Hematologists/Oncologists/Radiation Oncologists
- Preferences may be based on:
  - Tumor size/extent of disease
  - Comfort level with specific radionuclide or antibody
  - Patient response to previous antibody therapy
  - Education/training/continuing education
  - Patient request based on public reports
  - Perceived patient compliance with protocol
Bexxar® Therapy Rationale

- Anti-tumor monoclonal antibody (Tositumomab) against CD20 antigen:
  - Normal and malignant B-cell lymphocytes
  - >90% of B-cell NHLs

- Radiolabeled with I-131 (I-131 Tositumomab)

- Combination delivers a targeted therapeutic dose of radiation to CD20 positive B-lymphocytes

- Delivers radiation to neighboring tumor cells (crossfire effect)
Bexxar® Clinical Indications

Indicated for the treatment of patients with Non-Hodgkin Lymphoma (NHL), that is
- CD20 antigen-expressing,
- relapsed or refractory,
- low-grade,
- follicular,
- or transformed,
- including patients with rituximab-refractory NHL
Clinical Indications, cont.

- The effects of the Bexxar® therapeutic regimen on survival are not known.
- The Bexxar® therapeutic regimen is not indicated for the initial treatment of patients with CD20 positive non-Hodgkin’s lymphoma.
- The Bexxar® therapeutic regimen is intended as a single course of treatment.
Bexxar® is a product with a boxed warning

Serious hypersensitivity reactions, some with fatal outcome, have been reported

The majority of patients who received Bexxar® experienced prolonged and severe cytopenias

Bexxar® is pregnancy category X

Bexxar® should only be administered by health care professionals qualified by training in the safe use and handling of therapeutic radionuclides
Safety Overview for Bexxar® (cont'd)

- Bexxar® is contraindicated in patients with known hypersensitivity to murine proteins
- Bexxar® is contraindicated in pregnant women
- The biodistribution of Iodine I 131 Tositumomab should be assessed and if biodistribution is altered, the therapeutic dose should not be administered
Bexxar® Adverse Events

- Prolonged and severe cytopenias
- Hypersensitivity reactions, including anaphylaxis
  - Human Anti-Mouse Antibody (HAMA) reaction
  - Immunogenicity
- Infusional toxicities
- Gastrointestinal Symptoms
- Hypothyroidism
- Secondary leukemia, myelodysplastic syndrome (MDS) and secondary malignancies
Hematologic Toxicity
(N = 230)

- The most common hematologic adverse events were severe or life-threatening Grade 3 and 4 cytopenias, which occurred in 71% of patients
  - Neutropenia
  - Thrombocytopenia
  - Anemia
- Monitor blood counts weekly for 10-12 weeks following treatment
  - Time to nadir 4-7 weeks
  - Duration 30 days
## Hematologic Toxicity
*(N = 230)*

<table>
<thead>
<tr>
<th></th>
<th>Platelets</th>
<th>ANC</th>
<th>Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 3/4</strong>*</td>
<td>53%</td>
<td>63%</td>
<td>29%</td>
</tr>
<tr>
<td><strong>Median Duration Grade 3/4†</strong></td>
<td>32 days</td>
<td>31 days</td>
<td>23 days</td>
</tr>
<tr>
<td><strong>Grade 4‡</strong></td>
<td>21%</td>
<td>25%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Median Nadir</strong></td>
<td>43,000/mm³</td>
<td>690 cells/mm³</td>
<td>10 gm/dL</td>
</tr>
<tr>
<td><strong>Median Time to Nadir</strong></td>
<td>34 days</td>
<td>43 days</td>
<td>47 days</td>
</tr>
<tr>
<td><strong>Grade 3/4 Without Recovery to Grade 2</strong></td>
<td>7%</td>
<td>7%</td>
<td>5%</td>
</tr>
</tbody>
</table>

* Grade 3/4 toxicity was assumed if patient was missing 2 or more weeks of hematology data between Weeks 5 and 9.
† Duration of Grade 3/4 of 1000+ days (censored) was assumed for those patients with undocumented Grade 3/4 and no hematologic data on or after Week 9.
‡ Grade 4 toxicity was assumed if patient had documented Grade 3 toxicity and was missing 2 or more weeks of hematology data between Week 5 and Week 9.

