Radioimmunoconjugates are radioisotope-bound monoclonal antibodies that target radiation specifically to sites of lymphoma involvement. Initial studies of $^{131}$I–tositumomab in non-Hodgkin lymphoma ($\text{NHLL}$) have suggested benefit in patients with relapsed or refractory indolent disease. However, the routine adoption of this agent is tempered by concerns about associated toxicities and unclear long-term benefit. Based on a comprehensive search for studies on $^{131}$I–tositumomab use in lymphoma, this systematic review summarizes and evaluates the evidence on

- the benefits and risks of this novel therapy,
- the predictors for response and toxicity, and
- the role of dosimetry and imaging studies before treatment.

We identified 18 trials investigating the use of $^{131}$I–tositumomab for the treatment of adult patients with $\text{NHLL}$. In trials of patients with relapsed or refractory indolent $\text{NHLL}$, overall response rates ranged from 67% to 83%. In patients with follicular $\text{NHLL}$ refractory to the monoclonal antibody rituximab, response rates remained high (65%–72%). However, in rituximab-naïve patients with relapsed or refractory indolent or transformed $\text{NHLL}$, improvements in time to progression or survival have not been clearly established. $^{131}$I–Tositumomab is an active agent in relapsed and refractory non-Hodgkin lymphoma that should be considered in selected patients.

**KEY WORDS**

$^{131}$I–Tositumomab, Bexxar, indolent lymphoma, systematic review

1. **INTRODUCTION**

Non-Hodgkin lymphomas ($\text{NHLL}$s) constitute a heterogeneous group of malignancies with variable presentations that range from indolent to aggressive. Patients with follicular and other indolent lymphomas can sustain prolonged remission periods, but they eventually relapse and require subsequent courses of therapy that lead to fewer and shorter remissions. Novel treatment options are necessary to improve the natural history of this condition. Rituximab is a chimeric monoclonal antibody directed against the CD20 surface antigen found on most B-cell lymphomas. Although rituximab represents an important advance in indolent disease because of its efficacy, short duration of therapy, and acceptable toxicity profile, relapse remains inevitable. Therapies that are more effective are thus needed for patients who are refractory to or who relapse after currently available treatments, including rituximab.

Radioimmunoconjugates are monoclonal antibodies bound to radioisotopes, and this emerging class of...
agents has activity in lymphoma. These agents allow for the delivery of targeted radiation therapy with the binding of the monoclonal antibody to antigens on the surface of malignant cells. $^{131}$I–Tositumomab (Bexxar: Corixa Corporation, South San Francisco, CA, and GlaxoSmithKline, Philadelphia, PA, U.S.A.) is a radioimmunoconjugate consisting of an anti-CD20 murine monoclonal antibody (tositumomab) covalently bound to the gamma-emitting radioactive isotope $^{131}$I. Initial studies have reported on the use of $^{131}$I–tositumomab in patients with refractory or relapsed low-grade, follicular, or transformed lymphoma. Further research is exploring the role of this compound in other settings, including in patients with aggressive-histology lymphomas and in the setting of stem-cell transplantation. However, the routine adoption of this agent is tempered by concerns about increased costs, complex dosimetry requirements, and possible toxicities. With the recent availability of radioimmunoconjugates, a careful review of the risks and benefits of such therapy is warranted. The aim of the present systematic review is to address the following questions in patients with lymphoma of any type or stage:

- What are the benefits associated with treatment with $^{131}$I–tositumomab?
- What are the toxicities associated with the use of $^{131}$I–tositumomab?
- Which patients are more or less likely to benefit from treatment with $^{131}$I–tositumomab?
- Is imaging or dosimetry required for therapy to be safe and effective?

2. MATERIALS AND METHODS

The methodology guiding this systematic review was developed by the Cancer Care Ontario (CCO) Program in Evidence-Based Care (Pebc) according to the practice guidelines development cycle. Members of the Pebc Hematology Disease Site Group (DSG) selected, reviewed, and interpreted the evidence. The Hematology DSG has 25 members, including hematologists, medical and radiation oncologists, an epidemiologist, and two lay representatives.

2.1 Literature Search

We searched the Medline (1966 to July 2005), EMBASE (1980 to July 2005), and Cochrane Library (2005, Issue 3) databases using the search strategy shown in Table 1. In addition, we searched the conference proceedings of the American Society of Hematology (ASH) for 2000 to 2004 and those of the American Society of Clinical Oncology (ASCO) for 2000 to 2005. Reference lists of relevant trials and reviews were searched for additional publications. In addition, the authors searched their personal files. The Canadian Medical Association Infobase (mdm.ca/cpgsnew/cpgs/index.asp), the National Guidelines Clearinghouse (www.guideline.gov/index.asp), and the U.K. National Institute for Health and Clinical Excellence (www.nice.org.uk/) were also searched for existing evidence-based practice guidelines.

2.2 Inclusion Criteria

Randomized controlled trials, other comparative trials, prospective single-arm trials, systematic reviews (with or without meta-analyses), and evidence-based practice guidelines were considered for this review of the evidence if they met the following criteria:

- Study of adult patients with lymphoma of any type, at any stage, and for any performance status
- $^{131}$I–Tositumomab studied as a single agent or in combination with other regimens
- Results reported for one or more of the following outcomes: survival, quality of life (QOL), time to progression (TTP), response duration, response rate, adverse effects, tumour dosimetry or imaging
- Report published in English
Letters, comments, and editorial publications were excluded. Conference abstracts that preceded full-paper final results were not included; however, abstracts that provided updated results or novel data were included for further data abstraction.

2.3 Data Extraction and Interpretative Summary

Relevant articles and abstracts were selected in an unblinded manner independently by two members of the Hematology DSG. Data were extracted and summarized to address the following questions regarding adult patients with lymphoma of any type, at any stage, and for any performance status:

- Is 131I–tositumomab effective in improving survival, QoL, TTP, response duration, or response rate?
- What are the toxicities associated with the use of 131I–tositumomab?
- Which patients are more or less likely to benefit from treatment with 131I–tositumomab?
- Is imaging or dosimetry required for therapy to be safe and effective?

The analysis of the data uses descriptive statistics. Categorical variables are reported as numbers and proportions, and continuous data are reported as means and standard deviations. The heterogeneity among studies precluded any pooling of results using formal meta-analytic techniques.

3. RESULTS

We identified 255 citations in the literature searches of Medline, Embase, and the Cochrane Library, including twenty-one full publications of eleven trials. Eleven abstracts of seven trials were identified from the conference proceedings of ASH and ASCO. One additional abstract was identified that provided QoL data that were not reported in the relevant full publication. Only the most recent abstract or full publication was referenced for each trial, except where additional data were available in previous publications (Table IIa).

In total, this systematic review includes eighteen trials investigating the use of 131I–tositumomab for the treatment of adult patients with NHL. No systematic reviews, meta-analyses, or evidence-based practice guidelines were identified. We divided the trials into two categories based on patient treatment history: previously untreated, and previously treated patients with NHL. The “previously treated” category was further divided into randomized and single-arm trials of 131I–tositumomab. The single-arm trials included reports of patients with disease relapsed or refractory to chemotherapy without prior rituximab, disease relapsed or refractory to rituximab alone, and disease treated with 131I–tositumomab conditioning for autologous stem-cell transplantation (ASCT), and disease treated with 131I–tositumomab in alternative regimens or alternative populations of previously treated patients.

