Radioimmunotherapy in non-Hodgkin lymphomas

Andrei Iagaru, MD
Hodgkin vs. non-Hodgkin lymphomas

Nuclear Medicine Imaging in NHL

Radioimmunotherapy for NHL

Future directions
The American Cancer Society estimated 70,130 new cases of non-Hodgkin lymphoma (NHL) in the United States for 2012.

The estimated number of deaths for the same year was 18,940.
2012 Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Men 766,860</th>
<th>Women 678,060</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

2012 Estimated US Cancer Deaths*

Men 289,550
- Lung & bronchus 29%
- Colon & rectum 9%
- Prostate 9%
- Pancreas 6%
- Leukemia 5%
- Liver & bile duct 4%
- Esophagus 4%
- Non-Hodgkin lymphoma 4%
- Urinary bladder 3%
- Kidney 3%

Women 270,100
- Lung & bronchus 26%
- Breast 14%
- Colon & rectum 9%
- Pancreas 7%
- Ovary 6%
- Leukemia 4%
- Non-Hodgkin lymphoma 3%
- Uterine corpus 3%
- Liver and bile duct 2%
- Brain/ONS 2%

<table>
<thead>
<tr>
<th></th>
<th>Hodgkin</th>
<th>Non-Hodgkin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell of origin:</strong></td>
<td>B Lymphocyte</td>
<td>B Lymphocyte T Lymphocyte NK cell</td>
</tr>
<tr>
<td><strong>Spread:</strong></td>
<td>Contiguous</td>
<td>Non-contiguous</td>
</tr>
<tr>
<td><strong>Age Distribution:</strong></td>
<td>Bi-modal</td>
<td>50 % &gt; 60 years</td>
</tr>
<tr>
<td><strong>Basis of treatment:</strong></td>
<td>Mostly Stage</td>
<td>Mostly Subtype</td>
</tr>
<tr>
<td><strong>Prognosis:</strong></td>
<td>&gt; 80% OS</td>
<td>&lt; 50% OS</td>
</tr>
</tbody>
</table>
Hodgkin Disease

Sir Thomas Hodgkin
1798-1866

First to describe lymphoma as “a non-infectious disease of the lymph gland and spleen” in 1832.
Epidemiology

- 15% of lymphomas
- Most common malignancy in young adults
- 20,000 new cases annually in N. America and Europe
### NHL - WHO Classification 2001

**B-cell (85%)**

*Indolent*
- CLL/SLL
- LPL/immunocytoma/WM
- Hairy cell leukemia
- Splenic marginal zone lymphoma
- Marginal zone lymphoma (MALT-B cell
  - lymphoma, nodal (monocytoid))
- Follicular, small cell, grade 1
- Follicular, mixed small and large cell, grade 2

*Aggressive*
- Prolymphocytic lymphoma
- Plasmacytoma/MM
- Mantle cell lymphoma
- Follicular, large cell, grade 3
- Diffuse large B-cell (including immunoblastic
  - and diffuse large and centroblastic)
- Primary mediastinal large B-cell lymphoma
- High-grade B-cell lymphoma, Burkitt-like

*Very aggressive*
- Precursor B-lymphoblastic lymphoma
  - lymphoma/leukemia
- Burkitt’s lymphoma/B-cell acute leukemia

**Peripheral T & NK cell (15%)**

*Indolent*
- Large granular lymphocytic leukemia,
  - T and NK cell types
- Mycosis fungoides/Sezari syndrome
- Smoldering and chronic adult T-cell
  - leukemia/lymphoma (HTLV-1)

*Aggressive*
- Prolymphocytic leukemia
- Peripheral T-cell lymphoma, unspecified
- AITL
- Angiocentric lymphoma
- Intestinal T-cell lymphoma
- Anaplastic large cell lymphoma (T & null cell type)

*Very aggressive*
- Precursor T-lymphoblastic
- Adult T-cell lymphoma/leukemia
Most Common Subtypes: NHL WHO Classification 2001

- Diffuse Large Cell: 31%
- Follicular: 22%
- B cell: 85%
- T cell: 15%
- All Other: 12%
- Discordant: 12%
- MALT: 5%
- Peripheral T cell: 6%
- Mantle cell: 6%
- SLL: 6%
Indolent Lymphoma: When to Treat

