

## Criteria for Use of Rituximab (Rituxan®) March 2006

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

### Criteria for VA Patients

#### **A. Low grade, follicular Non-Hodgkin's Lymphoma**<sup>1,4,5,6,7</sup>

For relapsed or refractory disease, rituximab, either as monotherapy or in addition to standard chemotherapy, is one choice for therapy. For patients in a second or greater relapse, consideration should be given to using rituximab with ibritumomab tiuxetan as part of radioimmunotherapy. Although initial therapy of follicular lymphomas with rituximab has been reported in several phase II trials, there is no survival data reported and use in this setting cannot be recommended.

#### **B. Diffuse Large B-Cell lymphoma (DLBCL)**<sup>2,3,11,12,13,14</sup>

Based on the results from the GELA trial of CHOP vs R-CHOP (better response, event-free, progression-free, disease-free, and overall survival significantly better at 5 years follow-up in patients treated with R-CHOP), rituximab added to CHOP or CHOP-like regimens is superior to the same regimen without rituximab.

#### **C. Other CD20 expressing neoplasms:**<sup>15,16,19</sup>

mantle cell lymphoma, hairy cell leukemia, chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia

#### **D. Treatment or consolidation of minimal residual disease following autologous stem cell transplant for CD20 expressing neoplasms.**<sup>17,18</sup>

### Pharmacology:

Rituximab is a chimeric murine/human monoclonal antibody against the CD20 antigen found on the surface of normal and malignant B-lymphocytes. Rituximab binds to the CD20 antigen (expressed in >90% of B-cell non-Hodgkin's lymphoma). The Fc domain of the antibody recruits immune effector functions to mediate B-cell lysis through possible complement dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC).

Rituximab peak and trough levels are inversely correlated to the number of circulating B-cells and measures of tumor burden. Serum half-life increases from 76.3 hours after the first dose to 205.8 hours after the fourth infusion. Rituximab has been detectable in serum up to 3-6 months following completion of therapy.

### Black Box Warnings:

1. Fatal Infusion Reactions: Deaths within 24 hours of infusion have been reported following an infusion reaction characterized by hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock. About 80% of fatal reactions are associated with the first infusion. Patients who develop severe infusion reactions should have rituximab discontinued and receive appropriate medical care.
2. Tumor Lysis Syndrome (TLS): Acute renal failure, some with fatal outcomes, has been reported with TLS following rituximab therapy.
3. Severe Mucocutaneous Reactions: Severe mucocutaneous reactions, some fatal, have been reported.

### FDA Indications

1. Rituximab is indicated for the treatment of relapsed or refractory, low-grade or follicular, CD-20 positive, B-cell non-Hodgkin's lymphoma.
2. Rituximab is indicated for the first-line treatment of CD20-positive, diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP or other anthracycline-based chemotherapy regimens.