3.1 Patients with Previously Treated NHL

3.1.1 Study Quality

Only one of the thirteen trials of 131I–tositumomab in patients with previously treated NHL was a randomized...
controlled trial\textsuperscript{22}. That trial has been published in abstract form only, and therefore little information regarding study quality was reported. However, the authors did report that the trial was multicentred and open-label. The 78 study patients were randomized either to $^{131}$I–tositumomab or to unlabelled tositumomab and were followed for a median of 42.6 months. No sample-size calculation was provided.

One single-arm trial, reported as a full publication by Kaminski et al.\textsuperscript{5}, compared each patient’s duration of response after $^{131}$I–tositumomab with the duration of response to their last qualifying chemotherapy regimen (“paired control”). The remaining studies were single-arm noncomparative phase I or II trials. Eight of those trials\textsuperscript{5,8,11,12,17,19,22,28,32,34,40} have been fully published, with sample sizes ranging from 11 patients to 60 patients. The remaining three trials\textsuperscript{23,32,39} have been published in abstract form only, with sample sizes ranging from 11 patients to 32 patients. Eight of twelve single-arm trials reported median follow-up times that ranged from 12 months\textsuperscript{11} to 39 months\textsuperscript{34}.

3.1.2 Study Characteristics

Table\textsuperscript{11} presents study and patient characteristics for the trials of $^{131}$I–tositumomab in patients with previously treated NHL. The randomized trial reported by Davis et al.\textsuperscript{22} included patients with CD20+ NHL that was relapsed or refractory (defined as progression within 1 year of treatment) to a regimen containing either an anthracycline, an anthracenedione, or an alkylating agent. Patients were randomized to either $^{131}$I–tositumomab ($n = 42$) or to unlabelled tositumomab ($n = 36$). Patients who did not respond to unlabelled tositumomab could cross over to the $^{131}$I–tositumomab arm if they did not have a human anti-mouse antibody (HAMA) response. The authors did not report the doses given to patients in either arm. Patient characteristics were well matched between the two treatment arms.

Six of the single-arm trials enrolled patients with NHL that was relapsed or refractory to chemotherapy without rituximab: one phase I dose-escalation trial\textsuperscript{8}, one phase I/II dose-escalation trial\textsuperscript{12}, and four phase II trials\textsuperscript{5,11,19,28}. One of the phase II trials used each patient as a self paired control for comparing the duration of response to $^{131}$I–tositumomab with the duration of response in the patient’s last qualifying chemotherapy regimen\textsuperscript{5}. The phase I trial reported by Press et al.\textsuperscript{8} was a dose-escalation study that provided separate outcomes data for the 12 patients who received therapeutic doses of $^{131}$I–tositumomab. Gopal et al.\textsuperscript{10} reported a study that compared patients in sequential trials reported by Press et al.\textsuperscript{22,27} (treatment group, $n = 27$) with a historical control group of patients who received conventional high-dose therapy and ASCT (control group, $n = 98$).

Two single-arm phase II trials enrolled patients with NHL relapsed or refractory to rituximab, with or without chemotherapy. The first trial, reported by Horning et al.\textsuperscript{34} included patients who were relapsed or refractory to rituximab. Nair et al.\textsuperscript{39} reported a trial that enrolled patients with CD20+ NHL refractory to chemotherapy and rituximab.

Two single-arm phase I dose escalation trials treated patients who had chemotherapy-resistant NHL with a regimen including $^{131}$I–tositumomab conditioning for ASCT\textsuperscript{17,40}.

Mones et al.\textsuperscript{32} reported the results of a phase I trial that enrolled patients who had relapsed or refractory low-grade NHL and more than 25% bone marrow involvement. The first cohort of patients received $^{131}$I–tositumomab at a total body dose of 45 cGy, with incremental increases of 10 cGy for subsequent cohorts.

Four of the single-arm trials reported subgroup data for patients with transformed NHL\textsuperscript{5,12,19,28}. Three additional trials\textsuperscript{17,23,34} reported that 12%–23% of enrolled patients had transformed NHL, but they did not provide outcomes data for that subgroup of patients. An integrated pooled analysis of five of these studies\textsuperscript{5,12,19,28,34} reported outcomes unique to this subgroup of patients\textsuperscript{43,44,45}. In this population of 71 evaluable patients with transformed NHL, the median time from diagnosis to therapy was 74 months, and the median time from transformation was 21 months\textsuperscript{45}.

3.1.3 Response Rate

In previously treated patients, objective response rates ranged from 85% to 100%, with complete response (CR) rates of 20%–84%\textsuperscript{5,8,11,12,17,19,22,23,28,32,34,39,40} (Table IV). In the randomized trial\textsuperscript{22}, a statistically significant difference was observed in objective response between the $^{131}$I–tositumomab group and the unlabelled tositumomab group (55% vs. 19%), with CR rates of 33% versus 8% (statistical significance not reported). Response rates in rituximab-naive patients ranged from 57%\textsuperscript{19} to 100%\textsuperscript{8} with CR rates from 20%\textsuperscript{5} to 83%\textsuperscript{8}. Response to $^{131}$I–tositumomab appeared to compare favourably with the response to the preceding line of therapy (chemotherapy alone)\textsuperscript{8}. For patients that had relapsed after or were refractory to rituximab (with or without chemotherapy), response rates were 65%–34 and 72%–39, respectively.

The response rates were 65%\textsuperscript{40} and 87%\textsuperscript{17} in the trials that treated patients with $^{131}$I–tositumomab as part of multi-agent chemotherapy conditioning for ASCT, with CR rates of 57%\textsuperscript{40} and 77%\textsuperscript{17}.

One trial treated patients with more than 25% bone marrow involvement (a relative contraindication to the use of $^{131}$I–tositumomab) and observed an objective response rate of 18% in 11 patients\textsuperscript{32}.

A pooled analysis of five trials\textsuperscript{43,44,45} provided response data for the subgroup of patients with transformed NHL. A pooled response rate of 39% with a CR rate of 25% was reported.

