Treatment Approach to Indolent Non-Hodgkin’s Lymphoma

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University of Virginia Health System
Charlottesville, VA
Overview

♦ Epidemiology
♦ Classification
♦ Staging
♦ Treatment
Non-Hodgkin’s Lymphoma (NHL): Epidemiology (US)

Estimated annual incidence

- Non-Hodgkin’s Lymphoma (NHL):
  - Epidemiology (US)

~4% compound annual increase in incidence

Adapted from Greenlee et al. CA Cancer J Clin. 2001;5:15.

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**Estimated New Cancer Cases**: 10 Leading Sites, by Sex, United States, 2003

<table>
<thead>
<tr>
<th>Sex</th>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Prostate</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>Lung &amp; bronchus</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Colon &amp; rectum</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Urinary bladder</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Melanoma of skin</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Non-Hodgkin’s lymphoma</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Oral cavity</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Leukemia</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>All other sites</td>
<td>17%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Female</th>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32% Breast</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12% Lung &amp; bronchus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11% Colon &amp; rectum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6% Uterine corpus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4% Ovary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4% Non-Hodgkin’s lymphoma</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>3% Melanoma of skin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3% Thyroid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2% Pancreas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2% Urinary bladder</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20% All other sites</td>
<td></td>
</tr>
</tbody>
</table>

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.


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Incidence of NHL Is Increasing, Especially in the Elderly (>60 Years)

Etiologic Factors in NHL

- **Viral** - EBV, HTLV-1, Hepatitis C
- **Bacterial** - Helicobacter pylori
- **Immunodeficiency**
  - Congenital: Ataxia telangiectasia, Wiskott-Aldrich, SCID
  - Acquired: AIDS, organ transplant, aging, autoimmune disease
- **Environmental and Occupational**
  - Herbicides (e.g., 2,4-D), pesticides
Factors affecting treatment decisions

- Type of NHL (biopsy)
  - Cytology
  - Growth rate (Indolent, Aggressive)
- Stage of disease
- Presence of symptoms
- Co-morbid conditions
WHO Classification of Lymphoid Malignancies

Cellular Origin of Disease

**Precursor Cell**
- B-Cell
  - Lymphoblastic leukemia/lymphoma
- T-Cell

**Peripheral Cell**
- B-Cell
  - Small lymphocytic/CLL
  - Lymphoplasmacytic
  - Marginal Zone
  - Follicular
  - Mantle Cell
  - Diffuse large B cell
  - Burkitt/Burkitt-like
- T-Cell
  - Mycosis fungoides
  - Sezary Syndrome
  - Angioimmunoblastic
  - Peripheral (NOS)
  - Anaplastic large cell
WHO Classification of Haematopoietic and Lymphoid Tumours: B-Cell Neoplasms

<table>
<thead>
<tr>
<th>Indolent</th>
<th>Aggressive</th>
<th>Very Aggressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Small lymphocytic/CLL</td>
<td>• PLL</td>
<td>• Precursor B-lymphoblastic lymphoma/Leukemia</td>
</tr>
<tr>
<td>• Lymphoplasmacytic/IMC/WM</td>
<td>• Plasmacytoma/Multiple myeloma</td>
<td>• Burkitt’s lymphoma/B-cell acute leukemia</td>
</tr>
<tr>
<td>• Hairy Cell leukemia</td>
<td>• Mantle cell</td>
<td>• Plasma cell leukemia</td>
</tr>
<tr>
<td>• Marginal zone lymphoma</td>
<td>• Follicle center lymphoma, follicular, grade III</td>
<td></td>
</tr>
<tr>
<td>– Extranodal (MALT)</td>
<td>• Diffuse Large B-cell</td>
<td></td>
</tr>
<tr>
<td>– Nodal</td>
<td>• Primary mediastinal large B-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>– Splenic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Follicle center lymphoma, follicular, grade I-II</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Frequency of NHL Subtypes in Adults

Mantle cell (6%)
Peripheral T-cell (6%)
Indolent (35%)
Diffuse large B-cell (31%)
Composite lymphomas (13%)