Evidence Reviews

Review	Trials	Outcomes																															
<p><b>Relapsed or Refractory, Low-grade or follicular, B-cell lymphoma</b></p>	<p>Initial Treatment, weekly x4 (n=166)<sup>4</sup>                      Initial Treatment, weekly x8 (n=37)<sup>5</sup>                      Initial Treatment, bulky disease, x4 (N=39)                      Retreatment, weekly x4 (n=60)<sup>6</sup></p>	<table border="1"> <thead> <tr> <th>Variable</th> <th>Initial X4</th> <th>Initial X8</th> <th>Initial, Bulky, X4</th> <th>Retreat X4</th> </tr> </thead> <tbody> <tr> <td>Overall RR</td> <td>48%</td> <td>57</td> <td>36</td> <td>38</td> </tr> <tr> <td>CR</td> <td>6%</td> <td>14</td> <td>3</td> <td>10</td> </tr> <tr> <td>Med Duration Of response (months) [range]</td> <td>11.2 [1.9-42+]</td> <td>13.4 [2.5-36.5+]</td> <td>6.9 [2.8-25+]</td> <td>15 [3-25.1+]</td> </tr> </tbody> </table>	Variable	Initial X4	Initial X8	Initial, Bulky, X4	Retreat X4	Overall RR	48%	57	36	38	CR	6%	14	3	10	Med Duration Of response (months) [range]	11.2 [1.9-42+]	13.4 [2.5-36.5+]	6.9 [2.8-25+]	15 [3-25.1+]											
		Variable	Initial X4	Initial X8	Initial, Bulky, X4	Retreat X4																											
		Overall RR	48%	57	36	38																											
		CR	6%	14	3	10																											
	Med Duration Of response (months) [range]	11.2 [1.9-42+]	13.4 [2.5-36.5+]	6.9 [2.8-25+]	15 [3-25.1+]																												
	<p>Ibritumomab tiuxetan radioimmunotherapy with rituximab (no prior anti-CD20)<sup>7</sup></p>	<table border="1"> <thead> <tr> <th>Variable</th> <th>International workshop</th> <th>Protocol defined</th> </tr> </thead> <tbody> <tr> <td>CR %</td> <td>37</td> <td>33</td> </tr> <tr> <td>PR %</td> <td>40</td> <td>33</td> </tr> <tr> <td>ORR %</td> <td>83</td> <td>67</td> </tr> <tr> <td>95%CI</td> <td>64.5-93.7</td> <td>48.1 -85.2</td> </tr> </tbody> </table>	Variable	International workshop	Protocol defined	CR %	37	33	PR %	40	33	ORR %	83	67	95%CI	64.5-93.7	48.1 -85.2																
		Variable	International workshop	Protocol defined																													
		CR %	37	33																													
	PR %	40	33																														
	ORR %	83	67																														
95%CI	64.5-93.7	48.1 -85.2																															
<p>Ibritumomab tiuxetan radioimmunotherapy in patients with rituximab refractory follicular lymphoma<sup>8</sup></p>	<table border="1"> <thead> <tr> <th>Variable</th> <th>Ibritumomab</th> </tr> </thead> <tbody> <tr> <td>ORR %</td> <td>74</td> </tr> <tr> <td>CR%</td> <td>15</td> </tr> <tr> <td>PR%</td> <td>59</td> </tr> <tr> <td>TTP</td> <td>6.8 months</td> </tr> <tr> <td>Range</td> <td>1.1 -25.9+</td> </tr> </tbody> </table>	Variable	Ibritumomab	ORR %	74	CR%	15	PR%	59	TTP	6.8 months	Range	1.1 -25.9+																				
	Variable	Ibritumomab																															
	ORR %	74																															
CR%	15																																
PR%	59																																
TTP	6.8 months																																
Range	1.1 -25.9+																																
<p>Ibritumomab tiuxetan radioimmunotherapy vs Rituximab<sup>9</sup></p>	<table border="1"> <thead> <tr> <th>Variable</th> <th>Ibritumomab</th> <th>Rituximab</th> <th>P</th> </tr> </thead> <tbody> <tr> <td>ORR %</td> <td>80</td> <td>56</td> <td>0.02</td> </tr> <tr> <td>95%CI</td> <td>68.1-87.7</td> <td>43.4-67.4</td> <td></td> </tr> <tr> <td>CR</td> <td>30</td> <td>16</td> <td>0.04</td> </tr> <tr> <td>CCR/Cu</td> <td>4</td> <td>4</td> <td></td> </tr> <tr> <td>PR</td> <td>45</td> <td>36</td> <td></td> </tr> <tr> <td>TTP</td> <td>11.2 months</td> <td>10.1</td> <td>0.173</td> </tr> <tr> <td>Range</td> <td>0.8-31.5+</td> <td>0.7-26.1</td> <td></td> </tr> </tbody> </table>	Variable	Ibritumomab	Rituximab	P	ORR %	80	56	0.02	95%CI	68.1-87.7	43.4-67.4		CR	30	16	0.04	CCR/Cu	4	4		PR	45	36		TTP	11.2 months	10.1	0.173	Range	0.8-31.5+	0.7-26.1	
	Variable	Ibritumomab	Rituximab	P																													
	ORR %	80	56	0.02																													
95%CI	68.1-87.7	43.4-67.4																															
CR	30	16	0.04																														
CCR/Cu	4	4																															
PR	45	36																															
TTP	11.2 months	10.1	0.173																														
Range	0.8-31.5+	0.7-26.1																															
<p><b>Newly Diagnosed or Relapsed/Refractory low-grade or follicular non-Hodgkin's lymphoma</b></p>	<p>Rituximab and CHOP for six cycles<sup>10</sup></p>	<table border="1"> <thead> <tr> <th>Variable</th> <th>Rituximab</th> </tr> </thead> <tbody> <tr> <td>Overall Response Rate %</td> <td>95 (95%CI 88 -100)</td> </tr> <tr> <td>Complete Response %</td> <td>55</td> </tr> <tr> <td>Partial Response %</td> <td>40</td> </tr> <tr> <td>Newly diagnosed Med Duration of Response</td> <td>27.8+ months</td> </tr> </tbody> </table>	Variable	Rituximab	Overall Response Rate %	95 (95%CI 88 -100)	Complete Response %	55	Partial Response %	40	Newly diagnosed Med Duration of Response	27.8+ months																					
		Variable	Rituximab																														
Overall Response Rate %	95 (95%CI 88 -100)																																
Complete Response %	55																																
Partial Response %	40																																
Newly diagnosed Med Duration of Response	27.8+ months																																