Prescribing Information for BEXXAR, GlaxoSmithKline.
Hypersensitivity Reactions
(N = 230)

- During or following administration, 14 patients (6%) experienced 1 or more of the following adverse events: allergic reaction, face edema, injection site hypersensitivity, anaphylactic reaction, laryngismus, and serum sickness.

- Medications for the treatment of severe hypersensitivity should be available for immediate use in the event of allergic reactions (e.g., epinephrine, antihistamines, corticosteroids).

- The Bexxar® therapeutic regimen is contraindicated in patients with known hypersensitivity to murine proteins or any other component of the therapeutic regimen.

- Patients who have received murine proteins should be screened for HAMA prior to receiving Bexxar®.
Infusional Toxicity  
(N = 230)

- 29% of patients reported fever, rigors/chills, or sweating within 14 days following the dosimetric dose

- Adjustment of the rate of infusion to control adverse reactions occurred in 7% of patients and included temporary interruption of the infusion and reducing the rate by 50%

- The infusion was permanently discontinued in 2 patients

- Pretreatment with acetaminophen and antihistamine
  - Benefit of premedication in preventing infusion-related toxicity has not been evaluated
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 RN and/or physician at the time of infusion and followed, as necessary by nursing staff
The Bexxar® Therapeutic Regimen
Clinical Profile Summary

- In 2 key studies, Bexxar® has demonstrated efficacy in patients with CD20-positive relapsed or refractory follicular, low-grade, or transformed non-Hodgkin’s lymphoma:
  - Overall response rates: 47%-76%
  - Complete response rate: 20%-53%
  - Median duration of response: 12-41 months
  - Median duration of CR: 40 months-Not Reached Range: (4-47 months)
  - Median duration of follow-up = 26-30 months

40 NHL patients who failed rituximab therapy
  - 24 non-responders, 11 with response < 6 months, 5 with response ≥ 6 months
Median follow-up 54 months (range 1-119)
Overall response rate 72%; median duration 18.9 months
  - 40% continued response at 5 years
Estimate mean survival rate 6.7 years
No additional secondary leukemia beyond 5% reported in 2005 (2 of 40)

Poster presentation at ASH 2009

- 76 previously untreated follicular NHL patients, stage III and IV
- Median follow up 10 years (range 0.7-12.3 yrs)
- Overall response rate 97%; median duration 6 years
  - 75% complete remission
  - 40% progression free at 10 years

Poster presentation at ASH 2009
Why Use I-131 for RIT?

<table>
<thead>
<tr>
<th>Physical half-life (days)</th>
<th>Decay type</th>
<th>Particle energy (MeV)</th>
<th>Primary gamma energy (keV)</th>
<th>Particle pathlength ($\chi_{90}$, mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-131</td>
<td>$\beta, \gamma$</td>
<td>0.606</td>
<td>364</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Anti-tumor effect (Includes crossfire effect)

Dosimetry Calculation
Crossfire Effect

Naked antibody

Radiolabeled antibody
The Bexxar® Therapeutic Regimen

Treatment Schedule

Thyroprotection: Day -1 continuing through 14 days post therapeutic dose

Day 0

- Premedicate with acetaminophen and diphenhydramine*

**Dosimetric step**

- 450 mg Tositumomab (1-hr infusion)
- 5 mCi Iodine I 131
- Tositumomab (35 mg) (20-minute infusion)

- Dosimetric step used to calculate patient-specific activity and evaluate biodistribution

Day 7-14

- Premedicate with acetaminophen and diphenhydramine*

**Therapeutic step**

- 450 mg Tositumomab (1-hr infusion)
- mCi of Iodine I 131
tositumomab (35 mg) to deliver desired cGy TBD (20-minute infusion)

- Day 0
- Day 2, 3, or 4
- Day 6 or 7

- Administered activity (mCi) determined by gamma counts

*Benefit of premedication in preventing and/or reducing infusion-related toxicity has not been evaluated.