3.1.4 Time to Progression

In previously treated patients, TTP data were reported for ten trials (Table IV). One randomized trial\textsuperscript{22} reported that median TTP was longer in the $^{131}$I–tositumomab
**Trials of \(^{131}\)I–tositumomab (\(^{131}\)ITB) in patients with previously treated non-Hodgkin lymphoma (NHL): study characteristics**

| Reference | Study type | Patient characteristics | Intervention | Pts (n)\(^a\) |
|-----------|------------|-------------------------|--------------|--------------|
| Press et al., 1993 \(^8\) | Single-arm | CD20+ or CD37+ B-cell NHL unresponsive to conventional systemic therapy | \(^{131}\)ITB phase I [total body dose: 10–31 Gy (dose escalation)], autologous stem cell transplantation if needed | 12\(^b\) |
| Press et al., 1995 \(^11\) | Single-arm | CD20+ NHL relapsed after at least one chemotherapy regimen | \(^{131}\)ITB (total body dose: 25–31 cGy), autologous stem cell transplantation or peripheral stem cell transplantation if needed | 25 |
| Kaminski et al., 2000 \(^12\) | Single-arm | Relapsed or refractory CD20+ B-cell NHL | \(^{131}\)ITB phase I/I (phase II total body dose: 75 cGy) | 59 |
| Vose et al., 2000 \(^19\) | Single-arm | Low-grade or transformed low-grade CD20+ NHL relapsed or refractory to at least one anthracycline- or anthracenedione-containing chemotherapy regimen | \(^{131}\)ITB (total body dose: 75 cGy, 65 cGy if platelets ≤ 149,000/mm\(^3\)) | 47 |
| Kaminski, 2001 \(^5\) | Single-arm | Low-grade or transformed low-grade CD20+ B-cell NHL relapsed or refractory after at least two prior chemotherapy regimens | \(^{131}\)ITB (total body dose: 75 cGy, 65 cGy if platelets < 150,000/mm\(^3\)) | 60 |
| Davis et al., 2003 \(^22\) (abstract) | Randomized | Relapsed or refractory CD20+ NHL. | \(^{131}\)ITB (total body dose: NR) Unlabelled tositumomab | 42 |
| Davies et al., 2004 \(^28\) | Single-arm | | \(^{131}\)ITB (total body dose: 75 cGy, 65 cGy if platelets ≤ 149,000/mm\(^3\)) | 44 |
| Horning et al., 2005 \(^34\) (abstract) | Single-arm | Indolent or transformed NHL, relapsed or refractory to rituximab | \(^{131}\)ITB (total body dose: 75 cGy, 65 cGy if platelets < 150,000/mm\(^3\)) | 43 |
| Nair et al., 2005 \(^39\) (abstract) | Single-arm | CD20+ NHL refractory to chemotherapy plus rituximab | \(^{131}\)ITB (total body dose: 75 cGy, 65 cGy if platelets < 150,000/mm\(^3\)) | 11 |
| \(^{131}\)ITB conditioning for autologous stem cell transplantation | | | | |
| Press et al., 2000 \(^17\) | Single-arm | CD20+ NHL relapsed or refractory to previous chemotherapy, bone marrow involvement < 25% | \(^{131}\)ITB [total body dose: 0–27 Gy (dose escalation)], followed by etoposide (60 mg/kg), plus cyclophosphamide (100 mg/kg), plus autologous stem cell transplantation | 52 |
| Vose et al., 2005 \(^40\) | Single-arm | Previously treated chemotherapy-resistant CD20+ aggressive NHL. | \(^{131}\)ITB [total body dose: 30–75 cGy (dose escalation)], followed by \(BEAM\) (carmustine 300 mg/m\(^2\) day 1; plus etoposide 100 mg/m\(^2\) twice daily, days 2–5; plus cytarabine 100 mg/m\(^2\) twice daily, days 2–5; plus melphalan 140 mg/m\(^2\) day 6), plus autologous stem cell transplantation (day 7) | 23 |
| \(^{131}\)ITB in alternative regimens | | | | |
| Kaminski et al., 2003 \(^23\) (abstract) | Single-arm | Low-grade or transformed low-grade NHL previously treated with \(^{131}\)ITB | \(^{131}\)ITB phase I (total body dose: NR) | 32 |
| Mones et al., 2004 \(^32\) (abstract) | Single-arm | Relapsed or refractory low-grade NHL, bone marrow involvement > 25% | \(^{131}\)ITB phase I [total body dose: 45 cGy (10 cGy dose-escalation increments)] | 11 |

\(^a\) Randomized or enrolled/eligible.  \(^b\) Of the 43 enrolled patients, 19 received therapeutic doses, and only 12 of the 19 received \(^{131}\)ITB.  Pts = patients; NR = not reported.
| Reference          | Study type | Intervention                                | Pts (n) | OR (%) | CR (%) | TTP | Follow-up |
|--------------------|------------|---------------------------------------------|---------|--------|--------|-----|-----------|
| **Relapsed or refractory to chemotherapy without rituximab** |            |                                             |         |        |        |     |           |
| Press et al., 1993  | Single-arm | 
|                    |            | $^{131}$IItb phase I                        | 12*     | 100  | 83  | NR  | 11 | 21+ | 26 |
| Press et al., 1995  | Single-arm | 
| Kaminski et al., 2000 | Single-arm | $^{131}$IItb (total body dose: 75 cGy)      | 59      | 71   | 34  | 12  | NR | 41d | 37.2 |
| Vose et al., 2000 | Single-arm | $^{131}$IItb (total body dose: 75 cGy)      | 47      | 57   | 32  | 11.6 | NR | 9.9 | 36 |
| Kaminski et al., 2001 | Single-arm | $^{131}$IItb (total body dose: 75 cGy)      | 60      | 65   | 20  | 8.4 | NR | 6.5 | 22.8 |
| Davis et al., 2003 | Randomized | Unlabelled tositumomab                       | 42      | 55   | 33  | 6.3 | NR | Not yet reached | 42.6 |
| Davies et al., 2004 | Single-arm | $^{131}$IItb (total body dose: 75 cGy)      | 41c     | 76   | 49  | 9.6 | NR | 15 | Not yet reached | 36 |
| **Relapsed or refractory to rituximab with or without chemotherapy** |            |                                             |         |        |        |     |           |
| Horning et al., 2005 | Single-arm | $^{131}$IItb (total body dose: 75 cGy)      | 40f     | 65   | 38  | 10.4 | NR | Not yet reached | 39 |
| Nair et al., 2005  | Single-arm | $^{131}$IItb (total body dose: 75 cGy)      | 11      | 72   | 27  | NR  | NR | NR | 26 |
| **131I itb conditioning for autologous stem cell transplantation** |            |                                             |         |        |        |     |           |
| Press et al., 2000  | Single-arm | $^{131}$IItb [total body dose: 75 cGy]       | 52      | 87   | 77  | 40  | NR | 2-Year: 83% | 39 |
| Vose et al., 2005  | Single-arm | $^{131}$IItb [total body dose: 75 cGy]       | 23      | 65   | 57  | 34  | NR | 34d | 38 |
| **131I itb in alternative regimens** |            |                                             |         |        |        |     |           |
| Kaminski et al., 2003  | Single-arm | $^{131}$IItb phase I (total body dose: NR), previous treatment with $^{131}$IItb | 32      | 56   | 22  | 11.8 | 10.7 | NR | 26 |
| Mones et al., 2004 | Single-arm | $^{131}$IItb phase I                        | 11      | 18   | NR  | NR  | NR | NR | NR |

---

- a Only 12 of the 43 enrolled patients received a therapeutic dose of $^{131}$IItb.
- b Includes patients with complete, partial, or minor response.
- c Of 25 enrolled patients, 4 did not receive treatment and were not included in the response and survival data analysis.
- d Estimated from Kaplan–Meier survival curve.
- e Of 44 enrolled patients, 3 did not receive treatment and were not included in the final analysis.
- f Of 43 enrolled patients, 3 did not receive treatment and were not included in the final analysis.
- g Response rates were calculated based on 31 patients that were evaluable for response.
- h Estimated from Kaplan–Meier progression-free survival curve.
- i Event-free survival, estimated from Kaplan–Meier event-free survival curve.
arm as compared with the unlabelled tositumomab arm (6.3 months vs. 5.5 months, \( p = 0.031 \)). Six single-arm trials of patients who were previously treated with chemotherapy or rituximab, or both,\(^5,12,19,28,34\), or with prior \( ^{131} \text{I} \)-tositumomab\(^23\), reported median TTP ranges from 8.4 months to 12 months. One trial reported a 1-year progression-free survival of 66%\(^11\).