✓ Symptoms of disease
  ➢ cytopenias, pain, SOB
✓ Tumor burden
  ➢ > 3 LNs larger than 3 cm or a single mass > 7cm
✓ Impending involvement of critical organ
✓ Steady progression during a period of observation
✓ Evidence of histologic transformation
  ➢ rapid progression, elevated LDH, histologic proof
✓ Patient preference
Rituximab
(Rituxan®, MabThera®)

- 1st FDA-approved monoclonal Ab for cancer (1997)
- Relapsed/refractory follicular or transformed CD20+ NHL
- Chimeric (long half-life)
- ~50% ORR (pivotal trial)
  - most were PRs
  - duration 13+ months

CD20
rituximab

B cell
Indolent Lymphoma: Initial Therapy if Required

- Radiation Therapy (localized disease, palliation)
- Single agent Rituximab (low tumor burden)
- Combination chemotherapy immunotherapy
  - R-CVP (cyclophosphamide, vincristine, prednisone)
  - R-FND (fludarabine, mitoxantrone, dexamethasone)
  - R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
**Aggressive NHL: International Prognostic Index (IPI)**

**Prognostic Factors (APLES)**
- **Age** > 60 years
- **Performance status** > 1
- **LDH** > 1 x normal
- **Extranodal sites** > 1
- **Stage III or IV**

<table>
<thead>
<tr>
<th># Factors</th>
<th>Risk</th>
<th>5 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>Low</td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td>Low-int</td>
<td>51%</td>
</tr>
<tr>
<td>3</td>
<td>High-int</td>
<td>43%</td>
</tr>
<tr>
<td>4-5</td>
<td>High</td>
<td>26%</td>
</tr>
</tbody>
</table>

Shipp et. al., NEJM, 1993
R-CHOP: Overall Survival
18-month Median Follow-up

Survival

p=0.02

Years

R-CHOP
CHOP
- Hodgkin vs. Non-Hodgkin Lymphomas
- *Nuclear Medicine Imaging in NHL*
- Radioimmunotherapy for NHL
- Future directions
Imaging Patients with NHL

- Diagnostic imaging plays a major role in the evaluation of patients with NHL

- Imaging modalities include radiography, computed tomography, bone scintigraphy and PET
Diffuse Large B-Cell Lymphoma

**PRE RT EVALUATION**

- Complete response \(^r\) (PET negative)
- Partial response \(r,s\) (PET positive)
- No response or progressive disease \(r\)

**FOLLOW-UP THERAPY**

- Complete planned course of treatment \(t\)
- Complete course of therapy with higher RT dose \(m,t\)
- High dose therapy with autologous stem cell rescue \(\pm RT\)
- Pre- or post-transplant
- Clinical trial (may include allogeneic stem cell transplant \(\pm RT\)
- Pre- or post-transplant)

**END OF TREATMENT RESTAGING**

- At completion of treatment, repeat all positive studies. \(^t\) If PET-CT scan positive, rebiopsy before changing course of treatment.

**INITIAL RESPONSE**

- Complete response \(r,v\)
- Partial response \(r\)
- No response or progressive disease \(r\)

**FOLLOW-UP**

- Clinical
  - H&P and labs, every 3-6 mo for 5 y and then yearly or as clinically indicated
  - Imaging
    - CT scan no more often than every 6 mo for 2 y after completion of treatment, then only as clinically indicated

- Relapse, see Relapse or Refractory Disease (BCEL-6)
### Non-Hodgkin’s Lymphomas

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Nodal Masses</th>
<th>Spleen, Liver</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all evidence of disease</td>
<td>(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT</td>
<td>Not palpable, nodules disappeared</td>
<td>Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative</td>
</tr>
<tr>
<td>PR</td>
<td>Regression of measurable disease and no new sites</td>
<td>≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT</td>
<td>≥ 50% decrease in SPD of nodules(for single nodule in greatest transverse diameter); no increase in size of liver or spleen</td>
<td>Irrelevant if positive prior to therapy; cell type should be specified</td>
</tr>
<tr>
<td>SD</td>
<td>Failure to attain CR/PR or PD</td>
<td>(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsed disease or PD</td>
<td>Any new lesion or increase by ≥ 50% of previously involved sites from nadir</td>
<td>Appearance of a new lesion(s) &gt; 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node &gt; 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy</td>
<td>&gt; 50% increase from nadir in the SPD of any previous lesions</td>
<td>New or recurrent involvement</td>
</tr>
</tbody>
</table>
# Recommendations on the Use of $^{18}$F-FDG PET in Oncology