†Scans used for dosimetry and biodistribution evaluation.

If biodistribution is altered, the therapeutic dose should not be administered.

Prescribing Information for BEXXAR, GlaxoSmithKline.
Treatment Steps

- Concomitant Medication
- Infusion of Tositumomab
- Infusion of I-131 Tositumomab (5 mCi)
- Scan I-131 Tositumomab x 3
- Calculate therapeutic dose
- Infusion of Tositumomab
- Infusion of I-131 Tositumomab (x mCi)
Concomitant Medication

- **Oral thyroid-blocking agents: 15 days**
  Starting 24 hours prior to the dosimetric dose and continuing for 14 days after receiving the therapeutic dose
  - SSKI 4 drops orally 3 times/day
  - Lugol’s solution 20 drops orally 3 times/day
  - Potassium iodide tablets 130 mg orally once/day

- **Oral acetaminophen 650 mg and diphenhydramine 50 mg**
  - 30 minutes prior to administration of each of the Tositumomab doses
Concomitant Medication

- Emergency supplies, including medications for the treatment of hypersensitivity reactions should be available for immediate use in the event of an allergic reaction during administration
  - eg, epinephrine, antihistamines, and corticosteroids
Tositumomab Infusion
(For Dosimetric and Therapeutic Steps)

- Attach a primary IV infusion set to the 0.22-micron in-line filter set and the 100-mL bag of 0.9% NaCl.
- After priming the primary IV infusion set and IV filter set, connect the infusion bag containing 450 mg Tositumomab via a secondary IV infusion set.
Tositumomab Infusion, cont. (For Dosimetric and Therapeutic Steps)

- Infuse 50 mL of Tositumomab over 1 hour
- Monitor vital signs every 15 minutes
- Flush infusion system with 0.9% NaCl
Iodine I 131 Tositumomab Infusion
For Dosimetric and Therapeutic Steps

- Appropriate shielding should be used in the administration of the dosimetric and therapeutic dose
- Connect the extension set to the 3-way stopcock
- Connect the 50-mL bag of 0.9% NaCl to a secondary IV infusion set and connect the infusion set to the 3-way stopcock
- Prime the secondary IV set and extension set. Connect the extension set to a port in the primary IV set above the filter
Iodine I 131 Tositumomab Infusion, cont.  
For Dosimetric and Therapeutic Steps

- You must use the primary IV set and IV filter set that were used for the Tositumomab infusion. A change in filter may result in a loss of up to 7% of the Iodine I 131 Tositumomab dose.
- Attach syringe filled with the Iodine I 131 Tositumomab to the 3-way stopcock and place in the syringe pump.
- Set syringe pump to deliver entire Iodine I 131 Tositumomab dose over 20 minutes.
- Vitals every 15 min.
Iodine I 131 Tositumomab Infusion, cont.

For Dosimetric and Therapeutic Steps

- After infusion is complete, flush the extension set and the empty syringe with 0.9% NaCl from the 50-mL bag
- Disconnect the infusion setup and determine residual activity of the syringe and infusion set components by assaying in a dose calibrator
- Calculate and record the dose delivered to the patient by subtracting the residual activity in the syringe and infusion set components from the activity in the syringe prior to infusion
Notes on Residual Activity Measurement

- Required after each dosimetric and therapeutic dose infusion
- After flush of the “hot” dose, all infusion materials (infusion lines, filter, injection port, syringe, etc) must be measured for residual activity
- Place material in a glove or other impermeable material and measure in a dose calibrator (exercise caution to avoid contaminating the dose calibrator)
- More than 1 “dip” in the dose calibrator may be required to accommodate all materials – sum up all readings for total residual activity
- Residual activity information is entered on the Dosimetry Worksheets

Prescribing Information for BEXXAR, GlaxoSmithKline.
How to Manage Infusion-Related Reactions

- Infusional toxicities were managed by slowing and/or temporarily interrupting the infusion. Symptomatic management was required in more severe cases.