### 3.1.5 Response Duration

Data on response duration in previously treated patients were reported in eight trials (Table iv). In the randomized trial\(^22\), median response duration was not reached in the \( ^{131} \text{I} \)-tositumomab arm; it was 28.1 months in the unlabelled tositumomab arm (\( p \) = not reported). In previously treated patients who had not received rituximab, median response duration ranged from 6.5 months\(^5\) to 15 months\(^6\). In the trial that compared \( ^{131} \text{I} \)-tositumomab response with that attained for last chemotherapy regimen in the same patients\(^5\), 17 of 60 patients achieved a response duration after \( ^{131} \text{I} \)-tositumomab that was equivalent to their most recent lymphoma treatment; 53% achieved a longer response duration after \( ^{131} \text{I} \)-tositumomab (\( p < 0.001 \)). In individuals with transformed NHL, the pooled analysis of five trials documented a median response duration of 20 months. In addition, of the 25% of individuals who attained a CR, median response duration reached 36.5 months\(^45\).

### 3.1.6 Survival

In the trials that included patients who had NHL relapsed or refractory to chemotherapy without rituximab, the median OS ranged from 21 months\(^8\) to 41 months\(^12\), with two trials reporting that the median OS was not reached at 12 months\(^11\) and 36 months\(^28\) of follow-up (Table iv). In patients with disease that was relapsed or refractory to rituximab, median OS had not yet been reached at 39 months\(^34\). In patients who received \( ^{131} \text{I} \)-tositumomab conditioning for ASCT, one trial reported a median OS of 36 months\(^40\), and another trial reported a 2-year OS of 83%\(^17\).

### 3.1.7 Quality of Life

Only one of the thirteen trials of \( ^{131} \text{I} \)-tositumomab in previously treated patients reported data on QOL\(^20\). The European Organization for Research and Treatment of Cancer quality of life questionnaire was administered to the patient cohort receiving \( ^{131} \text{I} \)-tositumomab after previous lymphoma treatment without rituximab. The authors reported that the scales for emotional function, social function, global health status, nausea/vomiting, and appetite loss demonstrated statistically significant improvements at one or more time points; however, no data or \( p \) values were reported.

### 3.1.8 Adverse Events

The randomized trial\(^22\) comparing \( ^{131} \text{I} \)-tositumomab with unlabelled tositumomab reported comparative grade 4 hematologic toxicities. Thrombocytopenia (12% vs. 0%), neutropenia (17% vs. 3%), and anemia (5% vs. 0%) occurred more frequently with radioimmunotherapy, although whether these differences were statistically significant was not reported (Table v).

The rates of adverse events were similar in patients who had\(^34,39\) and who had not\(^5,8,11,12,19,28\) received prior rituximab. Myelosuppression was common, but tended to be delayed in onset, with cytopenia nadirs occurring 7–9 weeks after treatment. Eight trials reported on the rate of infection, with grades 1–4 infections occurring in 21%–55% of patients\(^5,8,11,12,19,23,34\). The rate of hospitalization from infection was reported in three trials and ranged from 2% to 15%\(^5,23,28\). Non-hematologic toxicity was common (reported in 80% of patients), generally mild, and related to drug infusion. Grades 1 and 2 adverse events occurred in a high proportion of patients in all trials, with the most common events being headache, fever, chills, infection, nausea, and vomiting. Table v summarizes these adverse events.

The rate of HAMA response was reported in ten single-arm trials, occurring in 0%–35% of patients\(^5,8,11,12,19,17,23,28,34,40\). Hypothyroidism was reported in six trials, and for the \( ^{131} \text{I} \)-tositumomab arm of the randomized trial, it occurred in 7%–42% of patients\(^5,8,11,12,22,23,34\).

The rate of myelodysplastic syndrome (MDS) was reported in eight trials and ranged from 0% to 9%\(^5,8,9,11,12,23,28,34,40\). One study that included patients from six trials and an expanded access program reported on MDS and acute myeloid leukemia (AML) in patients treated with \( ^{131} \text{I} \)-tositumomab\(^16\): 35 of 1071 patients developed MDS or AML for an annualized incidence of 1.4% per year (95% confidence interval: 1.0% to 2.0% per year).

### 3.1.9 Prognostic Factors

Predictors for overall response included tumour burden below 500 g\(^5\), grade 1 or 2 disease and tumour size 7 cm or less\(^24\), lymph node diameter less than 5 cm\(^28\), low-grade NHL\(^5,12\), bone marrow involvement\(^5\), fewer than 4 prior chemotherapy regimens\(^5\), and no prior radiotherapy\(^5\). The prior use of 2 or more chemotherapy regimens was associated with a shorter duration of remission\(^28\).

### 3.1.10 Dosimetry and Imaging

Dosimetry is a method of estimating the dose of radiation administered to specific organs. Imaging refers to the evaluation of gamma images to ensure that drug biodistribution is appropriate\(^46\). Dosimetry is required to determine the dose of \( ^{131} \text{I} \)-tositumomab to be administered\(^21,47\), and it was used in all trials in patients with previously treated NHL. No dose–response relationship was noted between absorbed dose and tumour response\(^21\). Also, no correlation was observed between total body tumour burden and objective response or toxicity\(^21\).
Trials of $^{131}$I–tositumomab ($^{131}$Tb) in patients with previously treated non-Hodgkin lymphoma: adverse events