James W. Fletcher$^1$, Benjamin Djulbegovic$^2$, Heloisa P. Soares$^2$, Barry A. Siegel$^3$, Val J. Lowe$^4$, Gary H. Lyman$^5$, R. Edward Coleman$^5$, Richard Wahl$^6$, John Christopher Paschold$^7$, Norbert Avril$^8$, Lawrence H. Einhorn$^1$, W. Warren Suh$^9$, David Samson$^{10}$, Dominique Delbeke$^{11}$, Mark Gorman$^{12}$, and Anthony F. Shields$^{13}$

## TABLE 6
Summary of Recommendations

<table>
<thead>
<tr>
<th>Disease</th>
<th>Objective</th>
<th>Recommended?</th>
<th>Net benefits?</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td>No*</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Staging</td>
<td>General staging</td>
<td>Suggested</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Bone marrow staging</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Recurrence$^+$</td>
<td>Yes, for HD and NHL after completion of initial treatment</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>No, for general follow-up of asymptomatic HD or NHL</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Synthesis of research data has not been performed.
18F-FDG-PET/CT evaluation of response to treatment in lymphoma: when is the optimal time for the first re-evaluation scan?

Andrei Iagaru¹, Yingbing Wang¹, Carina Mari², Andrew Quon¹, Michael L Goris¹, Sandra Horning³, Sanjiv Sam Gambhir¹

Hell J Nucl Med. 2008 Sep-Dec;11(3):153-6
75 year-old man with NHL. Pre-therapy FDG PET/CT shows extensive abdominal disease. PET/CT after 2 cycles of chemotherapy indicates partial metabolic response to R-CHOP therapy. At the end of therapy the scan remains positive.
19 year-old man with HD. Pre-therapy FDG PET/CT shows extensive disease involvement. PET/CT after 4 cycles of chemotherapy indicates complete metabolic response to Stanford V therapy. The scan at the end of therapy remained negative.
66 year-old man with NHL. Pre-therapy FDG PET/CT shows abdominal disease. PET/CT after 4 cycles of chemotherapy indicates partial metabolic response to R-CHOP therapy. At the end of therapy the scan is negative.
The ΔSUV from baseline to first PET/CT was 67.6% (range: 3.2 - 92.3%) in group A and 75.1% (range: 46.6 - 89.6%) in group B (P value: 0.31; F<F critical)

The ΔSUV from baseline to post-therapy PET/CT was 72.9% (range: 11.9 - 94.4%) in group A and 79.8% (range: 53.4-89.9%) in group B (P value: 0.24; F<F critical)
- Hodgkin vs. Non-Hodgkin Lymphomas
- Nuclear Medicine Imaging in NHL
- Radioimmunotherapy for NHL
- Future directions
<table>
<thead>
<tr>
<th></th>
<th>Bexxar®</th>
<th>Zevalin®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-emitter</strong></td>
<td>$^{131}$I (half life: 8.01 days)</td>
<td>$^{90}$Y (half life: 2.67 days)</td>
</tr>
<tr>
<td><strong>Anti-CD20 antibody</strong></td>
<td>Tositumomab</td>
<td>Ibritumomab Tiuxetan</td>
</tr>
<tr>
<td><strong>Antibody type</strong></td>
<td>Monoclonal murine</td>
<td>Monoclonal murine</td>
</tr>
<tr>
<td><strong>Pre-dose injection</strong></td>
<td>Unlabeled Tositumomab</td>
<td>Unlabeled Rituximab</td>
</tr>
<tr>
<td><strong>Pre-therapy imaging</strong></td>
<td>Yes (for dosimetry)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Pre-therapy dose</strong></td>
<td>$^{131}$I-Tositumomab (5 mCi)</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment dose</strong></td>
<td>75 cGy (whole-body)</td>
<td>0.4 mCi/kg (up to 32 mCi)</td>
</tr>
</tbody>
</table>
Radioimmunotherapy for NHL

- **Ibritumomab** (murine antibody parent of Rituximab)
- **Tiuxetan** (MX-DTPA) conjugated to antibody forming strong urea-type bond