Review	Trials	Outcomes																							
<p><b>Aggressive non-Hodgkin's Lymphoma</b><sup>11,12</sup>                      NHS Health Technology Assessment 2004<sup>13</sup></p>	<p>Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) VS Rituximab + CHOP (R-CHOP) (French Groupe d'Etude des Lymphomes de L' Adulte [GELA]) (60-80 years old)</p>	<table border="1"> <thead> <tr> <th>Variable</th> <th>R-CHOP N=202</th> <th>CHOP N=197</th> <th>Relative Risk (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Primary 2-year event free survival % (95% CI)</td> <td>57 (50-64)</td> <td>38 (32-45)</td> <td>0.55 (0.41-0.75) P&lt;0.001</td> </tr> <tr> <td>Secondary 2-year overall survival % (95% CI)</td> <td>70 (63-77)</td> <td>57 (50-64)</td> <td>0.53 (0.37-0.77) P=0.007</td> </tr> <tr> <td>CR N (%)</td> <td>152 (75)</td> <td>124 (63)</td> <td>1.2 (1.05-1.37) P=0.009</td> </tr> <tr> <td>Severe adverse events N (%)</td> <td>160 (79)</td> <td>145 (74)</td> <td>1.08 (0.96-1.2) P=0.19</td> </tr> </tbody> </table>	Variable	R-CHOP N=202	CHOP N=197	Relative Risk (95% CI)	Primary 2-year event free survival % (95% CI)	57 (50-64)	38 (32-45)	0.55 (0.41-0.75) P<0.001	Secondary 2-year overall survival % (95% CI)	70 (63-77)	57 (50-64)	0.53 (0.37-0.77) P=0.007	CR N (%)	152 (75)	124 (63)	1.2 (1.05-1.37) P=0.009	Severe adverse events N (%)	160 (79)	145 (74)	1.08 (0.96-1.2) P=0.19			
		Variable	R-CHOP N=202	CHOP N=197	Relative Risk (95% CI)																				
		Primary 2-year event free survival % (95% CI)	57 (50-64)	38 (32-45)	0.55 (0.41-0.75) P<0.001																				
		Secondary 2-year overall survival % (95% CI)	70 (63-77)	57 (50-64)	0.53 (0.37-0.77) P=0.007																				
		CR N (%)	152 (75)	124 (63)	1.2 (1.05-1.37) P=0.009																				
	Severe adverse events N (%)	160 (79)	145 (74)	1.08 (0.96-1.2) P=0.19																					
	<p>Long term (5 year) results from GELA<sup>14</sup></p>	<table border="1"> <thead> <tr> <th>Variable</th> <th>R-CHOP</th> <th>CHOP</th> </tr> </thead> <tbody> <tr> <td>Event-free survival years (95% CI)</td> <td>3.8 (2.37 – not reached) P=0.00002</td> <td>1.1 (0.8-1.5)</td> </tr> <tr> <td>5 yr EFS % (95% CI)</td> <td>47 (39.9-54.1)</td> <td>29 (23.1-35.8)</td> </tr> <tr> <td>Progression free survival- years (95% CI)</td> <td>Not reached (3.4- not reached) P=&lt;0.00001</td> <td>1 (0.8-1.5)</td> </tr> <tr> <td>Overall survival Years (95% CI)</td> <td>Not reached  P=0.0073</td> <td>3.1 (2.2-not reached)</td> </tr> </tbody> </table>	Variable	R-CHOP	CHOP	Event-free survival years (95% CI)	3.8 (2.37 – not reached) P=0.00002	1.1 (0.8-1.5)	5 yr EFS % (95% CI)	47 (39.9-54.1)	29 (23.1-35.8)	Progression free survival- years (95% CI)	Not reached (3.4- not reached) P=<0.00001	1 (0.8-1.5)	Overall survival Years (95% CI)	Not reached  P=0.0073	3.1 (2.2-not reached)								
		Variable	R-CHOP	CHOP																					
		Event-free survival years (95% CI)	3.8 (2.37 – not reached) P=0.00002	1.1 (0.8-1.5)																					
		5 yr EFS % (95% CI)	47 (39.9-54.1)	29 (23.1-35.8)																					
Progression free survival- years (95% CI)		Not reached (3.4- not reached) P=<0.00001	1 (0.8-1.5)																						
Overall survival Years (95% CI)	Not reached  P=0.0073	3.1 (2.2-not reached)																							
<table border="1"> <tbody> <tr> <td>5 yr overall survival, % (95% CI)</td> <td>58 (50.8-64.5)</td> <td>45 (39.1-53.3)</td> </tr> </tbody> </table>	5 yr overall survival, % (95% CI)	58 (50.8-64.5)	45 (39.1-53.3)																						
5 yr overall survival, % (95% CI)	58 (50.8-64.5)	45 (39.1-53.3)																							
<table border="1"> <tbody> <tr> <td>Low risk 5-yr overall survival, %</td> <td>80 P=0.023</td> <td>62</td> </tr> <tr> <td>High risk 5-yr overall survival, %</td> <td>48 P=0.062</td> <td>39</td> </tr> </tbody> </table>	Low risk 5-yr overall survival, %	80 P=0.023	62	High risk 5-yr overall survival, %	48 P=0.062	39																			
Low risk 5-yr overall survival, %	80 P=0.023	62																							
High risk 5-yr overall survival, %	48 P=0.062	39																							