Other subtypes with a frequency ≤2% (9%)


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Modified Ann Arbor Staging of NHL

Stage I  Involvement of a single lymph node region

Stage II  Involvement of $\geq 2$ lymph node regions on the same side of the diaphragm

Stage III  Involvement of lymph node regions on both sides of the diaphragm

Stage IV  Multifocal involvement of $\geq 1$ extralymphatic sites ± associated lymph nodes or isolated extralymphatic organ involvement with distant nodal involvement


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Staging of NHL

♦ CT scans of Chest, Abdomen and Pelvis

♦ Bone marrow biopsy

♦ PET scan:
  – Indicated for staging and follow up of both NHL and HL
  – High sensitivity for aggressive NHL, less for indolent
  – Several trials have demonstrated improved sensitivity over CT
  – Very useful for post-treatment evaluation and follow up

♦ CT/PET:
  – Further improvement in localization of PET signal
NHL: Treatment

- Indolent NHL
  - Follicular Lymphoma
  - Small lymphocytic lymphoma
  - Marginal zone NHL (MALT)

- Transformed lymphoma
  - Change from indolent to aggressive disease
    - (ie follicular to large cell)

Adapted from Horning. *Semin Oncol.* 1993;20(suppl 5):75.

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Treatment Strategies for Indolent NHL

Stage I-II Disease
- “Watchful waiting”
- Radiation
- Chemotherapy

Stage III-IV Disease
- “Watchful waiting”
- Purine analogs
- Alkylating agents
- Combination chemotherapy
- Monoclonal antibodies (conjugated and unconjugated)
- Chemotherapy + antibodies
- Intensive chemotherapy + stem cell transplantation
Follicular Lymphoma: Clinical Management

Indolent B Cell Lymphoma

- Localized
  - Involved/Extended Field Radiation

- Advanced Low Tumor Burden

- Advanced High Tumor Burden
  - Observation
  - Therapy
Follicular Lymphoma
Indications for Therapy in Advanced Disease

- Cytopenias secondary to BM infiltration
- Threatened end-organ function
- Symptoms attributable to disease
- Bulk at presentation
- Steady progression during a period of observation >6 months
- Presentation with concurrent histologic transformation
- Massive splenomegaly
Chemotherapy for Indolent Lymphoma

- Not curable with conventional therapy
- Observation is appropriate if there are no indications for therapy
- High initial response rates to chemotherapy, but majority will relapse
- Tend to remain chemotherapy sensitive at the time of relapse
- Response duration is generally shorter with each course of therapy
Indolent NHL Responds to Repeated Chemotherapy With Shorter Durations of Response

Responding patients (n = 110) in remission through 4 treatments

<table>
<thead>
<tr>
<th>CR</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.0</td>
</tr>
<tr>
<td>2</td>
<td>11.2</td>
</tr>
<tr>
<td>3</td>
<td>9.6</td>
</tr>
<tr>
<td>4</td>
<td>3.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cohort</th>
<th>10 Year DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanford</td>
<td>44%</td>
</tr>
<tr>
<td>St Barts</td>
<td>45%</td>
</tr>
</tbody>
</table>
Observation for Stage I/II Follicular Lymphoma

- 43 pts who deferred therapy for at least 3 mo
- Median follow-up of 86 months
  - 27 pts not yet treated (63%)
  - 16 pts: median time to treatment of 22 months
- Estimated survival:
  - 5 yr: 97%
  - 10 yr: 85%
  - 20 yr: 22%

Observation for Stage I/II Follicular Lymphoma

Progression-Free Survival

Overall Survival

Traditional Treatment Approaches For Advanced Stage Follicular Lymphoma

- Watch and wait
- Oral chlorambucil or cyclophosphamide +/- prednisone
- Cyclophosphamide, Vincristine, Prednisone (CVP)
- CHOP (CVP plus doxorubicin)
- Fludarabine -based regimens
Evolving Approaches To Treating Advanced Stage Follicular Lymphoma