- **Mild to moderate reactions or events**
  - The infusion rate should be reduced by 50%.

- **Severe reactions or events**
  - Discontinue the infusion and provide supportive measures as directed by the physician.
  - After complete resolution of toxicity, infusion may be resumed with a 50% reduction in the rate.

Prescribing Information for BEXXAR, GlaxoSmithKline.
Why Use Cold Antibody?

- Occupy accessible non-tumor sites
  - circulating B cells
  - B cells in spleen
- Enhance penetration of radiolabeled monoclonal antibody in tumor
- Slower clearance of radiolabeled monoclonal antibody
Distribution of Effect of Unlabeled Antibody – I-131 Tositumomab

1 h post Iodine I 131 Tositumomab injection

Pre-dose

No pre-dose
Checklist: Equipment

- Dual/Single head gamma camera system
  - High energy collimator
- Infusion Pump
  - Must accommodate a 60 ml syringe and a 20 minute infusion time
  - Doses are 30 ml in 60 ml syringe
- Appropriate survey equipment to accurately detect gamma and beta emissions
- Dose Calibrator
Checklist: Supplies

- **Syringe Shields:**
  - Lead – $^{131}$I
  - For 60 ml syringe
- **Infusion Pump Shield**
  - Lead “cave”
- **Patient doses:**
  - dosimetry
  - therapy

- **Infusion Supplies:**
  - IV infusion sets with injection port
  - IV extension set
  - 50 ml, 100 ml, 250 ml 0.9% normal saline
  - .22 micron filter
  - Butterfly needle or angiocath
  - Gloves
  - Alcohol prep pads
  - 2 x 2 gauze pads
  - Paper/adhesive tape
  - Band-Aids
  - Absorbent pads
  - 3-Way stopcocks
Checklist: Injection

- Practice – Practice – Practice
  - Practice the infusion technique as a ‘dry run’ using saline.
  - Make sure all members of the team are familiar with line set-up, filter placement and pump operation.

- Choosing an injection site:
  - Never establish IV access distal to a site that has been used within the past 24 hours for a blood draw or IV infusion.
  - The distal vessel may connect to the proximal site resulting in leakage and infiltration at the proximal site.
A Note About Imaging

- Imaging is performed:
  - As a safety precaution to assess the biodistribution of the dosimetric dose
  - for dosimetry calculations for the therapeutic dose (I-131 Tositumomab only)

- Imaging is NOT performed:
  - To identify disease
Obtaining Bexxar®

- Available for in-house preparation or from commercial radiopharmacies

- Components ordered on a per-patient basis:
  - Order placed through GSK Specialty Service Center
    - Cold antibody x 2 (McKesson Bioservices)
    - $^{131}$I-Tositumomab – dx/rx (MDS Nordion)
  - Quality control performed at MDS Nordion prior to shipment
Calculating Patient Dose

- **$^{131}$I Tositumomab imaging dose**
  - 30 ml volume in a 60 ml syringe
  - containing **35 mg** Tositumomab AND
  - **5.0 mCi** I-131 Tositumomab

- **$^{131}$I Tositumomab therapy dose**
  - 30 ml volume in a 60 ml syringe
  - containing **35 mg** AND
  - and a calculated activity to deliver a total body dose
  - (TBD) based on **patient specific parameters**
Patient Specific Parameters

- Total Body Residence Time
- Platelet Count
  - TBD 75 cGy for platelets > 150K
  - TBD 65 cGy for platelets 100K-149K
Dosimetry in RIT

- Heterogeneity in patient handling of drugs is addressed by prospective dosimetry.