Review	Trials	Outcomes
<b>Other</b>	<p>Persistent Idiopathic Thrombocytopenic Purpura following splenectomy<sup>15</sup></p> <p>Multiple Myeloma, Waldenstrom's macroglobulinemia, mantle cell lymphoma, Castleman's disease, rheumatoid arthritis, systemic lupus erythematosus<sup>16</sup></p> <p>Clearance of minimal residual disease following stem cell transplant for CD20 expressing neoplasms<sup>17,18</sup></p> <p>Chronic Lymphocytic Leukemia<sup>19</sup></p>	

RR=response rate, CR=complete response

**Dosing and Administration**

**Preparation:** The appropriate dose is withdrawn from the vial(s) and diluted to a final concentration of 1-4 mg/ml in either 0.9% Sodium Chloride or 5% Dextrose in Water.

**Premedication:** Premedication with acetaminophen 650mg orally and diphenhydramine 25-50mg orally before each dose of rituximab should be considered to decrease the incidence and severity of infusion reactions.

**Administration:**

*First Infusion:* The diluted rituximab should be infused at a rate of 50 mg/hour. Escalate the rate by 50 mg/hour every 30 minutes if no hypersensitivity or infusion reactions are present to a maximum rate of 400 mg/hour.

If a hypersensitivity or infusion reaction occurs at any time, temporarily slow or discontinue the infusion until the symptoms subside. The infusion can be restarted at one-half of the previous rate when symptoms improve.

*Subsequent Infusions:* If the first infusion was tolerated, start subsequent infusions at 100 mg/hour and increase by 100mg/hour every 30 minutes to a maximum of 400 mg/hour as tolerated.

In patients who did not tolerate the first infusion well, initiate subsequent infusion in the same manner as the initial infusion rates above.

*Dose:*

**Low-grade or follicular lymphoma**

1. Relapsed or Refractory Follicular Lymphoma as monotherapy: Rituximab 375 mg/m<sup>2</sup> infusion once weekly for 4 or 8 weeks.

For Retreatment in patients with Progressive Disease: Rituximab 375 mg/m<sup>2</sup> infusion once weekly for 4 doses. There is limited data on giving more than 2 courses.

Combination Therapy with CHOP: Rituximab 375 mg/m<sup>2</sup> infusion for six doses. Infusion 1 and 2 on days 1 and 6 before the first CHOP cycle; Infusion 3 and 4 given 2 days before cycle 3 and 5 of CHOP; Infusion 5 and 6 given on days 134 and 141 after the sixth dose of CHOP.

**Aggressive Non-Hodgkin's Lymphoma**

2. Aggressive non-Hodgkin's lymphoma in combination with CHOP chemotherapy: Rituximab 375mg/m<sup>2</sup> infusion on day 1 of each cycle of CHOP chemotherapy (every 21 days) for 8 cycles.

