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Evidence-based Series 6-17 EDUCATION AND INFORMATION 2013

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Ibritumomab Tiuxetan in Lymphoma

M. Cheung, A.E. Haynes, A. Stevens, R.M. Meyer, K. Imrie, and the members of the Hematology Disease Site Group

Report Date: July 17, 2006

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Section 1: Practice Guideline
Section 2: Systematic Review
Section 3: Guideline Development and External Review

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Evidence-based Series #6-17: Section 1

Ibritumomab Tiuxetan in Lymphoma: A Clinical Practice Guideline

M. Cheung, A.E. Haynes, A. Stevens, R.M. Meyer, K. Imrie,
and the members of the Hematology Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care, Cancer Care Ontario
Developed by the Hematology Disease Site Group

Report Date: July 17, 2006

Questions

In patients with lymphoma of any type or stage:

1. What is the role of yttrium-90 (^{90}Y) ibritumomab tiuxetan? Outcomes of interest include survival, quality of life, time-to-progression, response duration, response rate, and toxicity.
2. Which patients are more or less likely to benefit from treatment with ^{90}Y-ibritumomab tiuxetan?
3. Is performance of imaging or dosimetry required for therapy to be safe and effective?

Target Population

This evidence summary applies to adult patients with non-Hodgkin's lymphoma of any type, at any stage of disease, and for any level of performance status.

Recommendations

There is a lack of high-quality evidence to explicitly inform the guideline questions. Notwithstanding, the following recommendations, based on a consensus of expert clinical opinion of the Hematology Disease Site Group and the best available evidence, are offered:

- ^{90}Y-ibritumomab tiuxetan is an active agent in relapsed and refractory CD20+ non-Hodgkin's lymphoma that should be made available to selected patients. Based on currently available data, patients that should be prioritized for therapy with ^{90}Y-ibritumomab tiuxetan are those with follicular non-Hodgkin's lymphoma who are refractory to chemotherapy and rituximab and those with transformed non-Hodgkin's lymphoma that is refractory to at least one prior course of chemotherapy, with or without rituximab.

- It is the opinion of the Hematology Disease Site Group that the benefit of ^{90}Y-ibritumomab tiuxetan radioimmunotherapy may be generalizable to other relapsed or refractory indolent non-Hodgkin's lymphomas previously treated with rituximab. However, the benefit may not extend to patients with chronic lymphocytic leukemia/small

lymphocytic lymphoma (CLL/SLL), and ^{90}Y-ibritumomab tiuxetan radioimmunotherapy cannot be routinely recommended in this group of patients.

- The available evidence does not support the use of ^{90}Y-ibritumomab tiuxetan in patients with refractory or relapsed low-grade or follicular non-Hodgkin's lymphoma prior to the use of rituximab.

- Based on available evidence, dosimetry (calculation of actual radiation absorbed to specific organs) is not required in the routine administration of ^{90}Y-ibritumomab tiuxetan.

- There is insufficient evidence to support or refute the use of imaging studies (to ensure appropriate biodistribution) prior to drug administration. In the absence of evidence, we recommend that the use of imaging be guided by the manufacturer's product monograph.

Qualifying Statements

- ^{90}Y-ibritumomab tiuxetan should be administered according to published dosing strategies, based on actual patient body weight and initial platelet count. Patients with platelet counts greater than or equal to 150 x 10^9/L should receive a dose of 0.4 mCi/kg (the maximum dose, regardless of weight, is 32 mCi). Patients with platelet counts 100-149 x 10^9/L should receive a dose of 0.3 mCi/kg. The agent should not be given to patients with platelets less than 100 x 10^9/L, absolute neutrophil count less than 1.5 x 10^9/L, prior myeloablative therapy with stem cell support, or bone marrow involvement greater than 25%.
- The Hematology Disease Site Group appreciates that the key trial guiding the opinion regarding indolent non-Hodgkin's lymphoma included only patients with follicular non-Hodgkin's lymphoma. However, it is unlikely that future trials of ^{90}Y-ibritumomab tiuxetan will include patients with other indolent non-Hodgkin's lymphoma histologies. Therefore, the Hematology Disease Site Group agreed that an opinion was warranted regarding the generalizability of that evidence to indolent non-Hodgkin's lymphoma.

Key Evidence

The primary evidence regarding ^{90}Y-ibritumomab tiuxetan is described in four of the largest fully published trials:

1. A randomized controlled trial (1) comparing ^{90}Y-ibritumomab tiuxetan radioimmunotherapy to rituximab monotherapy in 143 patients with relapsed or refractory low-grade, follicular, or transformed lymphoma. ^{90}Y-ibritumomab tiuxetan radioimmunotherapy was associated with a higher objective response rate (80% versus 56%; p=0.002) but similar time-to-progression (10.6 versus 10.1 months; p=0.26) compared to rituximab treatment.
2. A single-arm trial of ^{90}Y-ibritumomab tiuxetan radioimmunotherapy in 57 patients with rituximab-refractory follicular lymphoma (2). ^{90}Y-ibritumomab tiuxetan radioimmunotherapy was associated with an objective response rate of 70% with a median time-to-progression of 6.8 months.
3. A single-arm phase II trial of ^{90}Y-ibritumomab tiuxetan in 30 patients with relapsed or chemotherapy-refractory low-grade lymphoma and mild thrombocytopenia (platelets 100-150x10^9/L) (3). ^{90}Y-ibritumomab tiuxetan radioimmunotherapy resulted in an 83% objective response rate and a median time-to-progression of 9.4 months.

4. A phase I/II dose escalation trial of ^{90}Y-ibritumomab tiuxetan radioimmunotherapy in 51 patients with low-, intermediate-grade, or mantle cell lymphoma (4). The objective response rate was 67%, and the median time-to-progression was 12.9+ months.

Future Research

^{90}Y-ibritumomab tiuxetan in combination with rituximab is being compared with rituximab alone in patients with relapsed or refractory follicular lymphoma. ^{90}Y-ibritumomab tiuxetan is also being compared to iodine I-131 tositumomab therapy in a similar population. ^{90}Y-ibritumomab tiuxetan is also being investigated as consolidation therapy in follicular lymphoma after initial response (5), as part of the preparative regimen for autologous (6,7) and allogeneic stem cell transplantation, and as part of initial therapy for intermediate-grade lymphoma.

Related Guidelines

Program in Evidence-based Care Evidence-based Series:

- #6-8: *Rituximab in Lymphoma and Chronic Lymphocytic Leukemia.*
- #6-19: *Iodine-131 Tositumomab in Lymphoma* (currently under development).

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Evidence-based Series #6-17: Section 2

Ibritumomab Tiuxetan in Lymphoma: A Systematic Review

M. Cheung, A.E. Haynes, A. Stevens, R.M. Meyer, K. Imrie,
and the members of the Hematology Disease Site Group

A Quality Initiative of the
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Report Date: July 17, 2006

QUESTIONS

In patients with lymphoma of any type or stage:

1. What is the role of yttrium-90 (^{90}Y) ibritumomab tiuxetan? Outcomes of interest include survival, quality of life, time-to-progression, response duration, response rate, and toxicity.
2. Which patients are more or less likely to benefit from treatment with ^{90}Y-ibritumomab tiuxetan?
3. Is performance of imaging or dosimetry required for therapy to be safe and effective?

INTRODUCTION

In Ontario, approximately 2400 people are diagnosed with non-Hodgkin's lymphoma (NHL) each year (1), with follicular and other indolent histologies comprising over 40% of the presentations (2). Patients with indolent lymphoma can sustain prolonged remission periods but eventually relapse and require subsequent courses of therapy that lead to fewer and shorter remissions. Rituximab, a monoclonal antibody directed against CD20, has been an important treatment advance in NHL because of its efficacy, short duration of therapy, and acceptable toxicity profile (3). However, relapse is still inevitable. More effective therapeutic options are thus needed for patients who are refractory to or relapse after currently available therapies, including rituximab.

Radioimmunoconjugates, monoclonal antibodies bound to radioisotopes, are an emerging class of agents with activity in lymphoma. These agents allow for the delivery of targeted radiation therapy via the binding of the monoclonal antibody to antigens on the surface of the malignant cells. ^{90}Y-ibritumomab tiuxetan (Zevalin, IDEC Pharmaceuticals, San Diego, CA) is an example of such an agent, consisting of an anti-CD20 monoclonal antibody bound to a pure β-emitting radioactive isotope (^{90}Y) (4). The CD20 antigen targeted by the agent is expressed on more than 90 percent of B-cell NHLs. Initial studies comparing ^{90}Y-ibritumomab tiuxetan radioimmunotherapy (^{90}Y-RIT) to rituximab in patients with refractory or relapsed low-grade/follicular or transformed CD20+ NHL have suggested promise for the new compound (4). However, the use of this agent may be associated with significant costs and additional toxicity. The licensing of this product is imminently expected in Canada. Therefore, the Hematology

Disease Site Group (DSG) has prioritized this systematic review based on the currently available evidence to guide appropriate use of this agent in lymphoma care.

METHODS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC) using the methods of the Practice Guidelines Development Cycle (5). Evidence was reviewed by one member of the Hematology Cancer DSG and a methodologist.

This systematic review is a convenient and up-to-date source of the best available evidence on ibritumomab tiuxetan in lymphoma. The body of evidence is comprised of data primarily from non-randomized controlled trial data or data available only in abstract form. That evidence forms the basis of a clinical practice guideline developed by the Hematology DSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of CCO and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

Entries to MEDLINE (Ovid) (1966 through May 2004), MEDLINE Daily Update (Ovid) (May 19, 2004), MEDLINE® In-Process & Other Non-Indexed Citations (Ovid) (May 19, 2004), HealthStar (Ovid) (1975 through April 2004), CINAHL (Ovid) (1982 through May 2004), and The Cochrane Library (Internet) (2004, Issue 2) databases were searched. The search strategy for MEDLINE is shown in Appendix I; searches in other Ovid databases were similar. Studies were limited to humans but not restricted for language of publication or for publication type or study design.

In addition, conference proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO) (1995-2004) and the American Society of Hematology (ASH) (1996-2004) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp), and the National Institute for Clinical Excellence (http://www.nice.org.uk/) were also searched for existing evidence-based practice guidelines. Personal files were also searched.

Relevant articles and abstracts were selected unblinded and independently by two reviewers. Reviewers scored each item as "yes" (meets inclusion criteria), "no" (if does not meet inclusion criteria), or "maybe" (if uncertainty regarding inclusion exists). If both reviewers agreed that the item met the inclusion criteria, the complete document was retrieved for further analysis. When disagreements occurred, both reviewers reassessed together to achieve consensus. When a score of "maybe" was given by both reviewers or if disagreement persisted, the full document was retrieved and the inclusion criteria reapplied. Reasons for excluding retrieved articles were documented. Agreement between the two reviewers was assessed statistically by using the kappa statistic.

Evidence was reviewed by two reviewers, and the reference lists from those sources were searched for additional trials. The number of non-English citations meeting inclusion is recorded in the Results section. Where needed, an attempt was made to contact the authors of studies for missing or additional data.

During the process of data extraction, the reviewers identified the question of whether dosimetry was clinically necessary as a question of clinical importance that needed to be addressed. This was added as a distinct question. The literature search strategy did not need to be amended for this to be addressed.

Study Selection Criteria

Inclusion Criteria

Published full report articles and published meeting abstracts were considered if they met the following criteria:

1. Studies were prospective phase I, II, or III clinical trials.
2. Studies included adult patients with lymphoma of any type, at any stage, and for any level of performance status.
3. Ibritumomab tiuxetan was examined as a single agent or in combination with other regimens.
4. For comparative trials, ibritumomab tiuxetan was compared with any agent, any combination of agents, or placebo.
5. Results were reported for one or more of the following outcomes: survival, quality of life, time-to-progression, response duration, response rate, or adverse effects.
6. They were systematic reviews, meta-analyses, or evidence-based practice guidelines that assessed ibritumomab tiuxetan in lymphoma.