**CD20 antigen**
- Expressed only on B lineage cells
- Does not shed, internalize or modulate

**Yttrium-90**
- $T_{1/2} = 64$ hours
- Outpatient administration
- Beta emission $\chi_{90} = 5$ mm

**90Y Zevalin**
- Ibritumomab (murine antibody parent of Rituximab)
- Tiuxetan (MX-DTPA) conjugated to antibody forming strong urea-type bond
- Stable retention of $^{90}$Y
Protocol

**Imaging dose**
- Rituximab 250 mg/m²
- \( {^{131}I}\)-Tositumomab (5 mCi)

**Therapeutic dose**
- Rituximab 250 mg/m²
- \(^{90}Y\) Zevalin 0.4mCi/kg or
- \( {^{131}I}\)-Bexxar (75 cGy)
NO Rituximab 250 mg/m²

Rituximab 250 mg/m²

Courtesy of Dr Goris
NO Rituximab 250 mg/m²

Rituximab 250 mg/m²

Courtesy of Dr Goris
Scheduling Overview

- Receive call / consult from oncologist
- 5 things have to be scheduled together!
  - Physician schedule
  - Patient schedule
  - Infusion Center schedule
  - Nuclear Medicine Clinic schedule
  - Radiopharmacy schedule
Diagnostic Dose Infusion
Imaging: Dosimetry and Biodistribution

Visit 1: Day 0
Visit 2: Day 2,3,4
Visit 3: Day 6,7
Bexxar® vs. Zevalin®

✓ $^{131}$I-tositumomab
✓ Cold infusion of tositumomab
✓ Imaging for dosimetry and biodistribution
✓ Interval imaging
  ▪ 1st: Day 0
  ▪ 2nd: Day 2,3,4
  ▪ 3rd: Day 6,7
✓ Requires thyroid blocking with SSKI or Pl pills

✓ $^{90}$Y ibritumomab
✓ Cold infusion of rituximab
✓ Imaging for biodistribution not required anymore
✓ Fewer special radiation safety precautions
### BEXXAR® Therapeutic Regimen Worksheet #1 - Equipment Settings Evaluation

**DATE**
- VISIT 1 (Day 6): 11/19/2008
- VISIT 2 (Day 2, 3 or 4): 11/21/2008
- VISIT 3 (Day 8 or 7): 11/24/2008

### DOSE CALIBRATOR ACTIVITY
- Time Measured
  - Visits 1: 10.18
  - Visits 2: 8.30
  - Visits 3: 4.70
- Indium-111 Source Activity (A) in μCi
  - Visits 1: 55.7
  - Visits 2: 47.0

### GAMMA CAMERA SETTINGS
- Camera Name: Infinia
- Energy Window Setting (20%-25%)
  - Visits 1: 20%
  - Visits 2: 20%
  - Visits 3: 20%
- Collimator: Rated to 384KEV
- Total Body Scan Speed (10-30 cm/min)
  - Visits 1: 15
  - Visits 2: 15
  - Visits 3: 15
- Scan Length (cm)
  - Visits 1: 195
  - Visits 2: 195
  - Visits 3: 195
- Camera Anterior Height above Table (cm)
  - Visits 1: 34
  - Visits 2: 34
  - Visits 3: 34

### SOURCE COUNTS (Anterior and Posterior)
- **TOTAL COUNTS**
  - **Immediately After Injection**
    - Anterior: 8.15
    - Posterior: 8.40
  - **24 Hours After Injection**
    - Anterior: 22661
    - Posterior: 23453
  - **72 Hours After Injection**
    - Anterior: 17692
    - Posterior: 24934

### BACKGROUND COUNTS (Anterior and Posterior)
- **TOTAL COUNTS**
  - **Immediately After Injection**
    - Anterior: 7.50
    - Posterior: 8.20
  - **24 Hours After Injection**
    - Anterior: 10996
    - Posterior: 10954
  - **72 Hours After Injection**
    - Anterior: 11763
    - Posterior: 11845

### CALCULATIONS
1. Background Corrected Source Count
   - 
   - 
2. Calibration Factor (counts per μCi)
   - CF = C_{24h}/A_{24h}
   - CF = 267/271