- A variation in radiation dose (mCi or MBq) from patient to patient is expected due to reactivity of antibody with CD20-positive B cells (in spleen and bone marrow) and varying volumes of CD20-positive tumors.

Administered vs Absorbed Dose

- **Administered Dose/Activity**
  - Activity (in mCi or MBq) of radioisotope injected as an immunoconjugate

- **Absorbed Dose**
  - Radiation delivered to the target (generally measured in cGy or Gy)

- **Dosimetry**
  - The process of relating an administered dose/activity to an absorbed dose
Dosimetry for I-131 Tositumomab

- Optimal therapeutic results achieved with a total body dose (TBD) of 75 cGy (65 cGy for patient with platelet counts between 100,000 and 150,000/mm³).

- Dosimetry studies confirm a 4-fold variation in clearance rate.

- Factors affecting clearance rate include:
  - Tumor size
  - Splenomegaly
  - Bone marrow involvement

- Administered activity (in mCi) must be adjusted individually to achieve prescribed Total Body Dose

Dosimetry for I-131-Tositumomab

- Patient-specific dosing, based on total body clearance
  - provided a consistent radiation dose
  - despite variable pharmacokinetics
  - allowed each patient’s dose to be adjusted for individual patient variables

- Patients with high tumor burden, splenomegaly, or bone marrow involvement were noted to have faster clearance, shorter terminal half-life, and larger volume of distribution
These images are for illustrative purposes only. They are intended to represent the concept of patient-specific dosing and are not derived from actual data.

Determining Total Body Residence Time

- Anterior/posterior whole body images acquired of:
  - I-131 calibrated source
  - Background
  - Patient
- Performed on:
  - Day 0: w/in 1 hour of dosimetric dose; pre-void
  - Day 2, 3, or 4: post-void
  - Day 6 or 7: post-void
- **Note**: Same camera, collimator and set-up must be used for each scanning session
Data Acquisition

$^{131}$I Tositumomab

- Single or dual-head gamma camera with a LFOV and digital interface
- Parallel hole, high energy collimator
- 364 keV with 20-25% window
- Whole body matrix (minimum 128x128)
- Scanning speed 10-30 cm/min
- Remove auto-contour
- Camera anterior height: consistent for all scans
Dose Range Required to Deliver 75cGy Total Body Radiation

*Targeted total body radiation dose 75cGy for patients with platelets 150,000/mm³ or 65cGy for patients with platelet counts between 100,000 and 150,000/mm³.

**BEXXAR® Therapeutic Regimen Worksheet #1 – Equipment Settings/Evaluation**

<table>
<thead>
<tr>
<th>DATE</th>
<th>VISIT 1 (Day 0)</th>
<th>VISIT 2 (Day 2, 3 or 4)</th>
<th>VISIT 3 (Day 6 or 7)</th>
</tr>
</thead>
</table>

**DOSE CALIBRATOR ACTIVITY**
- Time Measured
  - VISIT 1: 12:45
  - VISIT 2: 9:00
  - VISIT 3: 8:45
- Iodine-131 Source Activity ($A_s$) in $\mu$Ci
  - VISIT 1: 239.0
  - VISIT 2: 204.0
  - VISIT 3: 148.0

**GAMMA CAMERA SETTINGS**
- Camera Name: Siemens
- Energy Window Setting (20%-25%)
  - VISIT 1: 20%
  - VISIT 2: 20%
  - VISIT 3: 20%
- Collimator: Rated to 364keV
  - VISIT 1: ✔️
  - VISIT 2: ✔️
  - VISIT 3: ✔️
- Total Body Scan Speed (10-30 cm/min)
  - VISIT 1: 30
  - VISIT 2: 30
  - VISIT 3: 30
- Scan Length (cm)
  - VISIT 1: 200
  - VISIT 2: 200
  - VISIT 3: 200
- Camera Anterior Height above Table (cm)
  - VISIT 1: 30
  - VISIT 2: 30
  - VISIT 3: 30