Exclusion Criteria

Letters, comments, and editorial publication types were excluded. Studies published in languages other than English were excluded due to lack of funding for translation resources.

Synthesizing the Evidence

Primary outcomes of interest are listed above as part of the inclusion criteria. No secondary outcomes of interest or subset analyses were planned. Data appropriate for pooling or meta-analysis were not expected but will be investigated if the possibility exists.

RESULTS

Literature Search Results

A total of 463 citations were identified in the literature search. The agreement between the two reviewers was calculated as kappa=0.917. The two reviewers identified a total of 19 trials investigating the use of ibritumomab tiuxetan for the treatment of adult patients with NHL (6-27). No systematic reviews, meta-analyses, or evidence-based practice guidelines were identified. Two pooled analyses of safety data from five and four trials reported by Witzig et al 2003 (28) and Emmanouilides et al (29), respectively, were identified that treated patients with ^{90}Y-ibritumomab tiuxetan. However, the authors of both reports did not identify the trials included in their analyses (28,29). Two abstract reports were identified that included data from several prospective trials and reported on prognostic factors that correlated with response to treatment with ^{90}Y-ibritumomab tiuxetan (30,31). Two full publications (32,33) and one abstract (34) were identified that reported data on imaging and dosimetry for patients who were treated with ^{90}Y-ibritumomab tiuxetan.

The trials were divided into two categories based on the type of ^{90}Y-ibritumomab tiuxetan treatment patients received: The first category included trials that treated patients with relapsed, refractory, or transformed NHL with ^{90}Y-RIT in a standard regimen (Table 1) that included rituximab 250 mg/m^2 followed by ^{111}In-ibritumomab tiuxetan (on day zero) for dosimetry and imaging; rituximab 250 mg/m^2 was given again on day seven, immediately followed by ^{90}Y-ibritumomab tiuxetan. For the purposes of this systematic review, that regimen will be referred to as standard ^{90}Y-RIT. One randomized controlled trial (6,7,32,33), six single-arm phase II trials (8-10,13-16), and two single-arm phase I/II trials (11,12) were identified that examined standard ^{90}Y-RIT. Three of the trials have been reported in abstract form only in either the conference proceedings of ASCO or ASH (13-15). Six of the trials have also been fully published (6,8,9,11,12,16). Both the randomized trial (6) and the single-arm phase II trial reported by Wiseman et al (9) have had updated results fully published (7,10). The randomized

trial (6) has also had two reports published detailing biodistribution and dosimetry for patients who received ^{90}Y-RIT (32,33).

Table 1. Trials of standard ^{90}Y-ibritumomab tiuxetan radioimmunotherapy: study and patient characteristics.

Author, year (ref)[a]	Additional publications (ref)[b]	Patient characteristics	Treatment	N
Randomized trials of ^{90}Y-RIT				
Witzig, 2002 (6)	(7,32,33)	Relapsed/refractory low-grade, follicular, or transformed CD20+ NHL	^{90}Y-RIT[c] 0.4 mCi/kg	73
			Rituximab 375 mg/m^2 weekly x4	70
Single arm trials of ^{90}Y-RIT				
Witzig, 2002 (8)	N/A	Rituximab refractory follicular B-cell NHL (additional pts with small lymphocytic or transformed NHL from rituximab arm of RCT (6) were enrolled for safety analysis)	^{90}Y-RIT[c] 0.4 mCi/kg	57[d]
Wiseman, 2002 (9)	(10)	Relapsed/refractory low-grade, follicular, or transformed CD20+ NHL with mild thrombocytopenia (platelets 100-150x10^9/L)	^{90}Y-RIT[c] 0.3 mCi/kg	30
Witzig, 1999 (11)	N/A	1) Relapsed/refractory low-grade or follicular NHL who had failed prior treatment with two regimens or an anthracycline 2) Relapsed intermediate-grade or mantle-cell NHL	^{90}Y-RIT[c] dose escalation (0.2-0.4 mCi/kg)	51
Knox, 1996 (12)	N/A	Relapsed/refractory low-grade or intermediate-grade NHL	^{90}Y-RIT[c,e] dose escalation (13.5-50 mCi) + ASCT as needed	18
Morschhauser, 2004 (13) Abstract	N/A	Elderly pts with first relapsed or primary refractory diffuse large B-cell NHL who were not candidates for ASCT	^{90}Y-RIT[c] 0.4 mCi/kg	104
Oki, 2004 (14) Abstract	N/A	Relapsed/refractory mantle cell lymphoma	^{90}Y-RIT[c,f] 0.3-0.4 mCi/kg	15
Liu, 2003 (15) Abstract	N/A	Minimal residual disease after chemotherapy for chronic lymphocytic leukemia	^{90}Y-RIT[c,f] 0.3-0.4 mCi/kg	15
Tsimberidou, 2004 (16)	N/A	Histologically proven CD20+ Richter Syndrome and <25% lymphoma and/or chronic lymphocytic leukemia in the bone marrow	^{90}Y-RIT[c,f] 0.3-0.4 mCi/kg	7

Notes: ASCT – autologous stem cell transplantation; N/A – not applicable; NHL – non-Hodgkin's lymphoma; pts – patients; RCT – randomized controlled trial; ref – reference; ^{90}Y-RIT – ^{90}Y-ibritumomab tiuxetan radioimmunotherapy.

[a] First full publication or first abstract publication if trial not fully published.

[b] Abstracts or full publications with updated or additional data used in this systematic review.

[c] ^{90}Y-ibritumomab tiuxetan (standard treatment with ^{90}Y-ibritumomab tiuxetan includes a dose of rituximab 250 mg/m^2 followed by ^{111}In-ibritumomab tiuxetan (on day 0) for dosimetry and imaging and rituximab 250 mg/m^2 followed by ^{90}Y-ibritumomab tiuxetan (on day 7). Rituximab is given to enable clearance of peripheral B-cells and maximize biodistribution prior to RIT therapy.

[d] Three patients were previously enrolled in the rituximab arm of the RCT reported by Witzig et al (6) and were only to be included in the safety analysis.

[e] Unlabelled ibritumomab tiuxetan was used as the pre-treatment antibody.

[f] Dose dependent on platelet count.

The second category included trials that examined ^{90}Y-RIT in alternative regimens or as part of a combination chemotherapy regimen (Table 2). For the purposes of this systematic review, those regimens will be referred to as alternative ^{90}Y-RIT. Alternative regimens included ^{90}Y-RIT consolidation therapy after first-line induction therapy with chemotherapy, or ^{90}Y-ibritumomab tiuxetan combined with higher doses of rituximab, or ^{90}Y-ibritumomab tiuxetan given in sequential doses. One randomized controlled trial (17), five single-arm phase I trials (20-22,25,26), one single-arm phase I/II trial (24), and four single-arm phase II trials (18,19,23,27) were identified that examined alternative ^{90}Y-RIT. All of the trials have been reported in abstract form only.

Not all of the additional published reports of trials included in this systematic review have been referenced. Only the original publications of trials have been referenced, except in cases where more recent publications included data that the original publications did not. Full publications of trials were referenced, when available, rather than the original abstract publication.

Table 2. Trials of alternative ^{90}Y-ibritumomab tiuxetan radioimmunotherapy: study and patient characteristics.

Author, year (ref)	Patient characteristics	Treatment	N
	Randomized trials of ^{90}Y-RIT		
Radford, 2003 (17) Abstract	Stage III or IV CD20+ follicular NHL in remission (CR or PR) after first-line induction therapy with single agent chlorambucil, CVP, CHOP, or CHOP-like regimens	^{90}Y-RIT[a] 0.4 mCi/kg	14
		Observation	17
	Single arm trials of ^{90}Y-RIT		
Shipley, 2004 (18) Abstract	Untreated pts with stage II-IV (grade 1-3) follicular NHL; ECOG PS 0-2	Rituximab 375 mg/m^2 weekly x4 followed by CHOP-R x3 or CVP-R[b] x3 followed five weeks after last course by ^{90}Y-RIT[a], dose NR	33[c]
Sweetenham, 2004 (19) Abstract	Untreated pts with low-grade follicular NHL	^{90}Y-RIT[a,d] 0.3-0.4 mCi/kg + maintenance rituximab 375 mg/m^2 weekly x4 every 6 months over 2 years	10
Witzig, 2003 (20) Abstract	Relapsed low-grade CD20+ NHL	^{90}Y-RIT[a] 0.4 mCi/kg followed after 12-24 weeks by ^{90}Y-RIT[a] dose escalation (0.2-0.4 mCi/kg) for responders	18
Forero-Torres, 2003 (21) Abstract	Relapsed/refractory low-grade follicular or transformed NHL	Rituximab 375 mg/m^2 weekly x4 followed by ^{90}Y-RIT[a] dose escalation (0.4-0.7 mCi/kg)	5[e]
Winter, 2004 (22) Abstract	Relapsed/refractory CD20+ NHL	^{90}Y-RIT[a] dose escalation (patient-specific dose to deliver cohort-defined radiation doses ranging from 100-1100 cGy) + high-dose BEAM (dose NR) + ASCT	28
Fung, 2003 (23) Abstract	Patients with poor-risk aggressive CD20+ NHL and who are ≥55 years old or who had previously received dose-limiting radiation that precluded total body irradiation	^{90}Y-RIT[a] 0.4 mCi/kg followed by BEAM (carmustine 300 mg/m^2 + cytarabine 800 mg/m^2 + etoposide 800 mg/m^2 + melphalan 140 mg/m^2) + ASCT	12
Nademanee, 2004 (24) Abstract	Poor-risk or relapsed B-cell NHL	^{90}Y-RIT[a] dose escalation (40-100 mCi) followed by etoposide 40-60 mg/kg + CY (dose NR) + ASCT	31
Flinn, 2004 (25) Abstract	Relapsed/refractory low-grade, mantle cell, or diffuse large cell NHL	Rituximab 375 mg/m^2 weekly x4 followed by CY 2.5 g/m^2 followed by ^{90}Y-RIT[a] dose escalation (20-120 mCi) + ASCT	13
Vose, 2003 (26) Abstract	Relapsed B-cell NHL following high-dose chemotherapy + ASCT	^{90}Y-RIT[a] dose escalation (0.1-0.2 mCi/kg)	16
Jacobs, 2004 (27) Abstract	Relapsed/refractory B-cell NHL following ASCT	^{90}Y-RIT[a,d] 0.3-0.4 mCi/kg	6

Notes: ASCT – autologous stem cell transplantation; BEAM – carmustine, etoposide, cytarabine, and melphalan; CHOP – cyclophosphamide, adriamycin, vincristine, and prednisone; CHOP-R – cyclophosphamide, adriamycin, vincristine, prednisone, and rituximab; CR – complete response; CVP – cyclophosphamide, vincristine, and prednisone; CVP-R – cyclophosphamide, vincristine, prednisone, and rituximab; CY – cyclophosphamide; ECOG – Eastern Cooperative Oncology Group; NHL – non-Hodgkin's lymphoma; NR – not reported; PR – partial response; PS – performance status; ref – reference; ^{90}Y-RIT – ^{90}Y-ibritumomab tiuxetan radioimmunotherapy.

[a] ^{90}Y-ibritumomab tiuxetan (standard treatment with ^{90}Y-ibritumomab tiuxetan includes a dose of rituximab 250 mg/m^2 followed by ^{111}In-ibritumomab tiuxetan (on day 0) for dosimetry and imaging and rituximab 250 mg/m^2 followed by ^{90}Y-ibritumomab tiuxetan (on day 7). Rituximab is given to enable clearance of peripheral B-cells and maximize biodistribution prior to RIT therapy.

[b] Patients with cardiac ejection fraction <45% received CVP-R.