| Reference | Study type | Interventions | Study type | Pts | Thrombocytopenia (grades 3–4) (%) | Neutropenia (grades 3–4) (%) | Anemia (grades 3–4) (%) | Infection (grades 1–4) (%) | Febrile neutropenia (%) | Human anti-mouse antibody (%) |
|-----------|------------|---------------|-------------|-----|---------------------------------|-----------------------------|--------------------------|---------------------------|-------------------------|-----------------------------|
| **Relapsed or refractory to chemotherapy without rituximab** | | | | | | | | | | |
| Press et al., 1993 | Single-arm | $^{131}$Tb phase I [total body dose: 10–31 Gy (dose escalation)] | | 43 | NR | NR | NR | 21 | NR | 7 |
| Press et al., 1995 | Single-arm | $^{131}$Tb (total body dose: 27 Gy) | | 21 | NR | NR | NR | 38 | NR | 19 |
| Kaminski et al., 2000 | Single-arm | $^{131}$Tb phase I (total body dose: 75 cGy, 65 cGy if platelets ≤ 149,000/mm$^3$) | | 47 | NR | 11 (grade 4) | NR | 24 | NR | 2 |
| Vose et al., 2000 | Single-arm | $^{131}$Tb (total body dose: 75 cGy, 65 cGy if platelets < 150,000/mm$^3$) | | 60 | 2 (grade 4) | 18 (grade 4) | 0 (grade 4) | 25 | 2 | 8 |
| Kaminski et al., 2001 | Single-arm | $^{131}$Tb (total body dose: 75 cGy, 65 cGy if platelets < 150,000/mm$^3$) | | 42 | 12 (grade 4) | 17 (grade 4) | 5 (grade 4) | NR | NR | 27 |
| Davis et al., 2003 (abstract) | Randomized | Unlabelled tositumomab | | 36 | 0 (grade 4) | 3 (grade 4) | 0 (grade 4) | NR | NR | 19 |
| Davies et al., 2004 | Single-arm | $^{131}$Tb (total body dose: 75 cGy, 65 cGy if platelets ≤ 149,000/mm$^3$) | | 41 | 32 | 45 | 5 | 15 (grade 3–4) | 5 | 10 |
| **Relapsed or refractory to rituximab with or without chemotherapy** | | | | | | | | | | |
| Horning et al., 2005 | Single-arm | $^{131}$Tb (total body dose: 75 cGy, 65 cGy if platelets < 150,000/mm$^3$) | | 40 | 25 | 42 | 10 | 55 | NR | 0 |
| Nair et al., 2005 (abstract) | Single-arm | $^{131}$Tb (total body dose: 75 cGy, 65 cGy if platelets < 150,000/mm$^3$) | | 11 | 18 (grade 4) | NR | NR | NR | NR | NR |
| **$^{131}$Ib conditioning for autologous stem cell transplantation** | | | | | | | | | | |
| Press et al., 2000 | Single-arm | $^{131}$Tb [total body dose: 20–27 Gy (dose escalation)], followed by etoposide, plus cyclophosphamide, plus autologous stem cell transplantation | | 52 | 100 | 100 (grade 4) | NR | 71 | NR | 13 |
| Vose et al., 2005 | Single-arm | $^{131}$Tb [total body dose: 30–75 Gy (dose escalation)], followed by BEAM (carmustine, etoposide, cytarabine, melphalan), plus autologous stem cell transplantation | | 23 | 100 | 100 (grade 4) | NR | 52 | >90% | 35 |
| **$^{131}$Ib in alternative regimens** | | | | | | | | | | |
| Kaminski et al., 2003 (abstract) | Single-arm | $^{131}$Tb (total body dose: NR) | | 32 | 38 | 44 | NR | 50 | 3 | 10 |
| Mones et al., 2004 (abstract) | Single-arm | $^{131}$Tb (total body dose: 45 cGy (10 cGy dose escalation increments)) | | 11 | NR | NR | NR | NR | NR | NR |

---

a Twelve patients received a therapeutic dose of $^{131}$Tb; the number of patients that received a dosimetric dose of $^{131}$Tb was not reported.
b Of 25 enrolled patients, 4 did not receive treatment and were not included in the final analysis.
c Two patients had grade 3 or 4 infection, and one patient died from infection (grade 5).
d Of 44 enrolled patients, 3 did not receive treatment and were not included in the final analysis.
e Of 43 enrolled patients, 3 did not receive treatment and were not included in the final analysis.
f Four patients had grade 3 or 4 infection.

Pts = patients; NR = not reported.
3.2 Patients with Previously Untreated NHL

3.2.1 Study Quality
No randomized controlled trials of $^{131}$I–tositumomab in patients with previously untreated NHL were identified. All of the five studies located were single-arm noncomparative phase II trials with sample sizes ranging from 13 patients to 90 patients $^{25,27,29,31,35}$. Median follow-up ranged from 11 months to 61.2 months.

3.2.2 Study Characteristics
Table VI details the study and patient characteristics of trials of $^{131}$I–tositumomab in patients with previously untreated NHL.

3.2.3 Response Rate
Table VII presents response data for the five trials of $^{131}$I–tositumomab in the previously untreated patient population. In the four trials of $^{131}$I–tositumomab alone $^{35}$ or after chemotherapy $^{25,29,31}$, objective response rates ranged from 90% to 100%, with CR rates from 67% to 83%. In a trial of sequential therapy with $^{131}$I–tositumomab followed by CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy ($\times 6$ cycles) in patients with mantle-cell NHL, the response rate was 83% after $^{131}$I–tositumomab (CR rate: 50%) and by intention-to-treat analysis, the response rate was 75% after CHOP (all of which were CRs) $^{27}$.

3.2.4 Time to Progression
Table VII presents data on TTP. One trial reported a median TTP of 73.2 months $^{35}$ and another reported a 2-year progression-free survival of 81% $^{25}$. Median TTP had not yet been reached in two other trials in which the median follow-up periods were 28 and 53 months $^{29,31}$.

3.2.5 Response Duration
Only one trial $^{27}$ reported median response duration, which had not yet been reached after a median follow-up of 11 months (Table VII). Among the subset of patients who experienced a CR $^{35}$, 40 of 57 had experienced an ongoing CR for 4.3–7.7 years. A third trial $^{29}$ reported that the median duration of CR was not reached after a median follow-up of 52.8 months, with 72% of 29 patients with a CR remaining in remission.

3.2.6 Survival
Two trials reported survival data for previously untreated patients (Table VII). One reported a 5-year OS of 89% $^{35}$, and another reported a 2-year OS of 97% $^{25}$.

3.2.7 Quality of Life
None of the trials of patients with previously untreated NHL reported data on QOL.

3.2.8 Adverse Events
Table VIII summarizes adverse events in the previously untreated population. Grades 3 and 4 thrombocytopenia ranged from 11% to 29%; neutropenia, from 13% to 34%; and anemia, from 0% to 3% $^{25,29,31,35}$. Grade 3 infection occurred in 2% of patients $^{25}$, and febrile neutropenia was reported as 0% in one trial $^{35}$ and 42% in another $^{27}$. One trial reported a 0% rate of hospitalization as a result of infection $^{35}$; no other trials reported hospitalization data.

Elevated thyroid-stimulating hormone occurred in 7%–12% of patients $^{25,20,35}$, and HAMA occurred

---

**TABLE VI** Single-arm trials of $^{131}$I–tositumomab (ITB) in patients with previously untreated non-Hodgkin lymphoma (NHL): study characteristics

| Reference | Patient characteristics | Intervention | $Pts$ ($n$)$^a$ |
|-----------|-------------------------|--------------|----------------|
| Press et al., 2003 $^{25}$ | Previously untreated CD20+ stage II-IV follicular NHL | CHOP (cyclophosphamide 750 mg/m$^2$ day 1, plus doxorubicin 50 mg/m$^2$ day 1, plus vincristine 1.4 mg/m$^2$ day 1, plus prednisone 100 mg days 1–5) every 21 days for 6 cycles, followed by $^{131}$ITB (total body dose: 75 cGy) | 90 |
| Zelenetz et al., 2003 $^{27}$ (abstract) | Previously untreated mantle-cell lymphoma | $^{131}$ITB (total body dose: NR), followed 13–16 weeks later by CHOP$^b$ Fludarabine 25 mg/m$^2$ daily for 5 days, every 5 weeks for 3 cycles, followed by $^{131}$ITB (total body dose: 75 cGy) | 13 |
| Leonard et al., 2004 $^{29}$ (abstract) | Previously untreated advanced low-grade NHL | CVP (cyclophosphamide 400 mg/m$^2$ days 1–5, plus vincristine 1.4 mg/m$^2$ day 1, plus prednisone 100 mg/m$^2$ days 1–5) every 21 days for 6 cycles, followed by $^{131}$ITB (total body dose: 75 cGy) | 38 |
| Link et al., 2004 $^{31}$ (abstract) | Previously untreated follicular NHL | | |
| Kaminski et al., 2005 $^{35}$ | Previously untreated advanced-stage follicular NHL | | 76 |

$^a$ Number enrolled and eligible.