**IODINE-131 SOURCE COUNTS (Anterior and Posterior)**
- Time Started
  - VISIT 1: 12:55
  - VISIT 2: 9:15
  - VISIT 3: 9:00
- Total Anterior Count ($C_{GA}$)
  - VISIT 1: 44853
  - VISIT 2: 39101
  - VISIT 3: 29405
- Total Posterior Count ($C_{GP}$)
  - VISIT 1: 42656
  - VISIT 2: 37544
  - VISIT 3: 28237

**BACKGROUND COUNTS (Anterior and Posterior)**
- Time Started
  - VISIT 1: 13:10
  - VISIT 2: 9:25
  - VISIT 3: 9:10
- Total Anterior Count ($C_{BA}$)
  - VISIT 1: 6844
  - VISIT 2: 6719
  - VISIT 3: 6816
- Total Posterior Count ($C_{BP}$)
  - VISIT 1: 6802
  - VISIT 2: 6865
  - VISIT 3: 6509

**CALCULATIONS**
1. Background Corrected Source Count
   \[ C_o = \sqrt{\left(\frac{C_{GA}}{C_{BA}}\right) \left(\frac{C_{GP}}{C_{BP}}\right)} \]
   - VISIT 1: 37019
   - VISIT 2: 31519
   - VISIT 3: 22154
2. Calibration Factor (counts per $\mu$Ci)
   \[ CF = \frac{C_o}{A_o} \]
   - VISIT 1: 155
   - VISIT 2: 155
   - VISIT 3: 150
### PATIENT IDENTIFICATION
- Last 4 digits of SS#: 1234
- Patient Initials: abc

### SITE INFORMATION
- Institution: Memorial Hospital
- Auth. Physician: Dr. Sam Jones
- Address: 545 Apple St
- Phone: 123-456-7890
- Fax: 123-456-7899
- e-mail: 

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### BEXXAR® Therapeutic Regimen Worksheet #2A – Determination of Iodine-131 Activity for the Therapeutic Dose of BEXXAR®

#### A. Dosimetric Dose Infusion
- Infusion Date: 10/14/2007
- Start Time (t_{\text{INF}}): 13:25
- End Time: 13:45

#### B. Determination of Activity Hours
- Patient gender: M
- Patient height: 186.7 cm
- Patient weight: 107.5 kg
- Patient max effective mass: 116.14 kg
- Is patient weight greater than the maximum effective mass? NO

- Yes - Maximum effective mass used to determine Activity Hours
- No - Patient's actual weight used to determine Activity Hours

Activity Hours: 11304

#### C. Determination of Total Body Dose (cGy)
- Baseline platelet Count: 183000
- Date: 10/14/2007
- Prescribed Total Body Dose
- 65 cGy (for platelet count of 100,000 to < 150,000 platelets/mm³)
- 75 cGy (for platelet count of >= 150,000 platelets/mm³)

\[ = 75 \text{ cGy} \]
Residual Activity Measurement

- Residual activity must be measured by a dose calibrator following the administration of the dosimetric and therapeutic doses.
- Residual activity values must be recorded and either e-mailed or faxed to the Specialty Service Center during Site Certification.
  - The actual administered activity of the dosimetric dose should be within 10% of the prescribed activity.
  - The actual administered activity of the therapeutic dose should be within 5% of the prescribed activity.
- GSK will contact sites to review administration techniques if greater variations occur.