- Rituximab
- Chemotherapy + rituximab
- Interferon
- $^{90}$Y-Ibritumomab tiuxetan
- $^{131}$I-Tositumomab
- Autologous transplants*
- Allogeneic transplants*
- Vaccines*
- BCL2 antisense*
- Investigational*
# Initial Therapy of Follicular Lymphoma With Alkylator-Based Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response (%)</th>
<th>5-Year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>CR</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>74</td>
<td>13</td>
</tr>
<tr>
<td>(St. Bartholomew’s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVP</td>
<td>51</td>
<td>15</td>
</tr>
<tr>
<td>(Europe)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP-B</td>
<td>93</td>
<td>66</td>
</tr>
<tr>
<td>(CALGB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ProMACE/MOPP</td>
<td>83</td>
<td>47</td>
</tr>
<tr>
<td>(NCI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Problems with Traditional Chemotherapy

- Non-specific effects: target dividing cells
- Acute toxicity
  - Cytopenias with risk of bleeding, infection, transfusion
  - Hair loss
  - Nausea, vomiting
- Chronic toxicity
  - Risk of bone marrow damage: myelodysplasia, leukemia
  - Cardiac, neurotoxicity
- Duration of therapy generally 4 to 6 months
Target Antigens: Important Features for Immunotherapy

- Expressed on all tumor cells
  - Not present on critical host cells
  - No significant toxicity if all antigen+ cells eliminated
- High copy number
- No mutations or variant antigens
- Required for critical biologic function or cell survival
- Not shed or secreted
- Not modulated after antibody binding
CD20 Is Not Expressed on Stem Cells or Plasma Cells


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B-Cell Lymphomas Express Several Antigens That Can Be Targeted


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Proposed Mechanisms of Action for MoAbs

- CDC
- ADCC
- Apoptosis

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Rituximab in Relapsed or Refractory Low-Grade NHL

- Chimeric monoclonal antibody to CD20
- Dose: 375 mg/m²/wk × 4 or 8 weeks
- Response rate was 48%
- Response rates differed significantly in patients with follicular and small lymphocytic subtypes (60% vs 13%, P < .01)
- Median duration of response 11.2 months

Rituximab: Summary of Safety

- Infusion-related events are the most common toxicity with grade 3 or 4 in fewer than 10% of patients
- Infusion-related toxicity are most frequently associated with the first rituximab infusion
- Severe tumor lysis syndrome, which can be fatal, occurs rarely (<0.1%), and usually in patients with high circulating malignant lymphocyte counts, large tumor bulk
- Not associated with common chemotherapy-associated toxicities: marrow suppression, nausea, hair loss
Rituximab + Chemotherapy in First-Line Treatment of Indolent NHL

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of Evaluable Patients</th>
<th>CR Rate</th>
<th>Median Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP + R</td>
<td>40</td>
<td>55%</td>
<td>&gt; 62 months</td>
</tr>
<tr>
<td>Fludarabine + R</td>
<td>50</td>
<td>80%</td>
<td>&gt; 15 months</td>
</tr>
<tr>
<td>FND + R</td>
<td>52</td>
<td>73%</td>
<td>&gt; 12 months</td>
</tr>
<tr>
<td>CHOP → R</td>
<td>85</td>
<td>54%</td>
<td>38 months</td>
</tr>
<tr>
<td>FN → R</td>
<td>32</td>
<td>47%</td>
<td>24 months</td>
</tr>
</tbody>
</table>
CVP + Rituximab: Study Design

- Follicular NHL, stage III/IV
- No previous treatment

Randomize

CVP x 8 cycles

R-CVP x 8 cycles

- Both regimens administered Day 1, repeated q 21 d
  - CTX 750 mg/m2, VCR 1.4 mg/m2, Pred 40/m2 d 1-5
  - RTX 375/m2 day 1 for R-CVP
# CVP + Rituximab: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>CVP</th>
<th>R-CVP</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rates - overall</strong></td>
<td>57%</td>
<td>81%</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>complete</td>
<td>10%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td><strong>Median time-to-failure</strong></td>
<td>7 mo</td>
<td>26 mo</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td><strong>Median time-to-progression</strong></td>
<td>13 mo</td>
<td>27 mo</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