### RESIDENCE TIME GRAPH
- Graph to Estimate Total Body Residence Time

#### G. Estimated Indium-111 Activity from Visits 1 and 2

\[ \text{TBRT}_{24h} = \frac{t_2}{\ln(S/100)} = \frac{42.7}{\ln(688/100)} = 114 \]

- Indium-111 Activity (mCi) = Activity Hours (mCi/ h) × Desired Total Body Dose (cGy)
- Indium-111 Activity (mCi) = Activity Hours (mCi/ h) × Desired Total Body Dose (cGy)

#### II. Prescribed Indium-111 Activity

\[ \text{Indium-111 Activity (mCi)} = \frac{\text{Activity Hours (mCi/ h) \times Desired Total Body Dose (cGy)}}{75} \]

- Indium-111 Activity (mCi) = Activity Hours (mCi/ h) × Desired Total Body Dose (cGy)

### DATE AND TIME OF PLANNED ADMINISTRATION:
- Date/Time After completing this section, fax worksheets 1, 2A and 2B to the BEXXAR Service Center at (215) 751-5725 for dose verification (until certification process is completed). Provide prescrd activity to radiopharmacy for dose preparation.

### I. Calculation of Actual Administered Activity for Therapeutic Dose

- Measured Activity (Act_{me}) of Dose
- Prior to Administration
- Measured Residual Activity (Act_{res})
- After Administration

\[ \text{Actual Administered Activity (Act_{TA})} = \text{Act}_{me} - \text{Act}_{res} \]

### Instructions
- Fax this worksheet to the BEXXAR Service Center after completing scan 3 at (215) 751-5725 (until certification process is complete).

### References
- BEXXAR® Therapeutic Regimen Worksheet #1 - Equipment Settings Evaluation.
38 patients were treated with RIT for NHL (20 received Zevalin®; 18 received Bexxar®).
The 12-week ORR for all patients was 47% and the CR rate was 13%.
The 12-week ORR did not significantly differ between the Zevalin® and Bexxar® groups.
Grade 3 or 4 thrombocytopenia occurred in 57% and 56% of patients treated with Zevalin® and Bexxar®, respectively.
Grade 3 or 4 neutropenia was observed in 57% and 50% of patients treated with Zevalin® and Bexxar®, respectively.
14/30 patients (47%) had response at 12 wk after RIT: 4 had CR (13%) and 10 had PR (33%). Cumulative OS was significantly longer for patients who responded to RIT at 12 wk than for those who did not ($P \leq 0.05$).

Overall survival did not significantly differ between patients who Zevalin® and those who received Bexxar®.


Retrospective review (Jan 2000 – Dec 2008) of 71 patients with NHL, who were treated with Bexxar® (35 patients, group A) or Zevalin® (36 patients, group B) for refractory/relapsed disease

- Group A included 18 men and 17 women, 35-81 year old (average: 59.9 ± 12.7)
- Group B included 27 men and 9 women, 36-85 year old (average: 55.4 ± 13.8)
60 year-old woman with NHL and complete response after \(^{90}\)Y-Ibritumomab Tiuxetan (Zevalin\textsuperscript{®}) treatment. A) pre-therapy (1 month) \(^{18}\)F FDG PET shows cervical, axillary, abdominal, pelvic and inguinal lesions (arrowheads); B) \(^{18}\)F FDG PET after therapy (3 months) is negative for active disease.

65 year-old woman with NHL and complete response after \(^{131}\)I-Tositumomab (Bexxar\textsuperscript{®}) treatment. A) pre-therapy (1 month) \(^{18}\)F FDG PET shows abdominal lesions (arrowheads); B) \(^{18}\)F FDG PET after therapy (3 months) is negative for active disease.
57 year-old man with NHL and stable disease after Zevalin® treatment. MIP images of $^{18}$F FDG PET scans before (A) and after (B) treatment (3 months apart) show no changes of the lesions noted prior to therapy.
45 year-old man with NHL and progressive disease after Zevalin® treatment. MIP images of $^{18}$F FDG PET scans before (A) and after (B) treatment (3 months apart) show progression of the lesions noted prior to therapy.
# Observed Response Rates in Patients Treated with Bexxar® vs. Zevalin®