[c] Only 33 of 40 patients have been accrued.

[d] Dose dependent on platelet count.

[e] Data available only for the first cohort (0.4 mCi/kg) of five patients.

Trials of Standard ^{90}Y-ibritumomab Tiuxetan Radioimmunotherapy

Study Quality

Only one of the nine trials of standard ^{90}Y-RIT was a randomized controlled trial (6). The authors of that randomized trial did not report on the method of randomization. In addition, allocation concealment was not reported, and no statement was made on withdrawals or dropouts. A sample-size calculation included in the full report indicated that 150 patients were needed, at p=0.05, to yield a statistical power of 80% to detect a 25% difference in objective response rate for the treatment group compared to the control group. All of the 143 patients initially enrolled in the trial have been followed for a median of 44 months. Data analysis was conducted using an intention-to-treat approach. The remaining eight trials of standard ^{90}Y-RIT were non-comparative single-arm trials. Three trials have been fully published and included 54 (8), 30 (9), and 51 (11) patients. One trial, published in abstract form, included 104 (13) patients. The remaining four trials had small sample sizes or were published only as abstracts (12,14-16).

Study Characteristics

Study and patient characteristics of the trials of standard ^{90}Y-RIT can be found in Table 1. The randomized trial (6) included patients with relapsed or refractory low-grade, follicular, or transformed CD20+ NHL. Patients were randomized to either standard ^{90}Y-RIT 0.4 mCi/kg or to rituximab 375 mg/m^2 weekly for four doses. The primary study end point was objective response, and the secondary end points were response duration, time to progression, complete response, partial response, time to next anti-cancer therapy, and quality of life. The trial was designed to detect a 25% higher objective response rate in the standard ^{90}Y-RIT (treatment) group compared with the rituximab (control) group.

The single-arm trials included two phase I/II dose escalation trials (11,12) and six phase II trials (8,9,13-16) that used one of two doses of ^{90}Y-ibritumomab tiuxetan, 0.3 mCi/kg or 0.4 mCi/kg. Three of those trials used both doses, with the lower dose given to patients with a platelet count <150x10^9/L (14), or 100-149x10^9/L (16). The third trial did not report the platelet count required for patients to receive the lower dose (15). Two of the eight single-arm trials included patients with chronic lymphocytic leukemia (15,16), with one of those trials including only patients with CD20-positive Richter Syndrome and less than 25% lymphoma or chronic lymphocytic leukemia in the bone marrow (16). The remaining six trials included patients with refractory disease (8,9,11-14), and five trials included patients with relapsed disease (9,11-14). Four trials included patients with follicular B-cell NHL (8,9,11,12), with three of those trials including patients with any low-grade NHL (9,11,12). Wiseman et al (9) also included patients with transformed CD20-positive NHL. Witzig et al, 1999 (11) and Knox et al (12) also included patients with intermediate-grade NHL. Both Witzig et al, 1999 (11) and Oki et al (14) included patients with mantle cell lymphoma. Morschhauser et al (13) included only elderly patients with first relapsed or primary refractory diffuse large B-cell NHL. The number of patients in the single-arm trials ranged from seven to 104. Of note, Witzig et al, 2002 (8) included rituximab-refractory patients with small lymphocytic or transformed NHL who were previously enrolled in the control group of the randomized controlled trial reported by Witzig et al, 2002 (6).

Outcomes

Response rate

The response to standard ^{90}Y-RIT was evaluated in all nine trials (6,8,9,11-16) and is presented in Table 3. In the randomized trial comparing ^{90}Y-RIT with rituximab, differences in objective (80% versus [vs.] 56%; p=0.002) and complete (30% vs. 16%; p=0.04) response rates were significantly higher in patients allocated to receive ^{90}Y-RIT (6). In the eight single-arm trials, objective response rates ranged from 0% to 83%, and complete response rates ranged

from 0% to 37% (8,9,11-16). In trials of mainly indolent histology NHL, objective response rates ranged from 67% to 83% (6,8,9,11,12,14).

Table 3. Trials of standard ^{90}Y-ibritumomab tiuxetan radioimmunotherapy: response.

Author, year (ref)	Treatment	N	OR (%)	CR (%)	Median TTP (months)	Median DR (months)
Randomized trials of ^{90}Y-RIT						
Witzig, 2002 (6)	^{90}Y-RIT 0.4 mCi/kg	73	80	30	10.6	23.3
	Rituximab 375 mg/m^2 weekly x 4	70	56 *p*=0.002	16 *p*=0.04	10.1 *p*=0.26	10.9+ *p*=0.209
Single arm trials of ^{90}Y-RIT						
Witzig, 2002 (8)	^{90}Y-RIT 0.4 mCi/kg	57	70	14	6.8[a]	6.4[a]
Wiseman, 2002 (9)	^{90}Y-RIT 0.3 mCi/kg	30	83	37	9.4	11.5
Witzig, 1999 (11)	^{90}Y-RIT dose escalation (0.2-0.4 mCi/kg)	51	67	26	12.9+	11.7+
Knox, 1996 (12)	^{90}Y-RIT dose escalation (13.5-50 mCi) + ASCT as needed	18	72	33	3-29+ (range)	NR
Morschhauser, 2004 (13) Abstract	^{90}Y-RIT 0.4 mCi/kg for all patients[b]	A1: 33 A2: 10 A3: 33 B: 28 Overall: 104	A1: 52 A2: 40 A3: 58 B: 19 Overall: 44	NR	A1: 5.9 A2: 2.3 A3: 6.2 B: 1.6 Overall: NR	NR
Oki, 2004 (14) Abstract	^{90}Y-RIT 0.3-0.4 mCi/kg	15	33	22	4.9	5.7
Liu, 2003 (15) Abstract	^{90}Y-RIT 0.3-0.4 mCi/kg	15	N/A	1/12 patients MRD negative	NR	NR
Tsimberidou, 2004 (16)	^{90}Y-RIT 0.3-0.4 mCi/kg	7	0	0	1.3	NR

Notes: ASCT – autologous stem cell transplantation; CR – complete response; DR – duration of response; MRD – minimal residual disease; N/A – not applicable; NR – not reported; OR – objective response; ref – reference; TTP – time-to-progression; ^{90}Y-RIT – ^{90}Y-ibritumomab tiuxetan radioimmunotherapy.

[a] Calculated for 54 evaluable patients.

[b] Patients were divided into Group A (previously treated with chemotherapy alone) or Group B (previously treated with chemotherapy and rituximab). Patients in Group A were further divided into stratum A1 (primary refractory disease), stratum A2 (relapse within one year from presentation), and stratum A3 (relapse more than one year from presentation).

Time-to-progression

Data on median time-to-progression were reported in seven trials (Table 3). In the randomized trial, the median time-to-progression was 10.6 months in the group receiving ^{90}Y-RIT compared to 10.1 months in patients receiving rituximab, although that difference was not statistically significant (p=0.26) (7). A comparable duration of median time-to-progression periods was noted in single-arm trials of relapsed lymphoma patients, with results ranging from 1.6 months to 12.9+ months (8-11,13,14). Time-to-progression was also reported by Knox et al (12) and ranged from 3-29+ months.

Response duration

The median response duration was reported in five trials (Table 3). Updated response duration data was reported for the randomized trial by Gordon et al (7). Median response duration for patients with a complete response was reported as 23.3 months for patients receiving ^{90}Y-RIT compared to 10.9+ months for patients receiving rituximab, although that difference was not statistically significant (p=0.209). In the single-arm trials, response durations ranged from 5.7 months to 11.7+ months (8,9,11,14). Witzig et al, 2002 (8), reported that a

secondary exploratory analysis in patients with rituximab-refractory follicular lymphoma was performed at the request of the US Food and Drug Administration (FDA). That analysis demonstrated that, in 17 patients who responded to prior rituximab treatment, response duration was 11.5 months with ^{90}Y-RIT compared to three months with the prior rituximab treatment (p=0.001) (8).

In the randomized trial, the median time to next anti-lymphoma treatment was 17.6 months in patients receiving ^{90}Y-RIT and 13.1 months in patients receiving rituximab; however, this difference was not statistically significant (p=0.47) (7). For the single-arm trials of ^{90}Y-RIT administered in a standard treatment regimen, the median time to next anti-lymphoma treatment was reported for only one trial, as 14.6 months for rituximab-refractory patients (10).

Quality of life

Quality of life was analyzed in the randomized controlled trial (6) and in the non-randomized single-arm trial of rituximab-refractory patients (8), using the Functional Assessment of Cancer Therapy – General (FACT-G) quality-of-life questionnaire. Higher scores on the FACT-G questionnaire indicated improved quality of life. The randomized trial (6) reported an increase in the FACT-G score from baseline for both the rituximab group (N=36) and the ^{90}Y-RIT group (N=45). That difference was statistically significant only for the ^{90}Y-RIT group (86.9 at baseline compared to 93.3 at week 12; p=0.001). No comparison in scores between the ^{90}Y-RIT arm and the rituximab arm was presented. The single-arm trial (8) reported a significant increase in the mean score for 20 patients who completed the FACT-G survey (85 at baseline compared to 92.8 at week 12; p=0.003). The clinical relevance of that increase is unclear.

Survival

Survival data was reported only for two of the single-arm trials of standard ^{90}Y-RIT (10,13). Schilder et al (10) reported that median overall survival for 30 patients who received ^{90}Y-RIT 0.3 mCi/kg had not been reached after a median follow-up of 36.5 months. Morschhauser et al (13) reported median overall survival for patients with relapsed or refractory DLBCL. After a minimum follow-up of 32 months, median overall survival was 4.5 months for patients previously treated with chemotherapy and rituximab, 22.4 months for patients with primary refractory disease who were previously treated with chemotherapy alone, and not yet reached for patients with relapsed disease who were previously treated with chemotherapy alone. The sample sizes and preliminary nature of those reports precludes any conclusions regarding survival benefit gained from use of this agent.

Toxicity

Toxicity data for the trials of ^{90}Y-RIT can be found in Tables 4 and 5. The authors of the randomized trial reported that the overall incidence of non-hematological adverse events for the ^{90}Y-RIT arm was similar to the rituximab arm (p=0.36) (6). However, no further statistical comparisons were reported for either non-hematological or hematological adverse events. Grade 3 (absolute neutrophil count [ANC] <1.0 x 10^9/L; platelets <50 x 10^9/L) or grade 4 (ANC <0.5 x 10^9/L; platelets <10 x 10^9/L) neutropenia and thrombocytopenia occurred in 59% and 61%, respectively, of 73 patients who received ^{90}Y-RIT. The median duration of grade 3 or 4 neutropenia and thrombocytopenia was 27 days and 23 days, respectively. Grade 4 neutropenia and thrombocytopenia occurred in none of the 70 patients who received rituximab; however, no data were reported for grade 3 neutropenia or thrombocytopenia. Grade 3 or 4 anemia occurred in 2% of patients who received ^{90}Y-RIT. The percentage of patients who received rituximab and developed grade 3 or 4 anemia was not reported. Very few grade 3 or 4 toxicities were reported, with asthenia and pain occurring in 1% and 4% of patients who received ^{90}Y-RIT, and abdominal pain and pruritis occurring in 1% each of patients who

received rituximab. No other grade 3 or 4 non-hematological toxicities were reported. Grade 1 or 2 nausea and vomiting occurred in 43% and 19%, respectively, of patients who received ^{90}Y-RIT and in 19% and 7% of patients who received rituximab. Human anti-murine antibodies (HAMA) or human anti-chimeric antibodies (HACA) developed in 1.4% of patients in each arm of the randomized trial after treatment.