- Median follow-up 18 months

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R-CVP vs CVP in Stage III/IV Follicular NHL

Log-rank P values
Without Stratification by Center: <0.0001
With Stratification by Center: <0.0001

Marcus et al, Abstr. 87, ASH 2003
Current Role for Rituximab

- **Initial therapy**
  - With chemotherapy (R-CVP, R-CHOP, R-Fludarabine)
  - As a single agent

- **Relapsed disease**
  - Single agent x 4 or 8 weeks (FDA indication)
  - Can retreat if continuing to get response
  - With chemotherapy

- **Goal is control of disease, not cure**
Rationale for Radioimmunotherapy in NHL

- NHL is sensitive to radiation
- Radiotherapy may cure limited-stage indolent NHL but is too toxic for advanced-stage disease
- Radiolabeled antibodies deliver radiation to tumor cells
- Radioimmunotherapy can kill both bound and neighboring tumor cells, overcoming the problem of access in bulky or poorly vascularized tumors
Radioimmunotherapy Produces a Crossfire Effect

Naked antibody

Radiolabeled antibody

# Anti-CD20 Radioimmunoconjugates (RICs) for NHL

<table>
<thead>
<tr>
<th></th>
<th>Zevalin™</th>
<th>Bexxar™</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parent antibody</strong></td>
<td>IDEC-2B8/ Anti-B1/</td>
<td>Anti-B1/ Tositumomab (murine)</td>
</tr>
<tr>
<td></td>
<td>Ibritumomab (murine)</td>
<td></td>
</tr>
<tr>
<td><strong>Radionuclide</strong></td>
<td>Yttrium-90</td>
<td>Iodine-131</td>
</tr>
<tr>
<td><strong>Antibody (unlabeled)</strong></td>
<td>Rituximab (chimeric)</td>
<td>Anti-B1 (murine)</td>
</tr>
<tr>
<td><strong>Antibody (dosimetric)</strong></td>
<td>IDEC-In2B8</td>
<td>$^{131}$I-Anti-B1</td>
</tr>
<tr>
<td><strong>Properties</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emission</td>
<td>Pure $\beta$-emitter</td>
<td>$\gamma$- and $\beta$-emitter</td>
</tr>
<tr>
<td>Radiation penetration</td>
<td>5–10 mm</td>
<td>1 mm</td>
</tr>
<tr>
<td>Half-life</td>
<td>2.7 days</td>
<td>8.1 days</td>
</tr>
<tr>
<td>Dosimetry required</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Notes:**
- Zevalin™ and Bexxar™ are trademarks of GlaxoSmithKline.
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**90Y Ibritumomab Tiuxetan**

- **Ibritumomab**
  - Murine monoclonal antibody that binds to the CD20 antigen

- **Tiuxetan** (chelator)
  - Conjugated to antibody, forms strong urea-type bond with radioisotope

- **Isotope**: $^{90}$Y (pure $\beta$ emitter)
\( ^{90} \text{Y} \) Ibritumomab Tiuxetan: Approved Indication

- \( ^{90} \text{Y} \) ibritumomab tiuxetan is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL, including patients with rituximab-refractory follicular B-cell NHL.
**Tositumomab**

- Murine IgG2 alpha monoclonal antibody that binds to the CD20 antigen

- Tyrosine residue bond conjugates antibody with radionuclide

- **Radionuclide**—$^{131}$I ($\beta$ and $\gamma$ emitter)

$^{131}$I radionuclide

$\beta + \gamma$ radiation
The $^{131}$I tositumomab therapeutic regimen (tositumomab and $^{131}$I tositumomab) is indicated for the treatment of patients with CD20 positive, follicular NHL, with and without transformation, whose disease is refractory to rituximab and has relapsed following chemotherapy.
Radioimmunotherapy: Efficacy

- High single agent response rates
- Active in patients that are Rituximab-refractory
- Active in indolent and transformed lymphoma
- May be more effective when used earlier in treatment course
Objective: Compare the safety and efficacy of the ibritumomab tiuxetan regimen and rituximab alone in patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL.