$^b$ Standard CHOP, but with a cyclophosphamide dose of 1000 mg/m$^2$.

$Pts$ = patients; $NR$ = not reported.
in 0%–63%, with MDS or AML occurring in 0%–3% of patients.

3.2.9 Prognostic Factors
One trial reported on predictive factors. Nodal diameters of 5 cm or more were associated with lower response rates, and bone marrow involvement was also associated with lower response rates. Only bone marrow involvement had a significant effect on progression-free survival, predicting for a worse outcome.

3.2.10 Dosimetry and Imaging
All of the trials that enrolled patients with previously untreated NHL used dosimetry and imaging in the trial protocol. Dosimetry is part of the \(^{131}\)I–tositumomab regimen. One publication provided updated data on patients in three other publications and on an additional 19 patients. The authors reported that, for patients with previously untreated follicular NHL who received \(^{131}\)I–tositumomab, those with tumours receiving the highest radiation doses were more likely to achieve a CR; however, that association was not statistically significant.
4. DISCUSSION

The development of the monoclonal antibody rituximab has significantly advanced the treatment of lymphomas that express the target CD20 antigen. The anti-lymphoma benefit of rituximab is likely multifactorial, including antibody- and complement-dependent cellular cytotoxicity mechanisms. In addition to these immunobiologic effects, radioimmunoconjugates have the potential to direct radiation exclusively to the site of disease involvement, minimizing exposure to uninvolved organs. The adoption of these agents will depend on whether the incremental anti-lymphoma activity can translate into improved long-term outcomes without undue toxicity.

Patients with indolent lymphoma are treated episodically with chemotherapy, immunotherapy, or radiation often over a period of many years, sometimes decades. Therapy is initially highly effective in palliating symptoms and relieving potentially life-threatening complications, but it is not curative. Over time, response rates diminish and become less durable. The outcome for patients who are refractory to rituximab is particularly poor, and few alternative treatment options remain. In this context of heavily pretreated disease, the evidence supports the use of 131I–tositumomab. 131I–Tositumomab demonstrated significant anti-lymphoma activity in six single-arm trials in patients with NHL relapsed or refractory to chemotherapy without rituximab and in two single-arm phase II trials in patients with NHL relapsed or refractory to rituximab with or without chemotherapy.

For most of this heavily pretreated patient population, therapeutic options have been exhausted. A standard comparison therefore does not exist. However, one trial used each patient as a paired self control for comparing duration of response with the patient’s last qualifying chemotherapy regimen. That trial reported a significant difference in objective response (65% with 131I–tositumomab vs. 28% with last chemotherapy), and 53% of patients had a longer response duration after 131I–tositumomab than after their most recent chemotherapy. This longer response may represent a beneficial effect on the natural history of the disease because, typically, a lower response rate and shorter duration of response are observed with each successive treatment. In addition, a proportion of responders had very long durable remissions. For patients with a CR, median duration of response was 47.2 months as compared with only 4.8 months for their last qualifying chemotherapy. Given the limited available treatment options for pretreated patients, the use of 131I–tositumomab may offer benefit when other treatments (including rituximab) have failed.

The role of 131I–tositumomab in individuals with transformed low-grade NHL is also of interest, given the poor prognosis associated with currently available therapies. An integrated analysis of patients with transformation across five trials documented moderate response rates and a median response duration of 20 months, results that were commensurate with the heavily pretreated low-grade population. However, this small and selected population of patients with an extended time from transformation until treatment with 131I–tositumomab may not be reflective of all patients with transformed NHL, and further prospective data for this unique presentation are warranted. The data do not currently identify whether there is a differential benefit between the various indolent histologies (follicular vs. non-follicular) enrolled in these pivotal trials.

The data supporting the use of 131I–tositumomab in previously untreated patients with NHL are limited. No randomized controlled trials have compared 131I–tositumomab with standard therapy, and therefore the use of 131I–tositumomab in this patient population should be reserved until evidence becomes available supporting improved clinical outcomes with 131I–tositumomab as compared with current standard therapies.

The evidence for 131I–tositumomab as part of a conditioning regimen before ASCT is limited to two single-arm trials. Although encouraging, the limited data preclude any clear conclusions of benefit in that setting.

The toxicities of 131I–tositumomab are predictable. The main toxicity is hematologic, with delayed-onset cytopenias whose nadirs occur at 7–9 weeks from treatment. Particular attention to severe myelosuppression is warranted for patients with known bone marrow involvement and thrombocytopenia preceding therapy. Dose reductions are required if platelets reach 100–150×10^9/L, and the drug should not be administered if platelets are less than 100×10^9/L, absolute neutrophil count is less than 1.5×10^9/L, or bone marrow involvement is greater than 25%. The annualized incidence of MDS and AML in patients with previously treated NHL is 1.4% per year and would be considered acceptable in this group of patients who have often received prior leukemogenic anti-lymphoma therapies such as alkylating agents. The incidence of HAMA varied from 0% to 35% and is of questionable clinical significance.

The evidence has highlighted a number of predictors for response to radioimmunotherapy. Common predictors for response include indolent-histology disease (compared with transformed histology), non-bulky disease, and fewer prior therapies. However, these results should be considered hypothesis-generating at this time, given the limited sample sizes on which the subgroup analyses were based.

The final question that guided this review was the role of dosimetry in establishing the safety and efficacy of 131I–tositumomab. Although dosimetric findings did not correlate with tumour response, dosimetry was performed in all clinical studies involving this agent and is currently mandated in North American and European jurisdictions to determine the patient-specific therapeutic dose. Although there may
be logistic barriers to the performance of dosimetry, especially in smaller centres of practice, these limitations are out of the scope of the present review.

Currently, no comparative data addressing the use of one radioimmunoconjugate over another are available. Another radiolabelled anti-CD20 antibody, ⁹⁰Y-ibrutinumomab tiuxetan (Zevalin; IDEC Pharmaceuticals, San Diego, CA, U.S.A.), is being studied predominantly in indolent and transformed lymphoma. Important differences in radiation characteristics and dosimetry requirements may limit the class generalizability of these antibodies.

The strengths of the present review include the use of validated methods for the performance of systematic reviews, extension of the literature search to include preliminary abstract data to minimize publication bias, and objective data abstraction according to predefined outcome questions. However, the review does have limitations. For most of the trials, we did not formally appraise study quality because they were phase II studies and several were reported only in abstract form. This lack of appraisal limited the discrimination and utility of any methodologic grading scores. Also, the variability of the data precluded any pooling of results or use of meta-analytic summary techniques. We appreciate that the data come largely from single-arm studies and that the results are subject to selection bias; however, we have tempered our conclusions regarding this agent to reflect the currently available evidence. Finally, we acknowledge that the evidence regarding the role of ¹³¹I–tositumomab will continue to mature and evolve beyond this original systematic review and summary document.