Grade 3 or 4 neutropenia or granulocytopenia was reported in four single-arm trials and ranged from 29% of seven patients to 72% of 18 patients (12,14-16). Grade 4 neutropenia, was reported in five trials and ranged from 22% of 18 patients to 35% of 57 patients (8,9,11,12,15). Grade 3 or 4 thrombocytopenia was reported in four single-arm trials and ranged from 20% of 15 patients to 71% of seven patients (12,14-16). Grade 4 thrombocytopenia was reported in five trials and ranged from none of 15 patients to 50% of 18 patients (8,9,11,12,15). Grade 3 or 4 anemia, reported in four trials, ranged from 3% of 30 patients to 22% of 18 patients (8,9,12,15). Febrile neutropenia was reported in two trials as 3% of 30 patients and 11% of 18 patients (9,12). The most common non-hematological toxicities, of any grade, were asthenia, chills, fever, headache, nausea, vomiting, and infection. Sepsis, occurring in 14% of 15 patients (14), was the only grade 3 or 4 non-hematological toxicity that was reported to have occurred in more than 4% of patients in any of the single-arm trials. Four of the single-arm trials reported that HAMA or HACA developed after treatment and occurred in up to 22% of patients (8,9,11,12).

A pooled-analysis of patients with relapsed indolent lymphoma provided integrated safety data on 349 patients (28) that were included in five trials. Non-hematologic toxicity was common (reported in 80% of patients) but generally mild and related to drug infusion. Asthenia (35%), nausea (25%), and chills (21%) were the most common non-hematological toxicities of any grade. Grade 3 or 4 non-hematological toxicities occurred in 11% of patients. Myelosuppression was common but tended to be delayed in onset, with cytopenia nadirs occurring seven to nine weeks after treatment. Grade 4 neutropenia and thrombocytopenia occurred in 30% and 10% of patients receiving the standard 0.4 mCi/kg dose, respectively. Infections requiring hospitalization occurred in 7% of patients. A total of 211 patients were tested for HAMA or HACA after treatment; three patients were identified as HAMA or HACA positive.

Myelodysplasia or acute myeloid leukemia (MDS/AML) developed in seven of 211 patients (3.3%) from eight months to 50 months following ^{90}Y-RIT, after a median follow-up of 38 months in a pooled analysis of four trials reported in abstract form by Emmanouilides et al (29). Patients in those trials had been treated with a median of two prior therapies, most often including prior alkylator therapy. Most patients had chromosome five and/or seven abnormalities suggesting an association with previous alkylator treatment.

Table 4. Trials of standard ^{90}Y-ibritumomab tiuxetan radioimmunotherapy: hematological toxicities.

			Neutrophils				Platelets				Erythrocytes		
Author, year (ref)	Intervention	N	Median nadir (x10^9/L)	ANC <1.0x10^9/L (%)	ANC <0.5x10^9/L (%)	Median duration of G3/4 (days)	Median nadir (x10^9/L)	Platelets <50x10^9/L (%)	Platelets <10x10^9/L (%)	Median duration of G3/4 (days)	Anemia Grade 3/4 (%)	Hemoglobin median nadir (g/dL)	Febrile Neutropenia (%)
Randomized controlled trials of ^{90}Y-RIT													
Witzig, 2002 (6)	^{90}Y-RIT (0.4 mCi/kg)	73	0.9	25	32	27	41	55	6	23	2	10.8	NR
	rituximab (375 mg/m^2 weekly x4)	70	2.9	NR	0	NR	188.5	NR	0	NR	NR	12.9	NR
Single arm trials of ^{90}Y-RIT													
Witzig, 2002 (8)	^{90}Y-RIT (0.4 mCi/kg)	57	0.7	NR	35	22	33	NR	9	24	4	9.9	NR
Wiseman, 2002 (9)	^{90}Y-RIT (0.3 mCi/kg)	30	0.6	NR	33	28.5	26.5	NR	13	29.5	3	10.1	3
Witzig, 1999 (11)	^{90}Y-RIT dose escalation	30[a]	1.1	NR	27[b]	10.5	49.5	NR	10[b]	14	NR	9.9	NR
Knox, 1996 (12)	^{90}Y-RIT (13.5-50 mCi)[c]	18	NR	50[d]	22[d]	NR	NR	17	50	NR	22	NR	11
Morschhauser, 2004 (13) abstract	^{90}Y-RIT (0.4 mCi/kg)	104	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Oki, 2004 (14) abstract	^{90}Y-RIT (0.3-0.4 mCi/kg)	15	NR	33		0	NR	20		15	NR	NR	NR
Liu, 2003 (15) abstract	^{90}Y-RIT (0.3-0.4 mCi/kg)	15	NR	13	33	42 (G3) 13 (G4)	NR	67	0	42 (G3) 24 (G4)	13	NR	NR
Tsimberidou, 2004 (16)	^{90}Y-RIT (0.3-0.4 mCi/kg)	7	NR	29		NR	NR	71		NR	NR	NR	NR

Notes: ANC – absolute neutrophil count; G – grade; N – number of patients; NR – not reported; ref – reference; ^{90}Y-RIT – ^{90}Y-ibritumomab tiuxetan radioimmunotherapy.
[a] Toxicity data available for the 30 patients that received the 0.4 mCi/kg dose of ^{90}Y-ibritumomab tiuxetan.
[b] Grade 4 neutropenia and thrombocytopenia was reported as a percentage of all 51 patients included in the trial.
[c] Autologous stem cell transplantation and granulocyte-colony stimulating factor were given to patients as clinically indicated.
[d] Granulocytopenia.

Table 5. Trials of standard ^{90}Y-ibritumomab tiuxetan radioimmunotherapy: non-hematological toxicities*, any grade.

Author, year (ref)	N	Asthenia (%)	Chills (%)	Fever (%)	Headache (%)	Throat irritation (%)	Nausea (%)	Vomiting (%)	Dyspnea (%)	Cough (%)	Infection (%)	HACA / HAMA (%)	Patient deaths
Randomized controlled trials of ^{90}Y-RIT													
Witzig, 2002 (6)	73 ^{90}Y-RIT	NR	NR	NR	NR	NR	43[a]	19[a]	15[a]	15[a]	5[b]	1.4	NR
	70 rituximab	NR	NR	NR	NR	NR	19[a]	7[a]	7[a]	7[a]	1[b]	1.4	NR
Single arm trials of ^{90}Y-RIT													
Witzig, 2002 (8)	57	54	25	21	12	12	35	NR	12	NR	7[b], 2[c]	2	NR
Wiseman, 2002 (9)	30	40	37	23	27	17	33	23	10	17	NR	0	0
Witzig, 1999 (11)	30[d]	22[a]	28	22	10	NR	22	NR	NR	NR	6[b]	2	0
Knox, 1996 (12)	104	NR	11	78	6	NR	NR	NR	NR	NR	44	22	4
Morschhauser, 2004 (13) abstract	18	NR	NR	NR	NR	NR	NR	NR	NR	NR	7[b]	NR	NR
Oki, 2004 (14) abstract	15	NR	NR	NR	NR	NR	NR	NR	NR	NR	7[b]	NR	NR
Liu, 2003 (15) abstract	15	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tsimberidou, 2004 (16)	7	NR	NR	NR	NR	NR	NR	NR	NR	NR	22[c]	NR	NR

Notes: HACA – human anti-chimeric antibody; HAMA – human anti-murine antibody; N – number of patients; NR – not reported; ref – reference; ^{90}Y-RIT – ^{90}Y-ibritumomab tiuxetan radioimmunotherapy.

* Adverse events that occurred in ≥15% of patients.

[a] Grades 1 or 2 toxicities.

[b] Hospitalization for infection.

[c] Sepsis.

[d] Toxicity data available for the 30 patients that received the 0.4 mCi/kg dose of ^{90}Y-ibritumomab tiuxetan.

Predictive Factors for Treatment with ^{90}Y-ibritumomab Tiuxetan Radioimmunotherapy

In the randomized phase III trial reported by Witzig et al 2002, logistic regression analysis demonstrated that patients resistant to the last course of therapy and patients with follicular lymphoma were more likely to benefit from ^{90}Y-RIT than rituximab therapy (6). In smaller phase II studies, independent predictors for overall response included non-bulky disease (<5 cm) (11,30), absence of bone marrow involvement (9,11), fewer prior therapies before RIT treatment (9,31), and low-grade/follicular histology (9,11). Analyses were conducted using stepwise multivariate logistical regression (6,9,11,30), Fisher's exact test (9), or the method was not reported (31).

Bone marrow involvement with lymphoma was consistently noted to predict for hematologic toxicity with ^{90}Y-RIT (9,11,28). In the pooled analyses of 349 patients, any degree of bone marrow involvement resulted in significantly greater grade 4 neutropenia (p=0.001, Fisher's exact test) and thrombocytopenia (0.013, Fisher's exact test) compared to patients without bone marrow involvement and the incidence of cytopenias increased with degree of bone marrow involvement at baseline (28).

Dosimetry and Imaging

Dosimetry is a method of estimating the dose of radiation administered to specific organs. Radiation dosimetry was incorporated into early clinical trials prior to the administration of ^{90}Y-ibritumomab tiuxetan to ensure that the absorbed doses did not exceed the pre-defined thresholds. In the reported trials, all patients were predicted to receive acceptable radiation absorbed doses to non-involved organs and marrow (32). Dosimetry has not been found to correlate with toxicity or efficacy (33). Therefore, detailed dosimetry studies have not been routinely recommended for clinical use.

Imaging refers to the evaluation of gamma images to ensure that drug biodistribution is appropriate (11). Early commercial experience suggests that inappropriate biodistribution that would warrant discontinuation of ^{90}Y-labelled antibody occurs rarely (1.2% incidence) (34). The US Food and Drug Administration approval of ^{90}Y-ibritumomab tiuxetan was contingent on imaging studies as a safety measure prior to the administration of the agent. In contrast, the European Commission (European Agency for the Evaluation of Medicinal Products) approval did not require those precautions. Ongoing and future protocols will assess the safety of ^{90}Y-ibritumomab tiuxetan administration without the pre-dose imaging.

Trials of Alternative ^{90}Y-ibritumomab Tiuxetan Radioimmunotherapy

Study Quality

Only one of the 11 trials of alternative ^{90}Y-RIT was a randomized controlled trial (17). The abstract report of that trial included only interim results for toxicity for a total of 31 patients. The method of randomization, blinding, the length of follow-up, and the primary and secondary end points of the trial were not reported. Neither did the authors report the statistical power of the trial. The remaining 10 trials of alternative ^{90}Y-RIT were non-comparative single-arm trials (18-27).

Study Characteristics

Study and patient characteristics for the trials of alternative ^{90}Y-RIT can be found in Table 2. The randomized trial reported in abstract form by Radford et al (17) included patients with stage III or IV CD20-positive follicular NHL in remission after first-line induction chemotherapy. Patients were randomized to either consolidation ^{90}Y-RIT 0.4 mCi/kg or to observation. Thirty-one patients (^{90}Y-RIT, N=14; observation, N=17) have been enrolled to date. The abstract report was only an interim analysis for toxicity. No data were available for response rate, survival, time-to-progression, response duration, or quality of life.

The single-arm trials of alternative ^{90}Y-RIT included a variety of patients and treatments (Table 2). Four trials included rituximab 375 mg/m^2 weekly for four doses as either part of a regimen including chemotherapy followed by ^{90}Y-RIT (18,25), or preceding ^{90}Y-RIT (21), or as maintenance therapy following ^{90}Y-RIT (19). Two of those trials enrolled patients with untreated follicular NHL (18,19). Three trials used regimens including chemotherapy [carmustine/cytarabine/etoposide/melphalan (BEAM) (22,23) or etoposide plus cyclophosphamide (24)] and autologous stem cell transplantation (ASCT) following ^{90}Y-RIT. One trial enrolled patients on a regimen of two sequential doses of ^{90}Y-RIT (20). Vose et al (26) enrolled patients with relapsed B-cell NHL following high-dose chemotherapy and ASCT onto a phase I dose escalation trial of ^{90}Y-RIT 0.1-0.2 mCi/kg. Jacobs et al (27) included patients with relapsed or refractory B-cell NHL following ASCT in a phase II trial of ^{90}Y-RIT 0.3-0.4 mCi/kg. All of the single-arm trials of alternative ^{90}Y-RIT have had preliminary results reported in abstract form only. The number of patients in those trials ranged from five to 33.