Randomized Phase 3 Trial: Study Design

- Stratified by IWF groups A, B–D, or transformed
- Randomized
- Rituximab 375 mg/m²/wk × 4
- ⁹⁰Y ibritumomab tiuxetan and rituximab

**90Y Ibritumomab Tiuxetan vs Rituximab**

**Phase 3 Trial: Response Rates**

*As assessed by an independent review panel using International Workshop criteria.*


<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90Y ibritumomab tiuxetan (n = 73)</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>80</td>
</tr>
<tr>
<td>CR</td>
<td>30</td>
</tr>
<tr>
<td>CRu</td>
<td>4</td>
</tr>
<tr>
<td>Rituximab (n = 70)</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>56</td>
</tr>
<tr>
<td>CR</td>
<td>4</td>
</tr>
<tr>
<td>CRu</td>
<td>16</td>
</tr>
</tbody>
</table>

*P = .002  
P = .04*
# ¹³¹I Tositumomab Pivotal Trial in Relapsed NHL: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Last qualifying chemotherapy</th>
<th>¹³¹I tositumomab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
<td>17/60 (28%)</td>
<td>39/60 (65%)</td>
</tr>
<tr>
<td><strong>Median (95% CI)</strong> duration of response (mo)</td>
<td>3.4 (2.5–4.7)</td>
<td>6.5 (3.1–11.3)</td>
</tr>
<tr>
<td><strong>Complete response</strong></td>
<td>2/60 (3%)</td>
<td>12/60 (20%)</td>
</tr>
<tr>
<td><strong>Median (95% CI)</strong> duration of progression-free survival (mo)</td>
<td>6.3 (5.4–8.1)</td>
<td>8.4 (5.1–12.9)</td>
</tr>
</tbody>
</table>

Median follow-up, 10 mo; range, 6–20 mo.

Bexxar™ for Previously Treated NHL Survival


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## ⁹⁰Y Ibritumomab Tiuxetan: Durable Remissions

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Overall responses</th>
<th>CR,CRu</th>
<th>Range of ongoing response (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Median DR (mo)</td>
<td>%</td>
</tr>
<tr>
<td>Phase 1-2 (51)</td>
<td>73</td>
<td>11.7</td>
<td>29*</td>
</tr>
<tr>
<td>Phase 2 (30)</td>
<td>83</td>
<td>11.5</td>
<td>47</td>
</tr>
<tr>
<td>Phase 3 (73)</td>
<td>80</td>
<td>13.9</td>
<td>34</td>
</tr>
</tbody>
</table>

*Data in patients with CR only.

Durable CR with Bexxar

- 255 pts treated on 5 studies
  - Overall RR 47-65%, median duration 12-18 months
- 28% of pts treated on Rituxan-refractory trial and 23% of those treated on Rituxan-naïve protocols had durable CR
  - Durable CR = >12 month PFS
- Median 3-4 prior therapies, majority Stage III or IV
- 9-27% with transformed disease
- At median follow up of 4.6 years, 75% remain in CR

Coleman, et al. ASH 2003, Abstract 89
Radioimmunotherapy: Safety

- Adverse events are primarily hematologic
- Grade 3 or 4 toxicity occur later (7–9 weeks) than with myelosuppressive chemotherapy (1–2 weeks) and correlate with:
  - Bone marrow impairment
  - Bone marrow involvement by lymphoma
  - Number of prior therapies, purine analogues
- Nonhematologic AEs are:
  - Primarily grade 1 or 2
  - Not associated with hair loss, severe mucositis, or persistent nausea and vomiting
**90Y Ibritumomab Tiuxetan Integrated Safety (N = 349): Most Common Nonhematologic AEs (Incidence ≥10%)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grades 1, 2</th>
<th>Grades 3, 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>31</td>
<td>24</td>
</tr>
<tr>
<td>Asthenia</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>Fever</td>
<td>16</td>
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</tr>
<tr>
<td>Abdominal pain</td>
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</tr>
<tr>
<td>Dyspnea</td>
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</tr>
<tr>
<td>Pain</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Increased cough</td>
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<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Throat irritation</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