A current listing of phase III trials is provided in Table IX, and we invite practitioners and patients to review the Web site of the PBEC (www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=10269) to remain abreast of the update process mandated for these guidelines.

Despite limitations, the data suggest a role for ¹³¹I–tositumomab in selected patients with NHL. The current evidence supports a role in the management of indolent lymphoma refractory to prior therapy that includes rituximab with or without chemotherapy. The precise role of ¹³¹I–tositumomab within the lymphoma armamentarium will undoubtedly continue to evolve.

5. ACKNOWLEDGMENTS

Funding for this review process was provided by Cancer Care Ontario and the Ontario Ministry of Health.

| Protocol ID  | Title and details of trial                                                                 |
|-------------|--------------------------------------------------------------------------------------------|
| SWOG S0016  | Phase III Randomized Study of Cyclophosphamide, Doxorubicin, Vinleistine, and Prednisone (CHOP) with Either Rituximab or Iodine ¹³¹I–Tositumomab (Monoclonal Antibody Anti-B1) in Patients with Newly Diagnosed Follicular Non-Hodgkin’s Lymphoma |
| NCT00006721 | Outcomes: Progression-free survival, overall survival, response, toxicity                    |
| CALGB 50102 | Projected accrual: 500 patients                                                             |
|            | Status: Study is ongoing, but not recruiting participants                                   |
|            | Notes: A CHOP-only arm closed to recruitment on December 15, 2002                           |
|            | Summary last modified: April 14, 2009                                                        |
| BMT CTN0401 | Phases I–III Rituxan/BEAM vs. Bexxar/BEAM with Autologous Hematopoietic Stem Cell Transplantation (ASCT) for Persistent or Relapsed Chemotherapy Sensitive Diffuse Large B-Cell Non-Hodgkin’s Lymphoma |
| NCT00329030 | Outcomes: Progression-free survival, overall survival, response, toxicity                   |
|            | Projected accrual: 224 patients                                                             |
|            | Status: Currently recruiting                                                                |
|            | Summary last modified: April 8, 2009                                                         |
|            | Accessed: May 10, 2009                                                                      |
|            | Available at: www.clinicaltrials.gov/ct2/show/NCT00006721                                   |
| CCBX001-049 | A Comparative Study of Iodine I-131 Tositumomab Therapeutic Regimen Versus Ibritumomab Tiuxetan Therapeutic Regimen |
| NCT00078598 | Status: Withdrewd                                                                            |
| NCT00319332 | Summary last modified: January 24, 2007.                                                      |
|            | Accessed: May 10, 2009                                                                      |
|            | Available at: www.clinicaltrials.gov/ct2/show/NCT00319332                                   |
| CCBX001-049 | A Study of Rituximab Versus Iodine I-131 Tositumomab Therapy for Patients with Non-Hodgkin’s Lymphoma |
| NCT00078598 | Status: Terminated                                                                          |
| NCT00268983 | Summary last modified: November 8, 2005                                                       |
|            | Projected accrual: 506 patients                                                             |
|            | Status: Terminated                                                                          |
|            | Accessed: May 10, 2009                                                                      |
|            | Available at: www.clinicaltrials.gov/ct2/show/NCT00078598                                   |
and Long-Term Care, Government of Ontario, Canada. The Hematology DSG thanks Dr. Stacey Hubay for reviewing the document and providing important input.

6. REFERENCES

1. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin’s lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin’s Lymphoma Classification Project. *J Clin Oncol* 1998;16:2780–95.

2. Horning SJ. Natural history of and therapy for the indolent non-Hodgkin’s lymphomas. *Semin Oncol* 1993;20(suppl 5):75–88.

3. McLaughlin P, Grillo–Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol* 1998;16:2825–33.

4. Cartron G, Watier H, Golay J, Solal–Celigny P. From the bench to the bedside: ways to improve rituximab efficacy. *Blood* 2004;104:2635–42.

5. Kaminski MS, Zelenetz AD, Press OW, et al. Radioimmunotherapy of B-cell lymphoma with iodine-131 tositumomab for previously untreated follicular non-Hodgkin’s lymphoma: a multicentric, prospective randomized trial. *J Nucl Med* 1998;39:376–84.

6. References

7. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin’s lymphomas: clinical features of the major histologic subtypes. *Non-Hodgkin’s Lymphoma Classification Project. J Clin Oncol* 1998;16:2780–95.

8. Horning SJ. Natural history of and therapy for the indolent non-Hodgkin’s lymphomas. *Semin Oncol* 1993;20(suppl 5):75–88.

9. McLaughlin P, Grillo–Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol* 1998;16:2825–33.

10. Cartron G, Watier H, Golay J, Solal–Celigny P. From the bench to the bedside: ways to improve rituximab efficacy. *Blood* 2004;104:2635–42.

11. Kaminski MS, Zelenetz AD, Press OW, et al. Radioimmunotherapy of B-cell lymphoma with iodine-131 tositumomab for previously untreated follicular non-Hodgkin’s lymphoma: a multicentric, prospective randomized trial. *J Nucl Med* 1998;39:376–84.
29. Leonard JP, Coleman M, Kostakoglu L, et al. Durable remissions from fludarabine followed by the iodine 131 tositumomab Bexxar therapeutic regimen for patients with previously untreated follicular non-Hodgkin’s lymphoma (NHL) [abstract 6518]. Proc Am Soc Clin Oncol 2004;22:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=26&abstractID=4254; cited August 3, 2009]

30. Leonard JP, Coleman M, Kostakoglu L, et al. Abbreviated chemotherapy with fludarabine followed by tositumomab and iodine 131 tositumomab for untreated follicular lymphoma. J Clin Oncol 2005;23:5696–704.

31. Link B, Kaminski MS, Coleman M, Leonard JP. Phase II study of cvp followed by tositumomab and iodine 131 tositumomab (Bexxar therapeutic regimen) in patients with untreated follicular non-Hodgkin’s lymphoma (NHL) [abstract 6520]. Proc Am Soc Clin Oncol 2004;22:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=26&abstractID=4147; cited August 3, 2009]

32. Moes J, Coleman M, Kostakoglu L, et al. A dose-escalation study of tositumomab and iodine 131 tositumomab (Bexxar) in pts with previously treated non-Hodgkin’s lymphoma (NHL) with > 25% bone marrow involvement [abstract 6575]. Proc Am Soc Clin Oncol 2004;22:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=26&abstractID=4232; cited August 3, 2009]

33. Moes JV, Coleman M, Kostakoglu L, et al. Dose-attenuated radioimmunotherapy with tositumomab and iodine 131 tositumomab in patients with recurrent non-Hodgkin’s lymphoma (NHL) and extensive bone marrow involvement. Leuk Lymphoma 2007;48:342–8.

34. Horning SJ, Younes A, Jain V, et al. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. J Clin Oncol 2005;23:712–19.

35. Kaminski MS, Tuck M, Estes J, et al. 131I–Tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005;352:441–9.

36. Koral KF, Dewaraja Y, Clarke LA, et al. Tumor-absorbed-dose estimates versus response in tositumomab therapy of previously untreated patients with follicular non-Hodgkin’s lymphoma: preliminary report. Cancer Biother Radiopharm 2000;15:347–55.