Outcomes

Response

The response to alternative ^{90}Y-RIT was evaluated in seven trials (18-21,25-27) and is presented in Table 6. The randomized trial reported by Radford et al (17) that compared consolidation ^{90}Y-RIT with observation did not report data on response. Seven of the single-arm trials reported objective response rates that ranged from 17% to 83% (18-21,25-27). Six of those trials reported complete response rates that ranged from 17% to 80% (18,19,21,25-27).

Time-to-progression

None of the trials of alternative ^{90}Y-RIT reported data on time-to-progression.

Response duration

None of the trials of alternative ^{90}Y-RIT reported data on median response duration. Disease-free survival or progression-free survival was reported in five of the single-arm trials of alternative ^{90}Y-RIT (20,22-25) (Table 6). Disease-free survival was reported in four trials as 50% at six months (25), 80% at two years (23), 92% at a median follow-up of nine months (20), and 61% at a maximum follow-up of 27 months. Progression-free survival was reported by Winter et al (22) as 50% at three years for 28 patients.

Quality of life

None of the trials of alternative ^{90}Y-RIT reported data on quality of life.

Survival

Survival data was not reported for the randomized trial (17) or the majority of single-arm trials (18-21,23,25-27) of alternative ^{90}Y-RIT. However, both Winter et al (22) and Nademanee et al (24) did report estimated overall survival. Winter et al (22) reported that, for 28 patients that received ^{90}Y-RIT in a dose escalation trial followed by high-dose BEAM and ASCT, the three-year estimated overall survival was 60%, after a median follow-up of one year. Nademanee et al (24) reported that, for 31 patients that received ^{90}Y-RIT in a dose escalation trial (40-100 mCi) followed by etoposide, cyclophosphamide, and ASCT, the two-year estimated overall survival was 93%, after a median follow-up of 21 months. The sample sizes and preliminary nature of the reports for trials of alternative ^{90}Y-RIT preclude any conclusions regarding survival benefit gained from use of this agent.

Table 6. Trials of alternative ^{90}Y-ibritumomab tiuxetan radioimmunotherapy: response.

Author, year (ref)	Treatment	N	OR (%)	CR (%)	DFS / PFS
Randomized trials of ^{90}Y-RIT					
Radford, 2003 (17) Abstract	^{90}Y-RIT (0.4 mCi/kg)	14	NR	NR	NR
	Observation	17	NR	NR	NR
Single arm trials of ^{90}Y-RIT					
Shipley, 2004 (18) Abstract	Rituximab + CHOP-R/CVP-R + ^{90}Y-RIT (dose NR) in responders	33	67	58	NR
Sweetenham, 2004 (19) Abstract	^{90}Y-RIT[a] 0.3-0.4 mCi/kg + maintenance rituximab	10	80	50	NR
Witzig, 2003 (20) Abstract	^{90}Y-RIT 0.4 mCi/kg (first dose) + ^{90}Y-RIT dose escalation (0.2-0.4 mCi/kg; second dose)	18	83[b] 61[c]	NR	61% DFS maximum 27 months follow-up
Forero-Torres, 2003 (21) Abstract	Rituximab + ^{90}Y-RIT dose escalation (0.4-0.7 mCi/kg)	5	80	80	NR
Winter, 2004 (22) Abstract	^{90}Y-RIT dose escalation + high-dose BEAM + ASCT	28	NR	NR	3-yr PFS 50%
Fung, 2003 (23) Abstract	^{90}Y-RIT 0.4 mCi/kg + BEAM + ASCT	12	NR	NR	92% DFS Mdn 9 months (4-15) follow-up
Nademanee, 2004 (24) Abstract	^{90}Y-RIT dose escalation (40-100 mCi) + etoposide + Cy + ASCT	31	NR	NR	2-yr DFS 80%
Flinn, 2004 (25) Abstract	Rituximab + CY + ^{90}Y-RIT dose escalation (20-120 mCi) + ASCT	13	38	31	6-month DFS 50%
Vose, 2003 (26) Abstract	^{90}Y-RIT dose escalation (0.1-0.2 mCi/kg)	16	31	12	NR
Jacobs, 2004 (27) Abstract	^{90}Y-RIT[a] 0.3-0.4 mCi/kg	6	17	17	NR

Notes: ASCT – autologous stem cell transplantation; BEAM – carmustine, etoposide, cytarabine, and melphalan; CHOP-R – cyclophosphamide, adriamycin, vincristine, prednisone, and rituximab; CR – complete response; CVP-R – cyclophosphamide, vincristine, prednisone, and rituximab; Cy – cyclophosphamide; DFS – disease-free survival; Mdn – median; N – number of patients; NR – not reported; OR – objective response; PFS – progression-free survival; yr – year; ^{90}Y-RIT – ^{90}Y ibritumomab tiuxetan radioimmunotherapy.

[a] Dose dependent on platelet count.

[b] First dose of ^{90}Y-RIT 0.4 mCi/kg.

[c] Second dose of ^{90}Y-RIT 0.2-0.3 mCi/kg.

Toxicity

Toxicity data was not well reported in any of the trials of alternative ^{90}Y-RIT (Table 7). The randomized trial reported data on grade 3 or 4 hematological toxicities only for the ^{90}Y-RIT arm (17). Grade 3 or 4 thrombocytopenia, neutropenia, and anemia developed in 57%, 50%, and 7% of 14 patients, respectively. Only five of the single-arm trials reported data on hematological toxicities (18,19,21,26,27). Grade 3 or 4 thrombocytopenia ranged from 25% to 100% (20,26), with grade 4 thrombocytopenia ranging from 0% to 33% (18,27). Grade 3 neutropenia ranged from 0% to 17% (21,26,27), and grade 4 neutropenia ranged from 18% to 100% (18,21). Only Vose et al (26) reported on anemia, with 6% of 16 patients developing grade 3 anemia. Sweetenham et al (19) reported that 30% of 10 patients developed grade 3 cytopenia. Very little data was available for non-hematological toxicities. Gastrointestinal toxicities were reported in three trials and ranged from 0% to 17% (18,21,23). Febrile neutropenia was reported in three trials and ranged from 0% to 15% (18,25,27). Overall, toxicity data for the trials of alternative ^{90}Y-RIT was extremely limited.

Table 7. Trials of alternative ^{90}Y-ibritumomab tiuxetan radioimmunotherapy: toxicities

Author, year (ref)	Treatment	N	Hematological G3/4 (%)			GI (%)	Febrile neut (%)
			Platelets[a]	Neutrophils[b]	Anemia		
Randomized controlled trials of ^{90}Y-RIT							
Radford, 2003 (17) Abstract	^{90}Y-RIT (0.4 mCi/kg)	14	50/7	14/36	7/0	NR	NR
	Observation	17	NR	NR	NR	NR	NR
Single-arm trials of ^{90}Y-RIT							
Shipley, 2004 (18) Abstract	Rituximab + CHOP-R/CVP-R + ^{90}Y-RIT (dose NR) in responders	33	NR / 0	NR / 18	NR	5 G-NR	5
Sweetenham, 2004 (19) Abstract	^{90}Y-RIT[a] 0.3-0.4 mCi/kg + maintenance rituximab	10	All hematological – 30 / NR			NR	NR
Witzig, 2003 (20) Abstract	^{90}Y-RIT 0.4 mCi/kg (first dose) + ^{90}Y-RIT dose escalation (0.2-0.4 mCi/kg; second dose)	18	NR	NR	NR	NR	NR
Forero-Torres, 2003 (21) Abstract	Rituximab + ^{90}Y-RIT dose escalation (0.4-0.7 mCi/kg)	5	60 / 40	0 / 100	NR	0 G1-4	NR
Winter, 2004 (22) Abstract	^{90}Y-RIT dose escalation + high-dose BEAM + ASCT	28	NR	NR	NR	NR	NR
Fung, 2003 (23) Abstract	^{90}Y-RIT 0.4 mCi/kg + BEAM + ASCT	12	NR	NR	NR	17 G3/4	NR
Nademanee, 2004 (24) Abstract	^{90}Y-RIT dose escalation (40-100 mCi) + etoposide + Cy + ASCT	31	NR	NR	NR	NR	NR
Flinn, 2004 (25) Abstract	Rituximab + CY + ^{90}Y-RIT dose escalation (20-120 mCi) + ASCT	13	NR	NR	NR	NR	15
Vose, 2003 (26) Abstract	^{90}Y-RIT dose escalation (0.1-0.2 mCi/kg)	16	25 / NR	12 / NR	6/NR	NR	NR
Jacobs, 2004 (27) Abstract	^{90}Y-RIT[a] 0.3-0.4 mCi/kg	6	NR / 33	17 / NR	NR	NR	0

Notes: ANC – absolute neutrophil count; ASCT – autologous stem cell transplantation; BEAM – carmustine, etoposide, cytarabine, and melphalan; CHOP-R – cyclophosphamide, adriamycin, vincristine, prednisone, and rituximab; CVP-R – cyclophosphamide, vincristine, prednisone, and rituximab; CY – cyclophosphamide; G – grade of toxicity; GI – gastrointestinal; N – number of patients; neut – neutropenia; NR – not reported; ref – reference; ^{90}Y-RIT – ^{90}Y-ibritumomab tiuxetan radioimmunotherapy.

[a] Grade 3: platelets <50x10^9/L; Grade 4: platelets <10x10^9/L.

[b] Grade 3: ANC <1.0x10^9/L; Grade 4: ANC <0.5x10^9/L.

[c] Gastrointestinal bleeding, grade NR.

Predictive Factors for Treatment with ^{90}Y-ibritumomab Tiuxetan Radioimmunotherapy

None of the trials of alternative ^{90}Y-RIT reported data on predictive factors.

Dosimetry and Imaging

Only Radford et al (17) and Winter et al (22) reported data on dosimetry. The randomized trial (17) reported data for patients that received consolidation ^{90}Y-RIT and that maximum radiation doses to bone marrow (76-111 cGy) and major organs (lung, 76-111 cGy; liver, 313-499 cGy; spleen, 806-1280 cGy; kidney, 21-241 cGy) were well below the limits of 300 cGy for bone marrow and 2000 cGy for organs. Winter et al (22) reported on a phase I trial of ^{90}Y-RIT following high-dose BEAM and ASCT. Doses of ^{90}Y-ibritumomab tiuxetan were determined through dosimetry for each patient and were based on a cohort-specific radiation dose to the critical organ (liver for the majority of patients). The authors concluded that dosing based on weight would likely result in a wide range of absorbed doses to the critical organs and,

therefore, through the utilization of dosimetry, higher doses of ^{90}Y-ibritumomab tiuxetan could be combined with high-dose BEAM and ASCT.

DISCUSSION

The Hematology DSG recognizes a hierarchy of outcomes that influence policy decisions. Changes in treatment practice should be influenced primarily by evidence that a treatment practice extends life, improves quality of life, or provides economic benefit. In addition, the DSG considers making available new and promising agents to patients for whom few other options exist an important, albeit lesser, priority. In considering such agents, the DSG has considered the following attributes: the prognosis for the population of patients being considered is poor; there are few effective alternative options for treatment; and the treatment under consideration has demonstrated activity and manageable toxicity. In 1999, these principles led to a recommendation by the DSG that rituximab be made available to selected patients with follicular and other indolent lymphomas who had failed chemotherapy, based principally on a 50% response rate, a median response duration of 13 months, and a favourable toxicity profile. A similar recommendation was made by the DSG in 2001 to make available imatinib for patients with chronic phase chronic myeloid leukemia who were refractory to interferon alpha. With the emergence of higher quality comparative evidence on both these agents, the evidence summaries have been replaced with evidence-based guidelines with more specific recommendations for the use of these agents.