**Rituximab as a component of Zevalin (ibritumomab tiuxetan) Regimen**

3. Rituximab 250mg/m<sup>2</sup> within 4 hours prior to administering Indium-111-Zevalin and within 4 hours prior to administering Yttrium-90-Zevalin. Administration of rituximab plus Indium-111-Zevalin should precede administration of Yttrium-90-Zevalin by 7-9 days.

**Contraindications**

Rituximab is contraindicated in patients with known anaphylaxis or Ig-E mediated hypersensitivity to murine proteins or any component of the rituximab product.

**Warnings**

1. Severe Infusion Reactions: Severe reactions (some fatal) typically occur during the first infusion. Signs and symptoms include hypotension, angioedema, hypoxia, or bronchospasm. The most severe reactions include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock.

Interrupt the infusion in cases of severe reactions and provide supportive care as indicated with IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen. In most cases the infusion can be restarted when symptoms have resolved at a 50% rate reduction from the dose that caused the symptoms.

2. Tumor Lysis Syndrome: Rapid reductions of tumor volume can result in acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia. This syndrome generally occurs with the first infusion and patients with a higher number of circulating malignant cells are at greater risk. Prophylaxis should be considered for those at high risk.

Monitoring renal function and fluid balance, correction of electrolyte abnormalities, and supportive care should be used as needed.

3. Hepatitis B Reactivation: Hepatitis B reactivation with fulminant hepatitis, hepatic failure, and death has been reported. The majority of patients have received rituximab in combination with chemotherapy. Persons at high risk for hepatitis B infection should be screened before starting therapy and closely monitored for signs of active hepatitis B infection. If viral hepatitis is diagnosed, stop rituximab and chemotherapy. There is insufficient data on the safety of reinstating rituximab therapy in these patients.
4. Hypersensitivity Reactions: Rituximab is associated with non-IgE mediated hypersensitivity reactions that respond to lowering the infusion rate and medical management. Treatment of symptoms includes the use of acetaminophen, diphenhydramine, IV fluids, and bronchodilators. Patients with non-life threatening reactions are generally able to complete therapy with rituximab. Medications for hypersensitivity reactions (corticosteroids, epinephrine, and antihistamines) should be available for immediate use.
5. Cardiovascular: Discontinue infusion in cases of serious or life-threatening cardiac arrhythmias. Patients who develop serious arrhythmias should have cardiac monitoring prior to subsequent infusions. Those with pre-existing arrhythmias or angina may have recurrences during rituximab therapy and should be monitored throughout the infusion and the immediate post-infusion period.
6. Renal: Acute renal failure requiring dialysis and in some cases death has occurred with Tumor Lysis Syndrome and with concomitant cisplatin therapy. Discontinuation should be considered in patients with increasing serum creatinine or oliguria.
7. Severe Mucocutaneous Reactions: Mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis have been reported. Onset varies from 1-13 weeks after rituximab exposure. Patients with severe mucocutaneous reactions should not receive any further infusions.
8. Laboratory Monitoring: Complete blood counts and platelet counts should be measured at regular intervals and more frequently if cytopenias occur.
9. Drug/Laboratory Interactions: There have been no formal interaction studies. Renal toxicity was seen when rituximab was used along with cisplatin in clinical trials.
10. Immunization: Safety of live viral vaccines following rituximab has not been established.

11. Carcinogenesis, Mutagenesis, Impaired Fertility: No long-term animal studies available to determine carcinogenic or mutagenic potential, or to determine effects on fertility. Individuals of child-bearing potential should use appropriate contraceptive methods during therapy and for 12 months following rituximab.
12. Pregnancy Category C: No animal studies or reports in humans. Give with caution to pregnant women only if clearly needed.
13. Other Adverse Events:

Hematologic Events: Grade 3 or 4 cytopenias were reported in 48% and included lymphopenia (40%), neutropenia (6%), leukopenia, anemia, and thrombocytopenia. The median duration was 14 days for lymphopenia and 13 days for leukopenia.

Cardiac Events: Grade 3 or 4 events include hypotension. Rare, fatal cardiac failure with symptomatic onset weeks after rituximab.

Pulmonary Events: Most common are increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis, and a limited number of bronchiolitis obliterans. Post-marketing accounts of a limited number of cases of pneumonitis up to 3 months post-rituximab infusion have been reported; some fatal.

Immune/Autoimmune Events: Including uveitis, optic neuritis in a patient with systematic vasculitis, pleuritis in a patient with lupus-like syndrome, serum sickness with polyarticular arthritis, and vasculitis with rash.