### D. Calculation of Actual Administered Activity for Dosimetric Dose

<table>
<thead>
<tr>
<th>Measured Activity (Act_d) of Dose</th>
<th>5.180</th>
<th>xx</th>
<th>10/14/2007</th>
<th>11:10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to Administration Activity (mCi)</td>
<td>xx</td>
<td>Date</td>
<td>Time</td>
<td></td>
</tr>
<tr>
<td>Measured Residual Activity (Act_{DR}) After Administration</td>
<td>0.170</td>
<td>xx</td>
<td>10/14/2007</td>
<td>14:05</td>
</tr>
<tr>
<td>Activity (mCi)</td>
<td>Initials</td>
<td>Date</td>
<td>Time</td>
<td></td>
</tr>
</tbody>
</table>

Actual Administered Activity (Act_{DA})

\[
\text{Act}_{DA} = \frac{\text{Act}_D}{\text{Act}_{DR}}
\]

\[
\text{Act}_{DA} = \frac{5.180}{0.170} = 5.010
\]
### E. Determination of Residence Time (h) Using Total Body Gamma Camera Counts

**VISIT 1**
**Dosimetric Day**
**Day 0**
- **DATE:** 10/14/2007
- **SAME CAMERA AND ACQUISITION PARAMETERS AS WORKSHEET #1**
- **☑ Yes**

**GAMMA CAMERA COUNTS**
**PATIENT TOTAL BODY COUNTS (Anterior and Posterior)**
- Time Started ($t_0$)
  - **VISIT 1:** 13:58
  - **VISIT 2:** 9:45
  - **VISIT 3:** 9:20
- Total Anterior Count ($C_A$)
  - **VISIT 1:** 394413
  - **VISIT 2:** 248677
  - **VISIT 3:** 71453
- Total Posterior Count ($C_P$)
  - **VISIT 1:** 332808
  - **VISIT 2:** 201880
  - **VISIT 3:** 60322

**BACKGROUND COUNTS (Anterior and Posterior)**
- Time Started
  - **VISIT 1:** 13:10
  - **VISIT 2:** 9:25
  - **VISIT 3:** 9:10
- Total Anterior Count ($C_{BA}$)
  - **VISIT 1:** 6844
  - **VISIT 2:** 6719
  - **VISIT 3:** 6816
- Total Posterior Count ($C_{BP}$)
  - **VISIT 1:** 6802
  - **VISIT 2:** 6865
  - **VISIT 3:** 6509

**CALCULATIONS**
1. Background Corrected Patient Count
   \[ C = \sqrt{\left(\frac{C_A}{C_{BA}}\right) \times \left(\frac{C_P}{C_{BP}}\right)} \]
   - \[ C_1 = 355457 \]
   - \[ C_2 = 217222 \]
   - \[ C_3 = 58977 \]
2. Time from Start of Iodine-131 Tositumomab Infusion to Start of Patient Count
   \[ t_1 = t_0 - t_{INF} \]
   - \[ t_1 = 0.55 \]
   - \[ t_2 = 44.33 \]
   - \[ t_3 = 139.92 \]
3. Percent Injected Activity
   \[ \%IA = \left(\frac{C_2 \text{ or } C_3}{C_1}\right) \times 100 \]
   - \[ \%IA_1 = 100.0\% \]
   - \[ \%IA_2 = 61.1\% \]
   - \[ \%IA_3 = 16.6\% \]

**Date Recorded/Initials**
- **10/14/2007**
- **XX**
- **10/16/2007**
- **XX**
- **10/20/2007**
- **XX**

### F. Determination of Residence Time from Graph 1

**Total Body Residence Time (TBRT) = 79 hours**

**Unofficial Copy**

**Physician Signature**

**Date**
The estimated Iodine-131 Activity from Visits 1 and 2 must be communicated to the radiopharmacy no later than Day 4.