Patients with indolent lymphoma are treated episodically with chemotherapy, immunotherapy, or radiation over a period of years to decades. Therapy is initially highly effective in palliating symptoms and relieving potentially life-threatening complications but is not curative. Over time, responses to therapy become less frequent and shorter and are only achieved through the use of more intensive and more toxic therapy. The outcome of patients who are refractory to rituximab is particularly poor, and few alternative treatment options remain. It is in this context of heavily pre-treated disease that the DSG considered the evidence supporting the use of ^{90}Y-RIT.

The trials of alternative regimens of ^{90}Y-RIT or combination chemotherapy with ^{90}Y-RIT were generally small or underpowered and have had only preliminary results reported. Therefore, the Hematology DSG concluded that the trials of standard ^{90}Y-RIT constituted the best evidence for the use of ^{90}Y-ibritumomab tiuxetan in NHL. Based on the currently available evidence for standard ^{90}Y-RIT, the DSG has reached the following initial conclusions regarding the role of ^{90}Y-ibritumomab tiuxetan in NHL:

1. Although randomized controlled trial evidence in patients with relapsed or refractory low grade or transformed NHL demonstrates superior response rates with standard ^{90}Y-RIT compared to rituximab, there is no extension in time-to-progression or comparative data for quality of life or overall survival (6). Therefore, members of the DSG felt that there was insufficient evidence to support the use of standard ^{90}Y-RIT prior to the use of rituximab in relapsed indolent CD20+ lymphoma.
2. ^{90}Y-RIT demonstrated significant anti-lymphoma activity (high response rate in a single-arm trial) in patients with follicular NHL refractory to prior rituximab. A secondary analysis requested by the US Food and Drug Administration (FDA) demonstrated that response duration with ^{90}Y-RIT was favourable to the duration observed after prior rituximab therapy. The DSG appreciates that the response to treatment is relatively brief and that the secondary analysis was exploratory in nature. However, given the limited options in this heavily pre-treated population, the use of ^{90}Y-RIT may still offer benefit when other treatments (including rituximab) have failed. It is unlikely that future trials of ^{90}Y-RIT will include patients with indolent NHL histologies. Therefore, given the evidence for standard ^{90}Y-RIT in patients with relapsed or refractory follicular NHL previously treated with rituximab, it is the opinion of the Hematology DSG that patients with other relapsed or

refractory indolent NHL histologies, previously treated with rituximab, may also benefit from treatment with standard ^{90}Y-RIT. However, the benefit of treatment with ^{90}Y-RIT may not extend to patients with chronic lymphocytic leukemia or small lymphocytic lymphoma.

3. There was discussion among the members of the DSG regarding the role of ^{90}Y-RIT in patients with transformed NHL. It was noted that the evidence is limited to pooled analyses involving small sample sizes demonstrating moderate response rates. However, some of the members felt that, given the few alternative options available to this unique patient group, the availability of ^{90}Y-RIT offers potential benefit.
4. Members of the DSG agreed that ^{90}Y-RIT should be administered according to published dosing strategies (6,8,9), based on actual patient body weight and initial platelet count, with a maximum dose of 32 mCi, regardless of weight. The agent should be withheld in patients with platelets less than 100 x 10^9/L, absolute neutrophil count less than 1.5 x 10^9/L, prior myeloablative therapy with stem cell support, or bone marrow involvement greater than 25%.
5. Members of the DSG agreed that dosimetry studies are not required prior to drug administration. Detailed dosimetry has not been shown to predict efficacy or toxicity. There is insufficient evidence to support or refute the use of imaging studies to ensure appropriate biodistribution prior to drug administration.

ONGOING TRIALS

The National Cancer Institute (NCI) (http://www.cancer.gov/search/clinical_trials/), United Kingdom Coordinating Committee on Cancer Research (UKCCCR) (http://212.219.75.230/scripts/ ukcccr/ibmhpj/bin/DisText.exe), National Institute of Health (NIH) Clinical Trials (http://clinicaltrials.gov/), the European Organization for Research and Treatment of Cancer (EORTC) (http://www.eortc.be/), and BioMed Central (http://www.biomedcentral.com/home/) databases were searched for reports of new or ongoing trials. The US FDA has approved the use of ^{90}Y-RIT for the indication of relapsed or refractory follicular NHL, contingent on further phase III assessment (106-10; NCT00057343) comparing the agent to rituximab monotherapy. The primary outcome of interest will be event-free survival, as defined by absence of disease progression, initiation of additional lymphoma therapy, or death from any cause. Another FDA-required study will evaluate the efficacy and safety of the treatment in patients with transformed NHL. ^{90}Y-ibritumomab tiuxetan is being compared to iodine Iodine-131 tositumomab therapy in a relapsed/refractory low-grade population. All ongoing and closed trials are listed in Appendix 2.

CONCLUSIONS

^{90}Y-ibritumomab tiuxetan is an active agent in relapsed and refractory CD20+ NHL that should be made available to patients with follicular NHL who are refractory to chemotherapy and rituximab and to patients with transformed lymphoma that is refractory to at least one prior course of chemotherapy, with or without rituximab. It is the opinion of the Hematology DSG that the benefit of ^{90}Y-RIT may be generalizable to other relapsed or refractory indolent NHLs previously treated with rituximab. However, the benefit of treatment with ^{90}Y-RIT may not extend to patients with chronic lymphocytic leukemia or small lymphocytic lymphoma; therefore, ^{90}Y-RIT cannot be routinely recommended in this group of patients. There is insufficient evidence to support the use of ^{90}Y-ibritumomab tiuxetan in patients with refractory or relapsed low-grade or follicular NHL prior to the use of rituximab. ^{90}Y-ibritumomab tiuxetan should be administered according to published dosing strategies (6,8,9) and based on actual patient body weight and initial platelet count. Patients with platelet counts greater than or equal to 150 x 10^9/L should receive a dose of 0.4 mCi/kg. Patients with platelet counts 100-149 x 10^9/L should receive a dose of 0.3 mCi/kg. The maximum dose regardless of weight is 32 mCi. ^{90}Y-ibritumomab tiuxetan should not be given to patients with platelet counts less than 100 x 10^9/L,

ANC less than 1.5 x 10^9/L, prior myeloablative therapy with stem cell support, or bone marrow involvement greater than 25%. Based on the identified evidence, dosimetry is not required in the routine administration of ^{90}Y-ibritumomab tiuxetan. At present, there is insufficient evidence to support or refute the use of imaging studies, to ensure appropriate biodistribution, prior to drug administration.

CONFLICTS OF INTEREST

The members of the Hematology DSG disclosed potential conflicts of interest relating to the topic of this systematic review.

One DSG member reported research involvement with a clinical trial on ^{90}Y-ibritumomab tiuxetan (pharmaceutical company sponsored) and research involvement and membership on boards of directors or advisory committees for another agent reported in this systematic review. In addition, several DSG members, including a co-Chair, reported involvement with pharmaceutical companies that manufacture ^{90}Y-ibritumomab tiuxetan or other agents reported in this document, including research involvement, research funding, membership on boards of directors or advisory committees, provision of consultancy, or receipt of honoraria.

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For a complete list of the Hematology DSG members please visit the CCO Web site at http://www.cancercare.on.ca/

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Appendix 1. Literature search strategy used in MEDLINE.

1 zevalin.mp.
2 ibritumomab tiuxetan.mp.
3 anti-CD20.mp.[A]
4 antiCD20.mp.[A]
5 antiCD-20.mp.[A]
6 idec-y2b8.mp.
7 idecy2b8.mp.
8 idec-2b8.mp.
9 idec2b8.mp.
10 idec-In2b8.mp.
11 idecIn2b8.mp.
12 idec-129.mp.
13 idec129.mp.
14 or/1-13
15 lymphoma.mp.
16 exp lymphoma/
17 exp lymphoma, large-cell/[B]
18 or/15-17
19 14 and 18
20 limit 19 to human
21 limit 20 to english language
22 comment.pt.
23 letter.pt.
24 editorial.pt.
25 or/22-24
26 21 not 25[C]
27 20 not 21
28 27 not 25[D]

[A]Included in the original literature search (July 2003).
[B]Included in the May 2004 literature search.
[C]Results for citations in the English language.
[D]Results for citations in languages other than English.

Appendix 2. Ongoing trials.

Protocol ID(s)	Name and details of trial
MSKCC-04009; CDR0000360857; NCT00082836	Pilot study of rituximab and yttrium Y 90 ibritumomab tiuxetan in patients with recurrent primary CNS lymphoma. Outcomes: Tumour dosimetry and biodistribution, safety. Projected accrual: 10 patients. Status: active. Summary last modified: May 27, 2005. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=360857&version=HealthProfessional&protocolsearchid=2010125.
106-10; NCT00057343	A prospectively randomized, phase III, multicentre, controlled trial to evaluate the safety and efficacy of the Zevalin therapeutic regimen plus rituxan compared with rituxan alone in patients with relapsed or refractory follicular non-Hodgkin's lymphoma. Outcomes: event-free survival, response rate, overall survival, quality of life, safety. Projected accrual: 400 patients. Status: closed. Summary last modified: December 8, 2005. Accessed: December 21, 2005. Available at: http://clinicaltrials.gov/ct/show/NCT00057343?order=1.
CCBX001-053; NCT00078676	A multi-center, randomized, phase III study of iodine I 131 tositumomab therapeutic regimen versus ibritumomab tiuxetan therapeutic regimen for patients with relapsed or transformed follicular non-Hodgkin's lymphoma. Outcomes: safety and efficacy. Projected accrual: not reported. Status: approved, not active. Summary last modified: December 8, 2005. Accessed: December 21, 2005. Available at: http://clinicaltrials.gov/ct/show/NCT00078676?order=1.
ID01-233; IND 10258; NCT00048737	Safety and efficacy of 90Y Zevalin in nonmyeloablative transplantation for lymphoid malignancies. Outcomes: efficacy and safety. Projected accrual: 30 patients. Status: active. Summary last modified: NR. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=355759&version=HealthProfessional&protocolsearchid=2023165.
UNMC-535-00; NCI-V02-1691; CDR0000069211; NCT00031642	Phase I/II study of yttrium Y 90-labeled ibritumomab tiuxetan with rituximab in patients with B-cell non-Hodgkin's lymphoma who have relapsed after high-dose chemotherapy and autologous hematopoietic stem cell transplantation. Outcomes: maximum tolerated dose, safety, and efficacy. Projected accrual: 20 patients for phase I and 58 for phase II within two years. Status: active. Summary last modified: February 23, 2004. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=69211&version=HealthProfessional&protocolsearchid=2023180.