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Bexxar®</th>
<th>Zevalin®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective responses</td>
<td>24/35 (68.6%)</td>
<td>28/36 (77.8%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>12/35 (34.3%)</td>
<td>15/36 (41.7%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>8/35 (22.8%)</td>
<td>9/36 (25%)</td>
</tr>
<tr>
<td>Mixed response</td>
<td>4/35 (11.4%)</td>
<td>4/36 (11.1%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6/35 (17.1%)</td>
<td>4/36 (11.1%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>5/35 (14.3%)</td>
<td>4/36 (11.1%)</td>
</tr>
</tbody>
</table>
## Observed Toxicity Rates in Patients Treated with Bexxar® vs. Zevalin®

<table>
<thead>
<tr>
<th></th>
<th>Bexxar®</th>
<th>Zevalin®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelets</strong>*</td>
<td>36.9% ± 0.33</td>
<td>52.6% ± 0.32</td>
</tr>
<tr>
<td><strong>Lymphocites</strong>*</td>
<td>27.8% ± 0.27</td>
<td>34.2% ± 0.38</td>
</tr>
<tr>
<td><strong>Hemoglobin</strong>*</td>
<td>4.9% ± 0.15</td>
<td>7.6% ± 0.11</td>
</tr>
<tr>
<td><strong>Grade III/IV toxicity</strong></td>
<td>16/35 (45.7%)</td>
<td>22/36 (61.1%)</td>
</tr>
</tbody>
</table>

- Grade III and IV hematological toxicity was reversible

*Average decreases at post-therapy nadir*
90Y-Ibritumomab Therapy in Refractory Non-Hodgkin’s Lymphoma: Observations from 111In-Ibritumomab Pretreatment Imaging

Andrei Iagaru¹, Sanjiv Sam Gambhir², and Michael L. Goris³
Retrospective study (Jan 2000 – Jul 2006) of 31 patients with NHL, who were treated with Zevalin® for refractory / relapsed disease.

This cohort consisted of follicular (15), mantle cell (8), diffuse large B-cell (6), marginal zone (1) and immunoblastic (1) disease subtypes.

The group included 23 men and 8 women, with age range of 36 - 85 years (average: 56.9±13.3).

The administered therapeutic doses of Zevalin® ranged 17-34 mCi (average: 28.5 ± 4.45).
75 year-old man with NHL and complete response after Zevalin treatment. No lesions are seen on the pre-therapy $^{111}$In-Ibritumomab scan. FDG PET shows resolution of the lesions noted prior to therapy.
36 year-old woman with NHL and complete response after Zevalin treatment. Lesions are seen in the axillary and inguinal regions on the pre-therapy $^{111}$In-Ibritumomab scan. FDG PET shows resolution of the lesions noted prior to therapy.
60 year-old woman with NHL and complete response after Zevalin treatment. No lesions are seen on the pre-therapy $^{111}$In-Ibritumomab scan. FDG PET shows resolution of the lesions noted prior to therapy.
57 year-old man with NHL and stable disease after Zevalin treatment. Lesions are seen in the inguinal region on the pre-therapy $^{111}$In-Ibritumomab scan. FDG PET scans (3 months apart) show no changes of the lesions noted prior to therapy.
45 year-old man with NHL and progressive disease after Zevalin treatment. Lesions are seen in the abdominal region on the pre-therapy $^{111}$In-Ibritumomab scan. FDG PET scans (3 months apart) show progression of the lesions noted prior to therapy.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>111In-Zevalin positive scan</th>
<th>111In-Zevalin negative scan</th>
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<tbody>
<tr>
<td>Complete Response (9/28)</td>
<td>2 pts</td>
<td>7 pts</td>
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<tr>
<td>Partial Response (8/28)</td>
<td>7 pts</td>
<td>1 pt</td>
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<td>Mixed Response (4/28)</td>
<td>4 pts</td>
<td>0 pts</td>
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<tr>
<td>No Change (4/28)</td>
<td>3 pts</td>
<td>1 pt</td>
</tr>
<tr>
<td>Progressive Disease (3/28)</td>
<td>3 pts</td>
<td>0 pts</td>
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</tbody>
</table>
Hodgkin vs. Non-Hodgkin Lymphomas

Nuclear Medicine Imaging in NHL

Radioimmunotherapy for NHL

Future directions
Radio-chelated monoclonal antibodies labeled with relatively long half-life positron emitters $^{64}$Cu (12 hours) and $^{124}$I (4 days), which target tumor-specific antigens such as the CD-20 present on the surface of B-cells.