The radiopharmacy will contact the BEXXAR® Service Center for determination of whether a second vial will be required to prepare the appropriate therapeutic activity for the patient.
Graph to Estimate Total Body Residence Time

G. Estimated Iodine-131 Activity from Visits 1 and 2

\[ \text{TBRT}_{est} = \frac{t_2}{\ln(\%IA/100)} \]

\[ = \frac{44.3}{\ln(61.1/100)} = 90 \]

Iodine-131 Activity (mCi) = Activity Hours (mCi h) \times \text{Desired Total Body Dose (cGy)}

(Estimated)

\[
\begin{array}{ccc}
\text{Iodine-131 Activity (mCi)} & \text{Activity Hours (mCi h)} & \text{Desired Total Body Dose (cGy)} \\
\text{(Estimated)} & 11304 & 75 \\
& 90 & 75 \\
\end{array}
\]

\[ = 125.572 \text{ (mCi Est.)} \]

H. Prescribed Iodine-131 Activity

Iodine-131 Activity (mCi) = Activity Hours (mCi h) \times \text{Desired Total Body Dose (cGy)}

\[
\begin{array}{ccc}
\text{Iodine-131 Activity (mCi)} & \text{Activity Hours (mCi h)} & \text{Desired Total Body Dose (cGy)} \\
& 11304 & 75 \\
& 79 & 75 \\
\end{array}
\]

\[ = \frac{143.089}{(mCi)} \]
Expected Biodistribution

■ Post Injection:
  - Primarily blood pool activity
  - Liver/spleen < heart

■ 24-72hrs and 120-144 hrs:
  - ↓ Blood pool activity
  - ↓ Liver/Spleen activity
  - ↑ Tumor uptake
  - Possible uptake in thyroid, kidneys, urinary bladder and lung

■ Total body residence time
  50-150 hrs (median ~ 90 hrs)
Altered Biodistribution

First Image (shortly after dosimetric dose): 
- blood pool is not visualized (possible HAMA) 
- diffuse intense uptake in the liver and/or spleen 
- uptake suggestive of urinary obstruction 
- diffuse lung uptake > blood pool 

Second and third image: 
- uptake suggestive of urinary obstruction 
- diffuse lung uptake greater than blood pool 

Total body residence time outside the range of 50 - 150 hrs
Radiation Safety and Patient Release
10 CFR 35.75 permits health care providers (licensees) to authorize the release of any individual receiving radiopharmaceuticals or permanent implants containing radioactive materials if the total effective dose equivalent (TEDE) to any other individual is not likely to exceed 5 mSv (500 mrem).

Release of patients treated with Bexxar® is possible in 49 of the 50 states.
Patient Release

- Use standard I-131 patient release criteria
- Follow state or NRC guidance documents
- Provide written instructions to the patient
- Perform a patient-release calculation to determine if the patient can be released
- Maintain patient release records for a minimum of 3 years
- Consider the patient’s living/working conditions
- Urinary clearance is key consideration for Bexxar®
I-131 Patient Release Instructions

- Oral and written instructions given to patients must address ways to achieve ALARA principles to other individuals including:
  - Maintaining distance
  - Separate sleeping arrangements
  - Minimize time spent in public places
  - Precautions to reduce the spread of radioactive contamination including urine, and other body fluids
  - Length of time for each precaution
Radiation Safety for Nuclear Medicine

- 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
Handling and Administration

- **Time:**
  - Practice set-up
  - Test lines before handling hot dose

- **Distance:**
  - From patient while infusing and imaging
  - While imaging

- **Shielding:**
  - Syringe shield for high energy
  - Pump shielding available commercially
  - Double gloves
  - Personal protective clothing
Handling and Administration

- Spill management for drug or urine:
  - Follow I-131 guidelines as dictated by SOP and RSO

- Routes of contamination:
  - Skin
  - Eyes
  - Open wound
  - Inhalation
Therapy with Tositumomab and I-131-Tositumomab

- An effective treatment option for NHL patients (relapsed or refractory, low grade, follicular or transformed CD20+ B Cell NHL, or refractory to rituximab)
- High response rate and minimal adverse events (primarily hematologic, transient and reversible)
- Delivers targeted radiation directly to tumor with added crossfire effect
- Treatment completed in 7-14 days
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