Protocol ID(s)	Name and details of trial
AMC-037; CDR0000310158; NCT00064246	Phase I/II study of yttrium Y 90 ibritumomab tiuxetan and rituximab in patients with post-transplant lymphoproliferative disorder. Outcomes: maximum tolerated dose and safety. Projected accrual: 13 -28 patients within two years. Status: completed. Summary last modified: October 12, 2005. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=310158&version=HealthProfessional&protocolsearchid=2023189.
SWOG-S0313; CDR0000329864; NCT00070018	Phase II study of cyclophosphamide, doxorubicin, vincristine, and prednisone and radiotherapy followed by rituximab and yttrium Y 90 ibritumomab tiuxetan in patients with aggressive stage I or IE or non-bulky stage II or IIE CD20-positive non-Hodgkin's lymphoma. Outcomes: progression-free survival, toxicity. Projected accrual: 60 patients within 15 months. Status: active. Summary last modified: October 27, 2005. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=329864&version=HealthProfessional&protocolsearchid=2010120.
ECOG-E1499; CDR0000334470; NCT00070447	Phase II study of rituximab and CHOP chemotherapy comprising prednisone, cyclophosphamide, doxorubicin, and vincristine followed by yttrium Y 90 ibritumomab tiuxetan (yttrium Y 90 Zevalin®) in patients with previously untreated mantle cell lymphoma. Outcomes: time-to-treatment failure, response, and toxicity. Projected accrual: 57 patients within 2.8 years. Status: closed. Summary last modified: November 4, 2005. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=334470&version=HealthProfessional&protocolsearchid=2023193.
BIDMC-2003P-000182; CDR0000341437; NCT00073957	Phase II study of yttrium Y 90 ibritumomab tiuxetan and rituximab in patients with relapsed or refractory diffuse large B-cell non-Hodgkin's lymphoma. Outcomes: response, event-free survival, and toxicity. Projected accrual: 40 patients within two years. Status: active. Summary last modified: December 3, 2003. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=341437&version=HealthProfessional&protocolsearchid=2023205.
ID01-541; NCT00038623	A phase II study of yttrium-ibritumomab (Zevalin) for the treatment of patients with relapsed and refractory mantle cell lymphoma. Outcomes: safety and efficacy. Projected accrual: 35 patients. Status: active. Summary last modified: December 29, 2005. Accessed: January 2, 2006. Available at: http://clinicaltrials.gov/ct/show/NCT00038623?order=1.
MSKCC-02090; CR0000288830; NCT00058422	Phase II study of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone combined with yttrium Y 90 ibritumomab tiuxetan in patients age 60 and over with previously untreated diffuse large B-cell lymphoma. Outcomes: progression-free survival, overall survival, adverse events, and response. Projected accrual: 65 patients. Status: active. Summary last modified: April 25, 2003. Accessed: December

Protocol ID(s)	Name and details of trial
	21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=288830&version=HealthProfessional&protocolsearchid=2023240.
CALGB-50201; CDR0000304498; NCT00062114	Phase II study of yttrium Y 90 ibritumomab tiuxetan and rituximab in patients with transformed CD20+ B-cell non-Hodgkin's lymphoma. Outcomes: response rate, duration of response, safety, event-free survival. Projected accrual: 84 patients within 18-24 months. Status: active. Summary last modified: November 5, 2005. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=304498&version=HealthProfessional&protocolsearchid=2010115.
UAB-0127; UAB-F010806018; NCI-G02-2053; CDR0000069282; NCT00033423	Phase I study of yttrium Y 90 ibritumomab tiuxetan and rituximab in patients with relapsed or refractory low-grade, follicular, or transformed CD20-positive B-cell non-Hodgkin's lymphoma. Outcomes: maximum tolerated dose, toxicity, reversal of bone marrow involvement, and response. Projected accrual: 6-30 patients. Status: active. Summary last modified: April 1, 2002. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=69282&version=HealthProfessional&protocolsearchid=2023255.
NU-99H11; IDEC-NU99H11; CDR0000287244; NCT00058292	Phase I study of yttrium Y 90 ibritumomab tiuxetan and high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. Outcomes: maximum tolerated dose, response duration, survival. Projected accrual: 42 patients. Status: active. Summary last modified: November 10, 2005. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=287244&version=HealthProfessional&protocolsearchid=2010110.
MAYO-MC998C; NCI-312; CDR0000068503; NCT00012298	Phase I study of yttrium Y 90 ibritumomab tiuxetan and rituximab with and without filgrastim (G-CSF) and interleukin-11 in patients with relapsed or refractory low-grade or follicular CD20+ non-Hodgkin's lymphoma. Outcomes: maximum tolerated dose, toxicity, response rate, tumour dosimetry. Projected accrual: 24-60 patients within 2-4 years. Status: active. Summary last modified: December 12, 2005. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=68503&version=HealthProfessional&protocolsearchid=2010106.
JHOC-J0004; NCI-970; CDR0000068684; NCT00017381	Phase I study of rituximab, yttrium Y 90 ibritumomab tiuxetan, and autologous peripheral blood stem cell rescue in patients with indolent or diffuse large B-cell non-Hodgkin's lymphoma. Outcomes: maximum tolerated dose. Projected accrual: 10-30 patients. Status: active. Summary last modified: April 1, 2004. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=68684&vers

Protocol ID(s)	Name and details of trial
	ion=HealthProfessional&protocolsearchid=2023263.
CDR0000368452; MAYO-MC0283; NCI-127; NCT00085267	Phase I/II study of rituximab and fludarabine cytoreduction followed by yttrium Y 90 ibritumomab tiuxetan in patients with previously treated B-cell chronic lymphocytic leukemia or low-grade B-cell non-Hodgkin's lymphoma. Outcomes: maximum tolerated dose. Projected accrual: 35-50 patients within 1.75-2.5 years. Status: not yet open. Summary last modified: May 2004. Accessed: July 7, 2004. Available at: http://clinicaltrials.gov/ct/show/NCT00085267?order=4.
CDR0000301591; UCLA-0202063; IDEC-UCLA-0202063; NCT00060294	Phase I study of yttrium Y 90 ibritumomab tiuxetan in patients with Waldenstrom's Macroglobulinemia. Outcomes: maximum tolerated dose, response rate. Projected accrual: 3-24 patients. Status: completed. Summary last modified: December 8, 2005. Accessed: December 21, 2005. Available at: http://clinicaltrials.gov/ct/show/NCT00060294?order=5.
No ID provided.	Phase I dose-escalation trial in Waldenstrom's Macroglobulinemia. Outcomes: maximum tolerated dose in patients with 20%-50% bone marrow involvement. Projected accrual: NR. Status: not active as of date of publication. Source: Semin Oncol 2003;30:258-61.
CDR0000067697; UAB-9930; NCI-G00-1731; GUMC-00095; IDEC-106-98; NCT00005592	Phase II study of rituximab and ibritumomab tiuxetan radioimmunotherapy in patients with relapsed or refractory, low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. Outcomes: efficacy and safety. Projected accrual: 400 patients. Status: closed. Summary last modified: December 8, 2005. Accessed: December 21, 2005. Available at: http://clinicaltrials.gov/ct/show/NCT00005592?order=1.
BMT134; NCT00186589	90Y-ibritumomab tiuxetan and autologous hematopoietic cell infusion followed by high dose chemotherapy and autologous transplantation for relapsed or resistant non-Hodgkin’s lymphoma. Outcomes: maximum tolerated dose and dosimetry. Projected accrual: 30 patients. Status: active. Summary last modified: December 8, 2005. Accessed: December 21, 2005. Available at: http://clinicaltrials.gov/ct/show/NCT00186589?order=1.
NU-02H8; NU-0228-024; PCI-P-PCYC-0213; NCT00089284	Phase I/II study of motexafin gadolinium, rituximab, and yttrium Y 90 ibritumomab tiuxetan in patients with bulky stage II or stage III or IV relapsed or refractory CD20-positive non-Hodgkin’s lymphoma. Outcomes: maximum tolerated dose, dose limiting toxicity, and efficacy. Projected accrual: 6-30 patients within 24-30 months. Status: active. Summary last modified: May 17, 2005. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=378192&version=HealthProfessional&protocolsearchid=2023290.
ECOG-E3402; NCT00088881	Phase II study of rituximab, prednisone, cyclophosphamide, doxorubicin, and vincristine followed by rituximab and yttrium Y 90 ibritumomab

Protocol ID(s)	Name and details of trial
	tiuxetan in patients with stage I or II CD20-positive diffuse large cell lymphoma. Outcomes: response. Projected accrual: 62 patients within 17 months. Status: active. Summary last modified: September 23, 2005. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=377493&version=HealthProfessional&protocolsearchid=2023304.
BIDMC-2004P-000044; NCT00110149	Phase II study of rituximab and yttrium Y 90 ibritumomab tiuxetan as first-line treatment in patients with indolent non-Hodgkin's lymphoma. Outcomes: response, event-free survival, time-to-progression, time-to-next-antilymphoma therapy, molecular response, toxicity, and quality of life. Projected accrual: 18-28 patients within two years. Status: active. Summary last modified: May 11, 2005. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=409723&version=HealthProfessional&protocolsearchid=2023305.
FHCRC-1726.00; NCT00119392	Phase II study of a nonmyeloablative conditioning regimen comprising yttrium Y 90 ibritumomab tiuxetan, fludarabine, and low-dose total-body irradiation followed by allogenic peripheral blood stem cell transplantation in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. Outcomes: feasibility and toxicity. Projected accrual: 40 patients within four years. Status: active. Summary last modified: July 8, 2005. Accessed: December 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=430649&version=HealthProfessional&protocolsearchid=2023309.
04-251; NCT00119730	Abbreviated fludarabine/mitoxantrone/rituximab chemotherapy followed by Zevalin for relapsed mantle cell lymphoma. Outcomes: response, progression-free survival, and safety. Projected accrual: 30 patients. Status: active. Summary last modified: December 8, 2005. Accessed: December 21, 2005. Available at: http://clinicaltrials.gov/ct/show/NCT00119730?order=1.
Z-BEAM; NCT00138086	Targeted intensification by a new preparative regimen for patients with low-grade B-cell lymphoma utilizing standard-dose yttrium-90 ibritumomab tiuxetan (Zevalin) radioimmunotherapy (RIT) combined with high-dose BEAM followed by autologous stem cell transplantation (ASCT). Outcomes: event-free survival, response, toxicity, time-to-progression, disease-free survival, and overall survival. Projected accrual: 75 patients. Status: active. Summary last modified: December 12, 2005. Accessed: December 21, 2005. Available at: http://clinicaltrials.gov/ct/show/NCT00138086?order=1.
Ritux plus TNI; NCT00147953	A phase II study of rituximab plus low-dose radioimmunotherapy in patients with relapsed non-Hodgkin's lymphoma. Outcomes: response, toxicity, time-to-progression, response duration, and quality of life. Projected accrual: 30 patients. Status: active. Summary last modified: December 8, 2005. Accessed: December 21, 2005. Available at: http://clinicaltrials.gov/ct/show/NCT00147953?order=1.

Protocol ID(s)	Name and details of trial
UPCI #03-005; NCT00177554	Phase II trial of CHOP-R followed by Zevalin and Rituxan in follicular lymphoma. Outcomes: response, PET-CT conversion rate, adverse events, duration of response, and time-to-next antilymphoma therapy. Projected accrual: 39 patients. Status: active. Summary last modified: December 8, 2005. Accessed: December 21, 2005. Available at: http://clinicaltrials.gov/ct/show/NCT00177554?order=1.

Notes: NR – not reported.

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Evidence-based Series #6-17: Section 3

Ibritumomab Tiuxetan in Lymphoma: Guideline Development and External Review: Methods and Results

M. Cheung, A.E. Haynes, A. Stevens, R.M. Meyer, K. Imrie, and the members of the Hematology Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care, Cancer Care Ontario
Developed by the Hematology Disease Site Group

Report Date: July 17, 2006

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, other health care professionals, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-based Series is comprised of three sections:

- *Section 1: Clinical Practice Guideline*. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.

- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Hematology DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on ibritumomab tiuxetan in lymphoma, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

External Review by Ontario Clinicians

The systematic review on ibritumomab tiuxetan for patients with lymphoma is reported in Section 2. On the basis of that evidence and the interpretation by members of the DSG, draft recommendations were circulated to Ontario practitioners for feedback. This section comprises the results from Practitioner Feedback, any changes made to the draft document, and final recommendations that were submitted to the PEBC Report Approval Panel for review and final approval.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review on July 18, 2005)

Target Population

This evidence summary applies to adult patients with non-Hodgkin's lymphoma of any type, at any stage of disease, and for any level of performance status.