The anti-CD20 monoclonal antibodies used for NHL therapy can potentially be used for imaging if labeled with a positron emitter.

Perk and colleagues labeled Zevalin® with $^{89}$Zr and reported the first use in a human subject.
HO₂C-\text{N}⁻\text{N}⁻\text{N}⁻\text{CO}_₂\text{H} + \text{NH}_₂-\text{Rituximab}

1 hour \rightarrow \text{pH 7.35}

\text{HO₂C-}\text{N}⁻\text{N}⁻\text{N}⁻\text{CO}_₂\text{H}

\text{HO₂C-}\text{N}⁻\text{N}⁻\text{N}⁻\text{CO}_₂\text{H} + \text{NH}_₂-\text{Rituximab}

\text{HO₂C-}\text{N}⁻\text{N}⁻\text{N}⁻\text{CO}_₂\text{H} + \text{NH}_₂-\text{Rituximab}

\text{HO₂C-}\text{N}⁻\text{N}⁻\text{N}⁻\text{CO}_₂\text{H} + \text{NH}_₂-\text{Rituximab}

\text{64CuCl}_2

\text{pH 6.30}

45°C, 1 hour

\text{HO₂C-}\text{N}⁻\text{N}⁻\text{N}⁻\text{CO}_₂\text{H} + \text{NH}_₂-\text{Rituximab}
Transverse view

Coronal View

15.6% ID/g

Spleen

Without pre-dosing

With pre-dosing (2 ug/kg)
Positron Emission Tomography of $^{64}$Cu-DOTA-Rituximab in a Transgenic Mouse Model Expressing Human CD20 for Clinical Translation to Image NHL

Arutselvan Natarajan,¹ Gayatri Gowrishankar,¹ Carsten H. Nielsen,¹ Sen Wang,¹ Andrei Iagaru,¹ Michael L. Goris,² Sanjiv Sam Gambhir²,³,⁴
- Results of larger phase III trials currently underway will become available

- Better patient education and outreach to the community (support/advocacy groups)

- Engage medical oncologists and radiation oncologists in the practice of RIT

- Introduction of novel radiolabeled antibodies for targeted NHL therapy
Charges* for Bexxar®/Zevalin® vs. R-CHOP

<table>
<thead>
<tr>
<th>Bexxar®/Zevalin®</th>
<th>R-CHOP (6 cycles)</th>
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* Stanford University Medical Center pharmacy, 05/22/2009
Follicular Lymphoma (grade 1-2)

SUGGESTED TREATMENT REGIMENS

First-line Therapy
- Bendamustine + rituximab
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)
- RFND (rituximab, fludarabine, mitoxantrone, dexamethasone) (category 2B)
- Radioimmunotherapy (category 3)
- Rituximab

First-line Therapy for Elderly or Infirm (if none of the above are expected to be tolerable in the opinion of treating physician)
- Radioimmunotherapy
- Rituximab (preferred)
- Single agent alkylators (eg, chlorambucil or cyclophosphamide) + rituximab

For patients with locally bulky or symptomatic disease, consider IFRT 4-30 Gy ± additional systemic therapy.

First-line Consolidation or Extended Dosing (optional)
- Chemotherapy followed by radioimmunotherapy (category 1)
- Rituximab maintenance 375 mg/m² one dose every 8 wk up to 2 y for patients initially presenting with high tumor burden (category 1)

Second-line and Subsequent Therapy
- BVR (bendamustine, bortezomib, rituximab)
- Chemotherapy (as in first-line therapy)
- FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) (category 1)
- Fludarabine + rituximab
- Radioimmunotherapy (category 1)
- See Second-line Therapy for DLBCL (BCEL-C 1 of 3)

Second-line Consolidation or Extended Dosing
- High dose therapy with autologous stem cell rescue
- Allogeneic stem cell transplant for highly selected patients
- Rituximab maintenance 375 mg/m² one dose every 12 weeks for 2 years (category 1) (optional)

See Monoclonal Antibody Directed at CD20 and Viral Reactivation (NHODG-D)
Radioimmunotherapy in follicular lymphoma: Some like it hot...

Marie José Kersten

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THANK YOU!

http://nuclearmedicine.stanford.edu

http://mips.stanford.edu