(Witzig, et al. 2003)
Median Blood Cell Counts After Treatment

- Hemoglobin (g/dL)
  - Hgb = 10

- ANC (10^3/µL)
  - ANC = 1000
  - ANC = 1000

- Platelets (10^3/µL)
  - Platelets = 50,000

Study week

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RIT Safety and Efficacy: Summary

- Generally well tolerated; hematologic toxicity is dose limiting
  - Proper patient selection is important to ensure safety

- High overall and complete response rates in relapsed or refractory indolent, follicular or transformed B-cell NHL

- Efficacy in patients who no longer respond to Rituximab

- Regimens can be completed within 7-9 days in an outpatient setting

- Prolonged responses in some patients
Subsequent Therapy After $^{90}$Y Ibritumomab Tiuxetan Is Well Tolerated

- Retrospective analysis (N = 171)
  - Compared with control group not treated with ibritumomab tiuxetan
- Median number of subsequent therapies: 2 (range, 1–7)
  - CHOP +/or rituximab most common first therapy
- No significant differences in toxicity of chemotherapy between groups
- 7 patients underwent successful autologous transplantation with peripheral blood stem cells collected after treatment with ibritumomab tiuxetan; 1 patient required bone marrow collection

Ansell et al. ASH 2003, Abstract 4956.
Subsequent Therapy After Ibritumomab Tiuxetan: Response Rates

Cytotoxic chemotherapy after Tositumomab (Bexxar)

- 63 pts treated at Cornell who were refractory or relapsed after initial response
- Subsequent treatments included Rituximab, Radiation, Anthracyclines, Fludarabine, Platinum
- 24% received auto or allo SCT
- Treatments well tolerated, no unexpected toxicities


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RIT: Where Does It Fit in a Treatment Plan?

- Treatment plans differ with
  - Patient’s clinical status
  - Patient’s medical history
  - Histologic type
  - Presence of bulky disease
Where Does RIT Fit?

- In patients without compromised bone marrow
- In patients who are at greater risk for the side effects of chemotherapy
  - Elderly
  - Comorbidities
- In patients with transformed NHL who are not good candidates for aggressive chemotherapy
- In patients in whom a short and highly effective course of therapy is desirable
- May be more effective earlier in treatment continuum
## Risks And Benefits Of Primary Therapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Remission Rate</th>
<th>Durability</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watch and Wait</td>
<td>0/+</td>
<td>+</td>
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<tr>
<td>Single agent chemo</td>
<td>+</td>
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<tr>
<td>CVP, CHOP, FND</td>
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<td>Rituximab</td>
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<td>Rituximab-chemotherapy</td>
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<td>++</td>
<td>+</td>
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<tr>
<td>Auto transplant</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Allo transplant</td>
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<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

**Legend:**
- **Ri:** Remission Rate
- **Du:** Durability
- **Mo:** Morbidity
- **Mo:** Mortality
Follicular Lymphoma: Considerations for Treatment Approach

- **Patient Characteristics**
  - Age
  - Symptoms
  - Short & long term goals
  - Co-morbidity
  - Preserve future options
  - Reimbursement

- **Disease Characteristics**
  - Stage
  - Grade
  - Transformation
  - Sites of involvement
  - Prior therapy
  - Time from prior therapy
Radioimmunotherapy: Future Directions

- Other hematologic malignancies
  - Aggressive NHL
  - Mantle cell lymphoma

- Patients with significant marrow involvement

- Front-line

- Consolidation after chemotherapy

- Maintenance with rituximab

- Retreatment

- Preparative regimens for transplant