Recommendations

There is a lack of high quality evidence to explicitly inform the guideline questions. Notwithstanding, the following recommendations, based on a consensus of expert clinical opinion of the Hematology Disease Site Group and the best available evidence, are offered:

- ^{90}Y-ibritumomab tiuxetan is an active agent in relapsed and refractory non-Hodgkin's lymphoma that should be made available to selected patients. Based on currently available data, patients that should be prioritized for therapy with ^{90}Y-ibritumomab tiuxetan are those with follicular non-Hodgkin's lymphoma who are refractory to chemotherapy and rituximab, and those with transformed non-Hodgkin's lymphoma that is refractory to at least one prior course of chemotherapy, with or without rituximab.
- It is the opinion of the Hematology Disease Site Group that the benefit of ^{90}Y-ibritumomab tiuxetan radioimmunotherapy may be generalizable to other relapsed or refractory indolent non-Hodgkin's lymphomas previously treated with rituximab.
- There is insufficient evidence to support the use of ^{90}Y-ibritumomab tiuxetan in patients with refractory or relapsed low-grade or follicular non-Hodgkin's lymphoma prior to the use of rituximab.
- Based on available evidence, dosimetry (calculation of actual radiation absorbed to specific organs) is not required in the routine administration of ^{90}Y-ibritumomab tiuxetan.
- There is insufficient evidence to support or refute the use of imaging studies (to ensure appropriate biodistribution) prior to drug administration. In the absence of evidence, we recommend that the use of imaging be guided by the manufacturer's product monograph, when available.

Qualifying Statements

- ^{90}Y-ibritumomab tiuxetan should be administered according to published dosing strategies, based on actual patient body weight and initial platelet count. Patients with platelet counts greater than or equal to 150 x 10^9/L should receive a dose of 0.4 mCi/kg (the maximum dose regardless of weight is 32 mCi). Patients with platelet counts 100-149 x 10^9/L should receive a dose of 0.3 mCi/kg. The agent should not be given to patients with platelets less than 100 x 10^9/L, absolute neutrophil count less than 1.5 x 10^9/L, prior myeloablative therapy with stem cell support, or bone marrow involvement greater than 25%.
- The Hematology Disease Site Group appreciates that the key trial guiding the opinion regarding indolent non-Hodgkin's lymphoma included only patients with follicular non-Hodgkin's lymphoma. However, it is unlikely that future trials of ^{90}Y-ibritumomab tiuxetan will include patients with other indolent non-Hodgkin's lymphoma histologies. Therefore, the Hematology Disease Site Group agreed that an opinion was warranted regarding the generalizability of that evidence to indolent non-Hodgkin's lymphoma.

Methods

Feedback was obtained through a mailed survey of 170 practitioners in Ontario who treat hematological malignancies. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on July 18, 2005. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Hematology DSG reviewed the results of the survey.

Results

Seventy-eight responses were received out of the 170 surveys sent (46% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 50% indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

Table 1. Responses to eight items on the practitioner feedback survey.

Item	Number (%[a])		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a guideline, as stated in the "Introduction" section of the report, is clear.	38 (97)	1 (3)	0
There is a need for a guideline on this topic.	39 (100)	0	0
The literature search is relevant and complete.	34 (87)	5 (13)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	37 (95)	1 (3)	1 (3)
The draft recommendations in the report are clear.	35 (90)	4 (10)	0
I agree with the draft recommendations as stated.	34 (87)	3 (8)	2 (5)
This report should be approved as a practice guideline.	34 (87)	3 (8)	2 (5)
	Very likely or likely	**Unsure**	**Not at all likely or unlikely**
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?[b]	29 (76)	7 (18)	2 (5)

[a] Percentages may not add to 100% due to rounding.
[b] One practitioner did not answer this question.

Summary of Written Comments

Thirteen respondents (33.3%) provided written comments. The main points contained in the written comments were:

1. Several practitioners commented that despite the limitations of the published data, the recommendations are justified. One practitioner noted that the strongest evidence is for response, whereas there is limited evidence for progression-free survival, overall survival, and quality of life.
2. Two practitioners noted that Health Canada recently approved ^{90}Y-RIT for the treatment of CD20+ follicular NHL refractory or relapsed after rituximab; however, no mention was made of transformed lymphoma. The practitioners expressed concern that the data from the pooled analysis of transformed NHL overemphasizes the role of ^{90}Y-RIT.
3. One practitioner commented that the authors need to be more specific as to why ^{90}Y-RIT is not recommended before rituximab as the response rate in the trial of ^{90}Y-RIT versus rituximab was higher for patients in the ^{90}Y-RIT arm.
4. Several practitioners expressed concern that the recommendations are not justified given the high cost of ^{90}Y-RIT as well as the need for additional resources. The only appropriate recommendation is continued clinical study.
5. One practitioner commented that the recommendations should explicitly state that they apply to patients with CD20+ NHL as this may not be self-evident.
6. One practitioner commented that there is a hierarchy of treatments in NHL. The authors need to define "refractory to chemotherapy and rituximab". Specifically, do the authors mean refractory to just cyclophosphamide, etoposide, carmustine (CVB) and single-agent rituximab? Or do they mean refractory to anthracycline-based rituximab therapy? Also, should the patient have previously responded to rituximab therapy?
7. One practitioner commented that restrictions of platelet count could be lessened in patients with immune-mediated thrombocytopenia (ITP).
8. One practitioner replied that CLL should be excluded in "other indolent lymphoproliferative disorders."
9. One practitioner noted that there is a real but relatively small role for ibritumomab in patients with lymphoma who have advanced disease and likely in preparation for autologous stem cell transplantation (ASCT).

10. One practitioner commented that Gordon et al (3) could have been included.

Modifications/Actions

1. The Hematology DSG agreed with the practitioners' comments. No actions were required.
2. The Hematology DSG recognizes that there is no high-quality evidence guiding the role of ^{90}Y-RIT for transformed lymphoma. Patients with transformed histology were included in the key trials studying ^{90}Y-RIT in relapsed/refractory disease, including the randomized controlled trial and a pooled analysis of those patients. Based on the available evidence, members of the Hematology DSG felt that ^{90}Y-RIT could be considered for that select group of patients with a particularly poor prognosis and who otherwise have few palliative options. However, the DSG recognizes that the current Health Canada approval would restrict the availability of the drug for that indication.
3. Although a response rate benefit was detected in the pivotal randomized controlled trial comparing ^{90}Y-RIT to rituximab monotherapy, there was no demonstration that the improvement in this surrogate outcome would translate into more meaningful benefits in time-to-progression, quality of life, or overall survival outcomes. Given the added toxicity of ^{90}Y-RIT and the lack of data regarding these other outcomes, the Hematology DSG did not feel there was sufficient evidence to support prioritizing the use of ^{90}Y-RIT prior to treatment with rituximab.
4. The Hematology DSG agreed that there is a lack of high-quality evidence to definitively answer the guideline questions. The Hematology DSG used the systematic review of the clinical literature, the consensus interpretation of the DSG, and the formalized feedback of Ontario practitioners to develop the recommendations. This process occurred independently of considerations about funding and was meant to guide the appropriate use of ^{90}Y-RIT when or should the drug become available in Ontario. Even though the recommendations are based upon the best available evidence as well as expert clinical opinion, they are not definitive. The evidence-based report will be updated and revised when further evidence becomes available.
5. The recommendations have been adjusted to explicitly state that ^{90}Y-RIT be reserved only for patients with CD20+ NHL.
6. The Hematology DSG recognizes the heterogeneity of treatment options available for advanced stage indolent lymphoma. The DSG also appreciates that use of rituximab is shifting from a predominant role in relapse (monotherapy) to its incorporation in up-front care (in combination with alkylator- or anthracycline-based chemotherapy). Based on the evidence and in consideration of the evolving role of rituximab, patients who should be prioritized for therapy should be those that have previously received (1) prior chemotherapy (alkylator- or anthracycline-based) in combination with rituximab or (2) prior chemotherapy and subsequent rituximab monotherapy. In keeping with the pivotal trial that demonstrated anti-lymphoma activity in rituximab-refractory patients, ^{90}Y-RIT should be available to patients who have not responded to prior rituximab therapy.
7. There is little evidence that guides the use of ^{90}Y-RIT in patients with ITP. However, even patients with lymphoma, who had normal pre-treatment platelet counts and no evidence of bone marrow involvement, were prone to developing grade 3/4 thrombocytopenia. Patients with pre-treatment thrombocytopenia due to ITP would already be starting at a lower platelet count and could be at significant risk of further thrombocytopenia from treatment-related myelosuppression. Further evidence is required to determine if the use of this therapy is safe in these patients.
8. Chronic lymphocytic leukemia and small lymphocytic lymphoma (SLL) may respond differently to ^{90}Y-RIT treatment compared to other indolent NHL, analogous to the response to rituximab in these respective conditions. Until further evidence clarifies the

benefit of ^{90}Y-RIT in CLL/SLL patients, the Hematology DSG agreed that CLL/SLL should be excluded from the definition of "other indolent NHLs". The appropriate changes have been made to the evidence-based report.

9. The current evidence regarding the role of ^{90}Y-RIT in patients with aggressive histology lymphoma or prior to ASCT is still preliminary in nature. All reports are currently available only in abstract form, report on preliminary results, and generally involve small patient populations. The Hematology DSG agrees that the role of "alternative" ^{90}Y-RIT protocols warrants further study; however, the current evidence is insufficient to either recommend or refute the use of the drug for these indications.
10. The publication by Gordon et al (3) was published after the literature search was last completed. The Hematology DSG will add that full publication in a future update of the evidence-based report.

Report Approval Panel

The evidence-based report was submitted to the PEBC Report Approval Panel for final review and approval on October 21, 2005. Of the two Panel members, only one provided feedback, as the other was an author of this evidence-based series. The key issue raised by the Panel was that in the first recommendation, the DSG could clarify why patients with follicular NHL are required to be refractory to both chemotherapy and rituximab, while those with transformed NHL need only be refractory to chemotherapy. The Hematology DSG offered the following response: Patients with relapsed transformed lymphoma are not candidates for rituximab monotherapy (unlike patients with relapsed/refractory follicular lymphoma). Therefore, after these patients relapse from combination chemotherapy, few options remain, and the DSG agreed that the availability of ^{90}Y-RIT would be appropriate.

Policy Review

Evidence-based report #6-17, Ibritumomab in tiuxetan in lymphoma, was submitted to the Drug Quality and Therapeutics Committee (DQTC) for review in 2005. The draft recommendations that were sent for practitioner feedback (Box 1) were the same recommendations that were sent to the DQTC.

Implications for Policy

There are 2400 patients with lymphoma diagnosed annually in Ontario. Follicular and other indolent lymphomas account for approximately 40% of these. ^{90}Y-ibritumomab tiuxetan radioimmunotherapy (^{90}Y-RIT) is being proposed as a late stage treatment for those patients, with criteria not dissimilar to those initially used for single agent rituximab. Between December 2003 and November 2004, 238 new cases received single agent rituximab through the New Drug Funding Program. The DSG anticipates that the target population of Ontario patients eligible for ^{90}Y-RIT will be smaller than that for single agent rituximab due to the requirements for an adequate platelet count and minimal marrow involvement as well as the increased complexity associated with administration of the agent. The number of patients potentially eligible for this therapy is expected to be approximately 100 per year.

Peer Review Feedback

A manuscript of the systematic review section of this evidence-based series report was submitted to the journal *Leukemia and Lymphoma* for consideration for publication on October 14, 2005. The manuscript was accepted for publication on October 26, 2005. The reviewers provided feedback that required only minor editorial modifications to the original manuscript.

RELATED PRINT AND ELECTRONIC PUBLICATIONS

Cheung MC, Haynes AE, Stevens A, Meyer RM, Imrie K, the members of the Hematology Disease Site Group of the Cancer Care Ontario Program in Evidence-Based Care. Yttrium 90 ibritumomab tiuxetan in lymphoma. Leuk Lymphoma. 2006;47(6):967-77.

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