Infectious Events: Rituximab is associated with decreased immunoglobulins. Infectious events occurred in 31%: 19% bacterial, 10% viral, 1% fungal, 6% unknown.

---

## References

- <sup>1</sup> Freedman AS, Friedberg JW. Treatment of indolent non-Hodgkin's lymphomas. UpToDate 2005; version 13.3.
- <sup>2</sup> Sehn LH, Connors JM. Treatment of aggressive non-Hodgkin's lymphoma: a North American perspective. *Oncology* 2005; 19 (suppl):26-34.
- <sup>3</sup> Pettengell R, Linch D. Compiled on behalf of the Haemato-Oncology Task Force of the British Committee for Standards in Haematology. Position paper on the therapeutic use of rituximab in CD20-positive diffuse large B-cell non-Hodgkin's lymphoma. *British J Hematology* 2003; 121:44-48.
- <sup>4</sup> McLaughlin P, Grillo-Lopez AJ, ink BK, Levy R, Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy in relapsed indolent lymphoma: half of patients responds to a four-dose program. *J Clin Oncol* 1998; 16:2825-2833.
- <sup>5</sup> Piro LD, White CA, Grillo-Lopez AJ, Janakiraman N, Saven A, Beck TM, et al. Extended rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. *Ann Oncology* 1999; 10:655-661.
- <sup>6</sup> Davis TA, Grillo-Lopez AJ, White CA, McLaughlin P, Czuczman MS, Link BK, et al. Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: safety and efficacy of re-treatment. *J Clin Onc* 2000; 18:3135-3143
- <sup>7</sup> Wiseman GA, Gordon LI, Multani PS, Witzig TE, Spies S, Bartlett NL, et al. Ibritumomab tiuxetan radioimmunotherapy for patients with relapsed or refractory non-hodgkin's lymphoma and mild thrombocytopenia: a phase II multicenter trial. *Blood* 2002; 99:4336-4342.
- <sup>8</sup> Witzig TE, Flinn IW, Gordon LI, Emmanouilides C, Czuczman MS, Saleh MS, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol* 2002; 20:3262-3269.
- <sup>9</sup> Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed b-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2002; 20:2453-2463.
- <sup>10</sup> Czuczman MS, Grillo-Lopez AJ, White CA, Saleh M, Gordon L, LoBuglio AF, et al. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. *J Clin Onc* 1999; 17:268-276.

- 
- <sup>11</sup> Fisher RI, Miller TP, O'Connor OA. Diffuse aggressive lymphoma. *Hematology (Am Soc Hematology Education Program)* 2004; 221-236.
- <sup>12</sup> Coiffier B. Immunochemotherapy: the new standard in aggressive non-Hodgkin's lymphoma in the elderly. *Semin Oncol* 2003; 30 (Suppl 2):21-27.
- <sup>13</sup> Knight C, Hind D, Brewer N, Abbott V. Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation. *Health Technology Assessment* 2004; 8 (37).
- <sup>14</sup> Feugier P, Van Hoof A, Sebban C, Solal-Celigny P, Bouabdallah R, Ferme C, et al. Long-term results of the R-CHOP Study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *J Clin Oncol* 2005; 23:4117-4126.
- <sup>15</sup> Vesely SK, Perdue JJ, Rizvi MA, Terrell DR, George JN. Management of adult patients with persistent idiopathic thrombocytopenic purpura following splenectomy. *Ann Intern Med* 2004; 140:112-120.
- <sup>16</sup> Chambers SA, Isenberg D. Anti-B cell therapy (rituximab) in the treatment of autoimmune diseases. *Lupus* 2005; 14:210-214.
- <sup>17</sup> Brugger W, Hirsch, Grunebach F, Repp R, Brossart P, Vogel W, et al. Rituximab consolidation after high-dose chemotherapy and autologous blood stem transplantation in follicular and mantle cell lymphoma: a prospective, multicenter phase II study. *Ann Oncology* 2004; 15:1691-1698.
- <sup>18</sup> Brugger W. Clearing minimal residual disease with rituximab consolidation therapy. *Seminars in Oncology* 2004; 31 (Suppl 2): 33-37.
- <sup>19</sup> Imrie K, Stevens A, Meyer R, and members of the hematology disease site group. A quality initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO). Rituximab in lymphoma and chronic lymphocytic leukemia: a clinical practice guideline. Evidence-based Series #6-8 Version 2.2005.