37. Koral KF, Francis IR, Kroll S, Zasadny KR, Kaminski MS, Wahl RL. Volume reduction versus radiation dose for tumors in previously untreated lymphoma patients who received iodine-131 tositumomab therapy. Conjugate views compared with a hybrid method. Cancer 2002;94(suppl 4):1258–63.

38. Koral KF, Dewaraja Y, Li J, et al. Update on hybrid conjugate-view SPECT tumor dosimetry and response in 131I–tositumomab therapy of previously untreated lymphoma patients. J Nucl Med 2003;44:457–64.

39. Nair M, Mark R, Anderson P, Neumann T, Quick D. Bexxar protocol CP98-020: preliminary results with I-131 labeled antibody in patients with non-Hodgkin’s lymphoma refractory to chemotherapy and Rituxan [abstract 6716]. Proc Am Soc Clin Oncol 2005;23:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=34&abstractID=32765; cited August 3, 2009]

40. Vose JM, Bierman PJ, Enke C, et al. Phase I trial of iodine-131 tositumomab with high-dose chemotherapy and autologous stem-cell transplantation for relapsed non-Hodgkin’s lymphoma. J Clin Oncol 2005;23:461–7.

41. Buchegger F, Antonescu C, Delaloye AB, et al. Long-term complete responses after 131I–tositumomab therapy for relapsed or refractory indolent non-Hodgkin’s lymphoma. Br J Cancer 2006;94:1770–6.

42. Gopal AK, Rajendran JG, Gooley TA, et al. High-dose 131I tositumomab (anti-CD20) radioimmunotherapy and autologous hematopoietic stem-cell transplantation for adults > or = 60 years old with relapsed or refractory B-cell lymphoma. J Clin Oncol 2007;25:1396–402.

43. Kaminski MS, Zelenetz AD, Leonard J, et al. Bexxar radioimmunotherapy produces a substantial number of durable complete responses in patients with multiply relapsed or refractory low grade or transformed low grade non-Hodgkin’s lymphoma [abstract 1382]. Blood 2002;100:356a.

44. Fisher RI, Kaminski MS, Wahl RL, et al. Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin’s lymphomas. J Clin Oncol 2005;23:7565–73.

45. Vose JM. Bexxar: novel radioimmunotherapy for the treatment of low-grade or transformed low-grade non-Hodgkin’s lymphoma. Oncologist 2004;9:160–72.

46. Witzig TE, White CA, Wiseman GA, et al. Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20+ B-cell non-Hodgkin’s lymphoma. J Clin Oncol 1999;17:3793–803.

47. Koral KF, Dewaraja Y, Li J, et al. Initial results for Hybrid SPECT—conjugate-view tumor dosimetry in 131I–anti-B1 antibody therapy of previously untreated patients with lymphoma. J Nucl Med 2000;41:1579–86.

Correspondence to: Kevin Imrie, c/o Adam Haynes, Research Coordinator, Cancer Care Ontario Program in Evidence-Based Care, McMaster University, 1280 Main Street West, DTC, Room 317, Hamilton, Ontario L8S 4L8. E-mail: haynesa@mcmaster.ca

* Cancer Care Ontario, Program in Evidence-Based Care, McMaster University, Hamilton, ON.
† Division of Hematology/Medical Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON.
‡ Division of Oncology, Grand River Regional Cancer Centre, Kitchener, ON.
§ Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON.
¶ Divisions of Oncology, Medicine, and Community Health and Epidemiology, Queen’s University, Kingston, ON.
# For a complete list of current Hematology Cancer Disease Site Group members, visit the Program in Evidence-Based Care section of the Cancer Care Ontario Web site: www.cancercare.on.ca/cms/one.aspx?pageId=10277.
APPENDIX A  UPDATED LITERATURE SEARCH

To ensure that our systematic review and conclusions remained valid, we updated the MEDLINE literature search outlined in Table 1 to May 10, 2009, from 2005, with a focus on randomized controlled trials and single-arm noncomparative studies. The same inclusion criteria that defined the original search were again applied. The new literature search identified 165 citations. Seven full publications met the inclusion criteria. No randomized phase III studies were identified for this time period. All of the reports were single-arm phase II reports. One publication, an integrated analysis of five pivotal studies on $^{131}$I–tositumomab, had already been included in the systematic review. Another study provided a longer-term update of a published report identified in the review; three other reports represented the final publication of abstracts identified in the review. Thus, only two new single-arm studies were discovered (see Table A-1). The data from the updated reports and the two novel studies do not affect the summary answers to the questions that guided the original systematic review.
### TABLE A-1  Novel and updated trials of $^{131}$I–tositumomab ($^{131}$ITb) in patients with non-Hodgkin lymphoma

| Reference                  | Study type | Intervention                                                                 | Pts  | OR (%) | CR (%) | TTP     | Median results (months) for Response duration | OS | Follow-up |
|----------------------------|------------|-----------------------------------------------------------------------------|------|--------|--------|---------|-----------------------------------------------|----|----------|
| **Previously untreated patients** |            |                                                                             |      |        |        |         |                                               |    |          |
| Leonard et al., 2005       | Single-arm | Fludarabine followed by $^{131}$ITb (total body dose: 75 cGy)              | 35   | 100    | 86     | Not yet reached | NR | NR | 58 |
| Press et al., 2006         | Single-arm | $^{131}$ITb (total body dose: 75 cGy)                                       | 90   | 91     | 69     | 5-Year: 67% | NR | 5-Year: 87% | 5.1 Years |
| **$^{131}$ITb in alternative regimens (previously treated patients)** |            |                                                                             |      |        |        |         |                                               |    |          |
| Kaminski et al., 2005      | Single-arm | $^{131}$ITb phase I (total body dose: NR), previous treatment with $^{131}$ITb | 32   | 56     | 25     | 11.8    | 15.2 | NR | 35 |
| Mones et al., 2007         | Single-arm | $^{131}$ITb phase I (total body dose: 45 cGy (dose escalation)), bone marrow involvement > 25% | 11   | 18     | NR     | NR      | NR   | NR | NR |
| **Relapsed or refractory to chemotherapy (previously treated patients)** |            |                                                                             |      |        |        |         |                                               |    |          |
| Buchegger et al., 2006     | Single-arm | $^{131}$ITb (total body dose: 75 cGy, 65 cGy if platelets ≤ 149,000/mm$^3$) | 18   | 81$^b$ | 50$^b$ | 22.5    | NR   | Not yet reached | 48 |
| **$^{131}$ITb conditioning for autologous stem cell transplantation** |            |                                                                             |      |        |        |         |                                               |    |          |
| Gopal et al., 2006         | Single-arm | $^{131}$ITb (total body dose: 25–27 cGy$^c$), plus autologous stem cell transplantation | 24   | 67     | 54     | 3-Year: 59% | NR | 3-Year: 51% | 2.9 Years |

---

*a Number included in the analysis.

*b Calculated based on 31 patients that were evaluable for response.

c Dose to the critical normal organ predicted to receive the highest radiation exposure based on biodistribution study.

Pts = patients; OR = complete response, unconfirmed complete response, and partial response; CR = complete response and unconfirmed complete response; TTP = time to progression; OS = overall response; NR = not reported; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone.