



Evidence-based Series 6-19 EDUCATION AND INFORMATION 2013

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

Iodine-131 Tositumomab in Lymphoma

The Hematology Disease Site Group

Report Date: January 18, 2007

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Section 1: Clinical Practice Guideline

Section 2: Systematic Review

Section 3: Guideline Development and External Review

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Evidence-based Series #6-19: Section 1

Iodine-131 Tositumomab in Lymphoma: A Clinical Practice Guideline

The Hematology Disease Site Group

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

Report Date: January 18, 2007

Questions

In adult patients with lymphoma of any type, at any stage of disease, and for any level of performance status:

1. What are the benefits associated with treatment with Iodine-131 (¹³¹I) tositumomab? Outcomes of interest include survival, quality of life, time-to-progression, response duration, and response rate.
2. What is the toxicity associated with the use of ¹³¹I tositumomab?
3. Which patients are more or less likely to benefit from treatment with ¹³¹I tositumomab?
4. Is performance of imaging or dosimetry required for treatment with ¹³¹I tositumomab to be safe and effective?

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:

- ¹³¹I tositumomab 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 who should be prioritized for therapy with ¹³¹I tositumomab are those with follicular non-Hodgkin's lymphoma who are refractory to chemotherapy and rituximab and to patients 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 ¹³¹I tositumomab may be generalizable to other relapsed or refractory CD20+ indolent non-Hodgkin's lymphomas, including mantle cell lymphoma, previously treated with rituximab. However, the benefit may not extend to patients with chronic lymphocytic

leukemia/small lymphocytic lymphoma, and ^{131}I tositumomab cannot be routinely recommended in this group of patients.

- There is insufficient evidence to support the use of ^{131}I tositumomab in patients with refractory or relapsed low-grade or follicular non-Hodgkin's lymphoma prior to the use of rituximab.
- Based on the available evidence, dosimetry (calculation of actual radiation absorbed to specific organs) is required to determine the dose to be administered.

Qualifying Statements

- ^{131}I tositumomab should be administered according to published dosing strategies and based on each patient's pharmacokinetics as described in the package insert. A detailed description of dosing can be found in Vose et al (1). Dose reductions should occur if platelets are $100\text{-}150 \times 10^9/\text{L}$. ^{131}I tositumomab should not be administered if platelets are less than $100 \times 10^9/\text{L}$, absolute neutrophil count is less than $1.5 \times 10^9/\text{L}$, or bone marrow involvement is greater than 25%.

Key Evidence

The primary evidence regarding ^{131}I tositumomab is described in nine trials:

- A randomized trial (2) compared ^{131}I tositumomab to unlabelled tositumomab in patients with relapsed or refractory CD20+ non-Hodgkin's lymphoma. No conclusion could be drawn from the comparison of the two arms. The objective response rate in the ^{131}I tositumomab arm was 55%, with a median time-to-progression of 6.3 months.
- Six single-arm trials (1,3-7) included patients who had non-Hodgkin's lymphoma that was relapsed or refractory to chemotherapy without rituximab. The objective response rates ranged from 57% to 100%, with a median time-to-progression ranging from 8.4 months to 12 months. The complete response rates ranged from 20% to 84%, with median durations of complete response ranging from 19.9 months to not-yet-reached.
- Two additional single arm trials (8,9) included patients who had non-Hodgkin's lymphoma that was relapsed or refractory to rituximab. The objective response rates were 65% and 72%, with one trial reporting median time-to-progression of 10.4 months. The complete response rates were 27% and 38%.

Related Guidelines

Program in Evidence-based Care Practice Guideline (PG) or Evidence-based Series (EBS):

- PG #6-2: *Treatment with Fludarabine for Patients with Follicular and other Low Grade Non-Hodgkin's Lymphoma and Waldenstrom's Macroglobulinemia.*
- EBS #6-8: *Rituximab in Lymphoma and Chronic Lymphocytic Leukemia.*
- EBS #6-17: *Ibritumomab Tiuxetan in Lymphoma.*

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Contact Information

For further information about this series, please contact:

Dr. K. Imrie, Co-Chair, Hematology Disease Site Group, Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5; TEL (416) 480-5145; FAX (416) 480-6002;

or

Dr. C.T. Kouroukis, Co-Chair, Hematology Disease Site Group, Juravinski Cancer Centre, 699 Concession Street, Hamilton, Ontario, L8V 5C2; TEL (905) 387-9711 ext. 62484; FAX (905) 575-6340.

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Evidence-based Series #6-19: Section 2

Iodine-131 Tositumomab in Lymphoma: A Systematic Review

The Hematology Disease Site Group

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

Report Date: January 18, 2007

QUESTIONS

In adult patients with lymphoma of any type, at any stage of disease, and for any level of performance status:

1. What are the benefits associated with treatment with Iodine-131 (^{131}I) tositumomab? Outcomes of interest include survival, quality of life, time-to-progression, response duration, and response rate.
2. What is the toxicity associated with the use of ^{131}I tositumomab?
3. Which patients are more or less likely to benefit from treatment with ^{131}I tositumomab?
4. Is performance of imaging or dosimetry required for treatment with ^{131}I tositumomab to be safe and effective?

INTRODUCTION

In Ontario, approximately 2,400 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 monoclonal antibodies to antigens on the surface of the malignant cells. Examples of such agents include ^{131}I tositumomab (Bexxar™, GlaxoSmithKline) and ^{90}Y ibritumomab tiuxetan (Zevalin™, Biogen Idec). ^{90}Y ibritumomab was the subject of an evidence-based series (#6-17 *Ibritumomab Tiuxetan in Lymphoma*) completed by the Hematology DSG in 2005. ^{131}I tositumomab consists of an anti-CD20 monoclonal antibody bound to a gamma-emitting radioactive isotope (^{131}I) (4). The CD20 antigen targeted

by the agent is expressed on more than 90% of B-cell NHLs. There is emerging evidence that ^{131}I tositumomab has shown activity in previously untreated patients and that ^{131}I tositumomab can produce meaningful durable responses in heavily pretreated patients, including those who are refractory to their most recent treatment regimen. However, the use of this agent may be associated with significant costs and additional toxicity. Bexxar™ received a Notice of Compliance from Health Canada in 2005. Therefore, the Hematology Disease Site Group (DSG) has prioritized the development of 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). The evidence was selected and reviewed by two members of the PEBC Hematology Disease Site Group (DSG) and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on the use of ^{131}I tositumomab in patients with lymphoma. The body of evidence in this review is comprised of data from one randomized trial, one nonrandomized comparative trial, and several noncomparative trials. 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 Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

Entries to MEDLINE (Ovid) (1966 to July, Week 2, 2005), EMBASE (Ovid) (1980 to Week 30 [July], 2005), and the Cochrane Library (2005, Issue 3) databases were searched. The search strategy for MEDLINE is shown in Appendix I; searches in other databases were similar. Studies were limited to humans and English language reports.

In addition, the conference proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO) (2000-2005) and the American Society of Hematology (ASH) (2000-2004) 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>), 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 by two reviewers. Disagreements were resolved by consensus. Reference lists from relevant articles were searched for additional publications.

Study Selection Criteria

Inclusion Criteria

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

1. They were systematic reviews, with or without meta-analyses, or evidence-based practice guidelines that assessed ^{131}I tositumomab in lymphoma.
2. Studies were randomized controlled trials, other comparative trials, or prospective single arm trials.
3. Studies included adult patients with lymphoma of any type, at any stage, and for any level of performance status.
4. ^{131}I tositumomab was examined as a single agent or in combination with other regimens.
5. For comparative trials, ^{131}I tositumomab was compared with any agent, any combination of agents, or placebo.

6. Results were reported for one or more of the following outcomes: survival, quality of life, time-to-progression, response duration, response rate, adverse effects, tumour dosimetry, or imaging.
7. They were full publications of studies that reported pooled data on adverse events from two or more trials.

Exclusion Criteria

Letters, comments, and editorial publication types were excluded. Abstracts of studies that reported pooled data from two or more trials on adverse events were excluded. Studies published in languages other than English were excluded due to lack of funding for translation resources.

Synthesizing the Evidence

The 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

No systematic reviews, practice guidelines, or meta-analyses were identified. A total of 18 trials were identified that investigated the use of ^{131}I tositumomab in patients with NHL (5-29). Twenty-one full publications of 11 trials were identified from the literature searches of MEDLINE, EMBASE, and the Cochrane Library. Table 1 identifies the primary publication for each trial and also indicates whether additional information was obtained from other publications. One full publication (30) was identified that pooled data from six trials, as well as data from an expanded access program on the rate of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) in patients with NHL that received ^{131}I tositumomab. One publication (31) was identified that reported data on tumour dosimetry for patients included in the trials reported by Kaminski et al (7) and Vose et al (13). Four publications (32-35) reported on tumour dosimetry and imaging for the previously untreated patients with follicular NHL who were enrolled in the trial reported by Kaminski et al (25).

Table 1. Primary and additional publications of trials included in this systematic review.

Primary Publication author, year (ref)	Publications with additional information author, year (ref)
Davis, 2003 (5) (abstract)	Bennet, 2005 (30)
Davies, 2004 (6)	None
Kaminski, 2001 (7)	Kaminski, 2001 (8) (abstract) Bennet, 2005 (30) Sgouros, 2003 (31)
Kaminski, 2000 (12)	Kaminski, 1993 (9) Kaminski, 1996 (10) Wahl, 1998 (11) Bennet, 2005 (30)
Vose, 2000 (13)	Kaminski, 2001 (8) (abstract) Bennet, 2005 (30) Sgouros, 2003 (31)
Press, 1995 (14)	Liu, 1998 (16) Gopal, 2003 (17)
Press, 1993 (15)	Liu, 1998 (16) Gopal, 2003 (17)
Horning, 2005 (18)	Bennet, 2005 (30)
Nair, 2005 (19) (abstract)	None
Vose, 2005 (20)	None
Press, 2000 (21)	Gopal, 2002 (22)
Mones, 2004 (23) (abstract)	None
Kaminski, 2003 (24) (abstract)	None
Kaminski, 2005 (25)	Bennet, 2005 (30) Koral, 2000 (32) Koral, 2000 (33) Koral, 2002 (34) Koral, 2003 (35)
Leonard, 2004 (26) (abstract)	None
Link, 2004 (27) (abstract)	None
Press, 2003 (28)	None
Zelenetz, 2003 (29) (abstract)	None

A total of 65 abstracts were identified as relevant or possibly relevant, through searches of the annual meetings of ASCO and ASH. Many of those abstracts were preliminary reports of trials that were subsequently fully published, and therefore were not referenced in this systematic review. Eleven abstracts were identified of seven trials that have not yet been fully published. Only the most recent abstract report for each trial was referenced in this systematic review. One abstract of a trial by Kaminski et al (8) provided quality-of-life data that was not included in the full publication of that trial (7).

The trials were divided into two categories, based on patient treatment history: The first category included patients who had previously treated NHL (Table 2). This category was further divided into randomized trials (5) and single-arm trials of ¹³¹I tositumomab. The single-arm trials were further divided into relapsed or refractory to chemotherapy without rituximab (6,7,12-15); relapsed or refractory to rituximab with or without chemotherapy (18,19); ¹³¹I tositumomab conditioning for ASCT (20,21); and ¹³¹I tositumomab in alternative regimens or alternative populations of previously treated patients (23,24). The second main category included trials that enrolled patients with previously untreated NHL (Table 3) (25-29).

Table 2. Trials of ^{131}I tositumomab in patients with previously TREATED non-Hodgkin's lymphoma: study characteristics.

Author, year (ref)	Patient characteristics	Intervention	N
Randomized trials of ^{131}I tositumomab			
Davis, 2003 (5) (abstract)	Relapsed/refractory CD20+ NHL	^{131}I tositumomab TBD-NR	42
		Unlabelled tositumomab	36
Single arm trials of ^{131}I tositumomab			
Relapsed or refractory to CT without rituximab			
Davies, 2004 (6)	B-cell NHL in 1 st or 2 nd recurrence	^{131}I tositumomab TBD-75cGy (65cGy if plt $\leq$ 149,000/mm ³)	44
Kaminski, 2001 (7)	LG or transformed LG CD20+ B-cell NHL relapsed/refractory after at least two prior CT regimens	^{131}I tositumomab TBD-75cGy (65cGy if plt $<$ 150,000/mm ³)	60
Kaminski, 2000 (12)	Relapsed/refractory CD20+ B-cell NHL	^{131}I tositumomab phase I/II phase II – TBD-75cGy	59
Vose, 2000 (13)	CD20+ LG or transformed LG NHL relapsed/refractory to at least one anthracycline- or anthracenedione- containing CT regimen	^{131}I tositumomab TBD-75cGy (65cGy if plt $\leq$ 149,000/mm ³)	47
Press, 1995 (14)	CD20+ NHL relapsed after at least one CT regimen	^{131}I tositumomab TBD-25-31cGy ASCT or PSCT if needed	25
Press, 1993 (15)	CD20+ or CD37+ B-cell NHL who had not responded to conventional systemic therapy	^{131}I tositumomab phase I TBD-10-31Gy (dose escalation) ASCT if needed	12 ^a
Relapsed or refractory to rituximab with or without CT			
Horning, 2005 (18)	Indolent or transformed NHL relapsed/refractory to rituximab	^{131}I tositumomab TBD-75cGy (65cGy if plt $<$ 150,000/mm ³)	43
Nair, 2005 (19) (abstract)	CD20+ NHL refractory to CT+rituximab	^{131}I tositumomab TBD-75cGy (65cGy if plt $<$ 150,000/mm ³)	11
^{131}I tositumomab conditioning for ASCT			
Vose, 2005 (20)	Previously treated CT-resistant CD20+ aggressive NHL	^{131}I tositumomab TBD-30-75cGy (dose escalation), followed by BEAM + ASCT (carmustine 300 mg/m ² d1 + etoposide 100 mg/m ² bid d2-5 + cytarabine 100 mg/m ² bid d2-5 + melphalan 140 mg/m ² d6 + ASCT d7)	23
Press, 2000 (21)	CD20+ NHL relapsed/refractory to previous CT, BMI $<$ 25%	^{131}I tositumomab TBD-20-27Gy (dose escalation), followed by etoposide (60 mg/kg) + cyclophosphamide (100 mg/kg) + ASCT	52
^{131}I tositumomab in alternative regimens			
Mones, 2004 (23) (abstract)	Relapsed/refractory LG NHL with BMI $>$ 25%	^{131}I tositumomab phase I TBD-45cGy (10 cGy dose escalation increments)	11
Kaminski, 2003 (24) (abstract)	LG or transformed LG NHL previously treated with ^{131}I tositumomab	^{131}I tositumomab phase I TBD-NR	32

Notes: ASCT – autologous stem cell transplantation; BEAM – carmustine, etoposide, cytarabine, and melphalan; bid – twice daily; BMI – bone marrow involvement; CT – chemotherapy; d – day(s); LG – low-grade; N – number of patients randomized or enrolled/eligible; NHL – non-Hodgkin's lymphoma; NR – not reported; PSCT – peripheral stem cell transplantation; plt – platelets; ref – reference; TBD – total body dose.

^aNineteen of the 43 enrolled patients received therapeutic doses, and only 12 of those 19 patients received ^{131}I tositumomab.

Table 3. Single arm trials of ^{131}I tositumomab in patients with previously UNTREATED non-Hodgkin's lymphoma: study characteristics.

Author, year (ref)	Patient characteristics	Intervention	N
Kaminski, 2005 (25)	Previously untreated advanced stage follicular NHL	^{131}I tositumomab TBD-75cGy	76
Leonard, 2004 (26) (abstract)	Previously untreated advanced LG NHL	Fludarabine 25 mg/m ² /d x 5d q5w for 3 cycles followed by ^{131}I tositumomab TBD-75cGy	38
Link, 2004 (27) (abstract)	Previously untreated follicular NHL	CVP (cyclophosphamide 400 mg/m ² d1-5 + vincristine 1.4 mg/m ² d1 + prednisone 100 mg/m ² d1-5 q21d x 6 cycles) followed by ^{131}I tositumomab TBD-75cGy	30
Press, 2003 (28)	Previously untreated CD20+ stage II-IV follicular NHL	CHOP (cyclophosphamide 750 mg/m ² d1 + doxorubicin 50 mg/m ² d1 + vincristine 1.4 mg/m ² d1 + prednisone 100 mg d1-5 q21d x 6 cycles) followed by ^{131}I tositumomab TBD-75cGy	90
Zelenetz, 2003 (29) (abstract)	Previously untreated MCL	^{131}I tositumomab TBD-NR followed 13-16w later by CHOP ^a	13

Notes: CHOP – cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP – cyclophosphamide, vincristine, and prednisone; d – day(s); LG – low-grade; MCL – mantle cell lymphoma; N – number of patients enrolled and eligible; NHL – non-Hodgkin's lymphoma; NR – not reported; q – every; ref – reference; TBD – total body dose, w – weeks.

^aStandard CHOP, except cyclophosphamide dose was 1000mg/m².

Trials of ^{131}I Tositumomab in Patients with Previously Treated Non-Hodgkin's Lymphoma Study Quality

Only one of the 13 trials of ^{131}I tositumomab in patients with previously treated NHL was a randomized controlled trial (5). 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 an open-label, multicentre trial. Seventy-eight patients were randomized to either ^{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 (7), compared each patient's duration of response after ^{131}I tositumomab to the duration of response to their last qualifying chemotherapy regimen (paired control). The remaining studies were single-arm phase I or II trials. Eight of those trials (6,12-15,18,20,21) have been fully published, with sample sizes ranging from 11 to 60 patients. The remaining three trials (19,23,24) have been published in abstract form only, with sample sizes ranging from 11 to 32 patients. Eight of 12 single-arm trials reported median follow-up times that ranged from 12 months (14) to 39 months (18).

Study Characteristics

Study and patient characteristics of the trials of ^{131}I tositumomab in patients with previously treated NHL can be found in Table 2. The randomized trial reported by Davis et al (5) included patients with CD20+ NHL that was relapsed or refractory (defined as progression within one year of treatment) to a regimen containing either an anthracycline, 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 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 (6,7,12-15). There was one phase I dose-escalation trial (15), one phase I/II dose-escalation trials (12), and four phase II trials (6,7,13,14). One of the phase II trials used each patient as their own paired control in order to compare the duration of response to ^{131}I tositumomab to the duration of response in the patient's last qualifying chemotherapy regimen (7). Three of the phase II trials delivered a total body dose (TBD) of ^{131}I tositumomab of 75 cGy (6,7,13). The phase I/II trial delivered a TBD of 75 cGy to patients enrolled in the phase II part of the trial (12). The phase II trial reported by Press et al, 1995 (14) delivered ^{131}I tositumomab at a TBD of 27 Gy with ASCT or peripheral stem cell transplantation (PSCT) if needed. The phase I trial reported by Press et al, 1993 (15) was a dose-escalation study that delivered a TBD of 10 Gy to 31 Gy of ^{131}I labelled antibodies (tositumomab, MB1, or IF5) to a total of 19 patients. Separate outcome data were available for the 12 patients who received therapeutic doses of ^{131}I tositumomab. Gopal et al (17) reported a study that compared patients in the trials reported by Press et al, 1993 and 1995 (treatment group, n=27) to 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 that was relapsed or refractory to rituximab, with or without chemotherapy. The first trial, reported by Horning et al (18) included patients who were relapsed or refractory to rituximab and treated them at a TBD of 75 cGy. The second trial, reported in abstract form by Nair et al (19), enrolled patients with CD20+ NHL that was refractory to chemotherapy and rituximab. Patients in that trial received a TBD of 75 cGy.

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. Vose et al (20) treated patients with aggressive NHL with ^{131}I tositumomab (dose escalation, 30-75 cGy) followed by carmustine, etoposide, cytarabine, and melphalan (BEAM) and ASCT. Press et al, 2000 (21) treated patients who had NHL with ^{131}I tositumomab (dose escalation, 20-27 Gy) followed by etoposide, cyclophosphamide, and ASCT.

Mones et al (23) 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 TBD at 45 cGy, with incremental increases of 10 cGy for subsequent cohorts.

Four of the single-arm trials reported subgroup data for patients who had transformed NHL (6,7,12,13). Three additional trials (18,21,24) reported that 12% to 23% of enrolled patients had transformed NHL but did not provide outcome data for that subgroup of patients.

Outcomes

Response rate

The response to therapy including ^{131}I tositumomab was reported in all of the trials in patients with previously treated NHL and is presented in Table 4. In that setting, objective response rates ranged from 18% to 100% with complete response (CR) rates of 20% to 84% (5-7,12-15,18-21,23,24). In the randomized trial (5), a statistically significant difference was observed in objective response between the ^{131}I tositumomab group and the unlabelled tositumomab group (55% versus [vs.] 19%), respectively; $p=0.002$). The CR rate was also higher in the ^{131}I tositumomab group compared to the unlabelled tositumomab group (33% vs. 8%), although the authors did not report whether that difference was statistically significant.

Table 4. Trials of ¹³¹I-tositumomab in patients with previously TREATED non-Hodgkin's lymphoma: response and survival.

Author, year (ref)	Intervention	N	OR (%)	CR (%)	Median time- to- progression (months)	Median response duration (months)	Median overall survival (months)	Median follow-up (months)
Randomized trials of ¹³¹ I tositumomab								
Davis, 2003 (5) (abstract)	¹³¹ I tositumomab TBD-NR	42	55	33	6.3	NYR	NR	42.6
	Unlabelled tositumomab	36	19	8	5.5	28.1	NR	
p=0.002p=0.031								
Single arm trials of ¹³¹ I tositumomab								
Patients relapsed or refractory to chemotherapy without rituximab								
Davies, 2004 (6)	¹³¹ I tositumomab TBD-75cGy (65cGy if plt≤ 149,000/mm ³)	41 ^a	76	49	9.6	15	NYR	36
Kaminski, 2001 (7)	¹³¹ I tositumomab TBD-75cGy (65cGy if plt<150,000/mm ³)	60	65	20	8.4	6.5	22.8	NR
Kaminski, 2000 (12)	¹³¹ I tositumomab phase I/II Phase II – TBD-75cGy	59	71	34	12	NR	41 ^b	37.2
Vose, 2000 (13)	¹³¹ I tositumomab TBD-75cGy (65cGy if plt≤ 149,000/mm ³)	47	57	32	11.6	9.9	36	NR
Press, 1995 (14)	¹³¹ I tositumomab TBD-27Gy	21 ^c	90 ^d	76	NYR	NR	NYR	12
Press, 1993 (15)	¹³¹ I tositumomab phase I TBD-10-31Gy (dose escalation)	12 ^f	100 ^d	83	NR	11	21+	26
Patients relapsed or refractory to rituximab with or without chemotherapy								
Horning, 2005 (18)	¹³¹ I tositumomab TBD-75cGy (65cGy if plt<150,000/mm ³)	40 ^g	65	38	10.4	NR	NYR	39
Nair, 2005 (19) (abstract)	¹³¹ I tositumomab TBD-75cGy (65cGy if plt<150,000/mm ³)	11	72	27	NR	NR	NR	26
¹³¹ I tositumomab conditioning for ASCT								
Vose, 2005 (20)	¹³¹ I tositumomab TBD-30-75cGy (dose escalation), followed by BEAM + ASCT	23	65	57	34 ^h	NR	34 ^b	38
Press, 2000 (21)	¹³¹ I tositumomab TBD-20-27cGy (dose escalation), followed by etoposide + cyclophosphamide + ASCT	52	87 ⁱ	77 ⁱ	40 ^e	NR	2yr 83%	NR
¹³¹ I tositumomab in alternative regimens								
Mones, 2004 (23) (abstract)	¹³¹ I tositumomab phase I TBD-45cGy (dose escalation) BMI>25%	11	18	NR	NR	NR	NR	NR
Kaminski, 2003 (24) (abstract)	¹³¹ I tositumomab phase I TBD-NR previous tx with ¹³¹ I tositumomab	32	56	22	11.8	10.7	NR	26

Notes: ASCT – autologous stem cell transplantation; BEAM – carmustine, etoposide, cytarabine, and melphalan; BMI – bone marrow involvement; CR – complete response and unconfirmed complete response; N – number of patients included in analysis; NR – not reported; NYR – not yet reached; OR – complete response, unconfirmed complete response, and partial response; plt – platelets; ref – reference; TBD – total body dose; tx - treatment.

^aThree of 44 enrolled patients did not receive treatment and were not included in the final analysis.

^bEstimated from Kaplan-Meier survival curve.

^cFour of 25 enrolled patients did not receive treatment and were not included in the response/survival data analysis.

^dIncludes patients with complete, partial, or minor response.

^eEstimated from Kaplan-Meier progression-free survival curve.^fOnly 12 of the 43 enrolled patients received a therapeutic dose of ¹³¹I tositumomab.

^gThree of 43 enrolled patients did not receive treatment and were not included in the final analysis.

^hEvent-free survival – estimated from Kaplan-Meier event-free survival curve.

ⁱResponse rates were calculated based on 31 patients that were evaluable for response.

The objective response rates in the single-arm trials of relapsed or refractory patients who had not received prior rituximab ranged from 57% (13) to 100% (15). The complete response rate ranged from 20% (7) to 83% (15). Kaminski et al (7) reported a significant difference in objective response rate for ^{131}I tositumomab compared to the patients' last qualifying chemotherapy regimen (65% vs. 28%, respectively; $p < 0.001$, McNemar's test), although response rate was not the primary outcome.

In the two trials that enrolled patients with NHL that relapsed after or was refractory to rituximab with or without chemotherapy, the objective response rates were 65% (18) and 72% (19), and the complete response rates were 38% (18) and 27% (19).

The objective response rates were 65% (20) and 87% (21) in the two trials that treated patients with ^{131}I tositumomab conditioning for ASCT. The complete response rates were 57% (20) and 77% (21).

Mones et al (23) treated patients who had greater than 25% bone marrow involvement and observed an objective response rate of 18%. Kaminski et al (24) enrolled patients who had previously received treatment with ^{131}I tositumomab and observed an objective response rate of 56% and a complete response rate of 22%.

The four trials that provided response data for the subgroup of patients with transformed NHL reported objective responses in 39% to 79% of patients (6,7,12,13). Three of the trials reported complete responses in 13% to 50% of patients (7,12,13).

Time-to-progression

Time-to-progression data were reported for 10 trials (Table 4). The randomized trial (5) reported that median time-to-progression was significantly longer in the ^{131}I tositumomab arm compared to the unlabelled tositumomab arm (6.3 months vs. 5.5 months, respectively; $p = 0.031$).

Six single-arm trials of patients who were previously treated with chemotherapy and/or rituximab (6,7,12,13,18), or ^{131}I tositumomab (24) reported median time-to-progression ranging from 8.4 months to 12 months. Press et al (14) reported a one-year progression-free survival of 66%. Of note, the two trials of ^{131}I tositumomab in conditioning for ASCT reported longer median time-to-progression, 34 months (20) and 40 months (21).

Gopal et al (17) compared 27 patients enrolled in the trials reported by Press et al, 1993 and 1995 (14,15) and treated with ^{131}I tositumomab to 98 historical control patients who received conventional high-dose therapy and ASCT. The authors calculated an unadjusted hazard ratio (HR) for progression or death of 0.6 (95% confidence interval [CI], 0.3-1.0; $p = 0.06$) and an adjusted HR for progression or death of 0.5 (95% CI, 0.3-0.9; $p = 0.03$) for ^{131}I tositumomab compared to conventional high-dose therapy. The authors adjusted the HR for elevated serum lactate dehydrogenase, presence of transformed disease, and International Prognostic Index score.

Kaminski et al (12) reported that the median progression-free survival for 11 patients with transformed NHL who had an objective response was 13.9 months.

Response duration

Data on response duration were reported in eight trials (Table 4). In the randomized trial (5), median response duration was not reached in the ^{131}I tositumomab arm and was 28.1 months in the unlabelled tositumomab arm ($p = \text{not reported [NR]}$).

Median response duration ranged from 6.5 months (7) to 15 months (6) in the four trials of patients who had NHL that was relapsed or refractory to chemotherapy without rituximab that reported on that outcome. Kaminski et al (7) reported that 28% of 60 patients had an equivalent response duration (defined as ≤ 30 days difference) after their last qualifying chemotherapy regimen, compared to ^{131}I tositumomab. Twenty-six percent of the remaining 43 patients had a longer response duration after their last qualifying chemotherapy regimen, and 74% had a

longer response duration after ^{131}I tositumomab, with that difference being statistically significant ($p < 0.001$, McNemar's test). Press et al, 1995 (14) reported that response duration after 12 months of follow-up ranged from three months to 23 months among the 21 patients that responded to treatment. None of the trials of patients who had NHL that was relapsed or refractory to rituximab (18,19) reported data on response duration, nor did the trials of patients treated with ^{131}I tositumomab, chemotherapy, and ASCT (20,21). Mones et al (23) reported a response duration of one month and 43.6+ months for the two patients who had a response in the trial of patients with bone marrow involvement greater than 25%. Kaminski et al (24) reported that, for patients who were previously treated with ^{131}I tositumomab, the median response duration was 10.7 months.

Five trials (6,7,13,15,24) reported median durations of complete response that ranged from 19.9 months to not yet reached after a median follow-up of 26 months to 36 months. Liu et al (16) also reported that 13 of 23 patients with a complete response who were in the trials reported by Press et al 1993 (15) and 1995 (14), continue in unmaintained remission after a median follow-up of 42 months.

In patients with transformed NHL, durable complete responses of 35+, 37, and 47+ months were observed in the trial reported by Kaminski et al (7). Vose et al (13) reported that the median duration of complete response was 19.9 months.

Survival

Overall survival data was reported in nine trials (Table 4). The randomized trial (5) did not report data on overall survival, and neither did the three single-arm trials reported in abstract form only (19,23,24). For the trials that included patients who had NHL that was relapsed or refractory to chemotherapy without rituximab, the median overall survival ranged from 21+ months (15) to 41 months (12), with two trials reporting that the median overall survival was not reached at 36 months (6) and 12 months (14) of follow-up. Horning et al (18) reported that median overall survival was not reached at 39 months follow-up for patients with NHL that had relapsed or was refractory to rituximab. For patients who received ^{131}I tositumomab conditioning for ASCT, Vose et al (20) reported a median overall survival of 36 months, and Press et al (21) reported two-year overall survival of 83%.

Gopal et al (17) reported HRs for the endpoint of death for 27 patients who received ^{131}I tositumomab in two trials reported by Press et al, 1993 and 1995 (14,15) compared to 98 historical control patients who received conventional high-dose therapy—unadjusted HR 0.4 (95% CI, 0.2-0.9; $p = 0.02$) and adjusted HR 0.3 (95% CI, 0.1-0.7; $p = 0.004$).

None of the trials reported survival data for the patients who attained a complete response.

Quality of life

Only one of the 13 trials of ^{131}I tositumomab in patients with relapsed or refractory NHL had data reported for quality of life. Kaminski et al (8), reported, in abstract form, the quality-of-life data for the trial that was fully published as Kaminski et al (7). The authors compared quality of life at baseline to quality of life at weeks three, seven, 13, 19, 25, and 38, using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ). The authors reported that, at week three, the mean nausea/vomiting score was significantly higher (worse), with an increase of 8.3/100 ($p < 0.05$). The authors reported that the emotional function, social function, global health status, nausea/vomiting, and appetite loss scales demonstrated statistically significant improvements at one or more time points; however, no data or p -values were reported. The authors also reported that by week 19 the mean change in baseline scores was improved for all scales except insomnia and that those changes persisted through week 38 ($p = \text{NR}$).

Adverse events

Adverse events for the trials of patients with relapsed or refractory NHL can be found in Table 5. The randomized trial (5) did not report whether the differences observed in the rates of grade four thrombocytopenia (^{131}I tositumomab, 12% vs. unlabelled tositumomab, 0%), neutropenia (17% vs. 3%), and anemia (5% vs. 0%) were statistically significant. The rate of HAMA response in the ^{131}I tositumomab group was higher than in the unlabelled tositumomab group (27% vs. 19%, respectively; $p=\text{NR}$). The authors reported no other adverse events.

The rates of adverse events in the trials of patients with NHL relapsed or refractory to chemotherapy without rituximab (6,7,12-15) were similar to the rates observed in the trials of patients with NHL relapsed or refractory to rituximab (18,19) and to the rates observed in the trial of patients who had previously been treated with ^{131}I tositumomab (24). Among those trials, four reported on grade 3/4 thrombocytopenia, which occurred in 32% to 40% of patients. Kaminski et al (7) and Nair et al (19) reported grade four thrombocytopenia in 2% and 18% of patients, respectively. Grade 3/4 neutropenia was reported in four trials and occurred in 42% to 55% of patients. In addition, Kaminski et al (7) and Vose et al (13) reported grade four neutropenia in 11% and 18% of patients, respectively. Grade 3/4 anemia was reported in three trials and occurred in 5% to 10% of patients. Kaminski et al (7) reported that grade 4 anemia occurred in none of 60 patients. Eight trials reported on the rate of infection, with grade 1-4 infections occurring in 21% to 55% of patients (7,12-15,18,24). Press et al (14) also noted that 10% had grade 3/4 infections, and one patient died due to infection. Davies et al (6) reported that 15% of patients had grade 3/4 infections. Three trials reported that febrile neutropenia occurred in 2% to 5% of patients (6,7,24). Grade 1/2 adverse events occurred in a high proportion of patients in all trials, with the most common including headache, fever, chills, infection, and nausea/vomiting.

Adverse events were reported in higher rates in the two trials of ^{131}I tositumomab conditioning for ASCT, compared to the other single-arm trials. Grade 3/4 thrombocytopenia, and grade four neutropenia occurred in all patients in both trials (20,21). The rate of grade 3/4 anemia was not reported in either trial. Grade 1-4 infections occurred in 52% (20) and 71% of patients (21). Press et al (21) also reported that 8% of patients had grade 3/4 infections. Vose et al (20) reported that more than 90% of patients had febrile neutropenia.

The rate of HAMA response was reported in ten single-arm trials and occurred in 0% to 35% of patients (6,7,12-15,18,20,21,24). The number of patients with elevated thyroid stimulating hormone (TSH) was reported for six trials and for the ^{131}I tositumomab arm of the randomized trial, and occurred in 7% to 42% of patients (5,7,12,14,15,18,24). The rate of hospitalization from infection was reported in three trials and ranged from 2% to 15% of patients (6,7,24).

The rate of MDS was reported for eight trials and ranged from 0% to 9% (6,7,12,14-16,18,20,24). Bennett et al (30) reported a study on MDS and AML in patients treated with ^{131}I tositumomab. They included patients from six trials and an expanded access program. The authors reported that 35 of 1071 patients developed MDS/AML, for an annualized incidence of 1.4%/year (95% CI, 1.0%/year to 2.0%/year). The authors also performed a blinded independent review of MDS/AML in each patient and determined that 23 of 1061 patients developed MDS/AML, for an annualized incidence of 0.9%/year (95% CI, 0.6%/year to 1.4%/year).

Table 5. Trials of ¹³¹I tositumomab in patients with previously TREATED non-Hodgkin's lymphoma: adverse events.

Author, year (ref)	Intervention	N	Thromb (G3/4) (%)	Neut (G3/4) (%)	Anemia (G3/4) (%)	Infection (G1-4) (%)	Febrile neut (%)	HAMA (%)
Randomized trials of ¹³¹I tositumomab								
Davis, 2003 (5) (abstract)	¹³¹ I tositumomab TBD-NR	42	12 (G4)	17 (G4)	5 (G4)	NR	NR	27
	Unlabelled tositumomab	36	0 (G4)	3 (G4)	0 (G4)	NR	NR	19
Single arm trials of ¹³¹I tositumomab								
Patients relapsed or refractory to chemotherapy without rituximab								
Davies, 2004 (6)	¹³¹ I tositumomab TBD-75cGy (65cGy if plt ≤ 149,000/mm ³)	41 ^a	32	45	5	15 (G3/4)	5	10
Kaminski, 2001 (7)	¹³¹ I tositumomab TBD-75cGy (65cGy if plt < 150,000/mm ³)	60	2 (G4)	18 (G4)	0 (G4)	25	2	8
Kaminski, 2000 (12)	¹³¹ I tositumomab phase I/II Phase II – TBD-75cGy	59	40	55	10	22	NR	17
Vose, 2000 (13)	¹³¹ I tositumomab TBD-75cGy (65cGy if plt ≤ 149,000/mm ³)	47	NR	11 (G4)	NR	24	NR	2
Press, 1995 (14)	¹³¹ I tositumomab TBD-27Gy	21 ^b	NR	NR	NR	38 ^c	NR	19
Press, 1993 (15)	¹³¹ I tositumomab phase I TBD-10-31Gy (dose escalation)	43 ^d	NR	NR	NR	21	NR	7
Patients relapsed or refractory to rituximab with or without chemotherapy								
Horning, 2005 (18)	¹³¹ I tositumomab TBD-75cGy (65cGy if plt < 150,000/mm ³)	40 ^e	25	42	10	55	NR	0
Nair, 2005 (19) (abstract)	¹³¹ I tositumomab TBD-75cGy (65cGy if plt < 150,000/mm ³)	11	18 (G4)	NR	NR	NR	NR	NR
¹³¹I tositumomab conditioning for ASCT								
Vose, 2005 (20)	¹³¹ I tositumomab TBD-30-75cGy (dose escalation), followed by BEAM + ASCT	23	100	100 (G4)	NR	52	>90%	35
Press, 2000 (21)	¹³¹ I tositumomab TBD-20-27cGy (dose escalation), followed by etoposide + cyclophosphamide + ASCT	52	100	100 (G4)	NR	71 ^f	NR	13
¹³¹I tositumomab in alternative regimens								
Mones, 2004 (23) (abstract)	¹³¹ I tositumomab TBD-45cGy (10 cGy dose escalation increments)	11	NR	NR	NR	NR	NR	NR
Kaminski, 2003 (24) (abstract)	¹³¹ I tositumomab TBD-NR	32	38	44	NR	50	3	10

Notes: ASCT – autologous stem cell transplantation; BEAM – carmustine, etoposide, cytarabine, and melphalan; G – grade; HAMA – human anti-mouse antibody; N – number of patients included in analysis; Neut – neutropenia; NR – not reported; plt – platelets; ref – reference; TBD – total body dose; Thromb – thrombocytopenia.

^aThree of 44 enrolled patients did not receive treatment and were not included in the final analysis.

^bFour of 25 enrolled patients did not receive treatment and were not included in the final analysis.

^cTwo patients had grade 3/4 infections and one patient died due to infection (grade 5).

^dTwelve patients received a therapeutic dose of ¹³¹I tositumomab; the number of patients that received a dosimetric dose of ¹³¹I tositumomab was not reported.

^eThree of 43 enrolled patients did not receive treatment and were not included in the final analysis.

^fFour patients had grade 3/4 infections.

Predictive Factors for Treatment with ¹³¹I Tositumomab

Predictors for overall response included tumour burden <500g (7), grade 1 or 2 disease and tumour size ≤ 7cm (18), lymph node diameter <5cm (6), low-grade NHL (7,12), bone marrow involvement (7), less than four prior chemotherapy regimens (7), and no prior radiotherapy (7). Davies et al (6) also reported that whether a patient had two or more prior chemotherapy regimens was associated with a shorter duration of remission (p=0.040). Analyses were conducted using the log-rank test (6), or multivariate logistical regression (6,7,12,18).

Dosimetry and Imaging

All of the trials that included patients with previously treated NHL used dosimetry and imaging in the trial protocol, as this is part of the ¹³¹I tositumomab regimen. Sgouros et al (31) reported dosimetry results for 15 patients enrolled in the trials reported by Kaminski et al (7) and Vose et al (13). That study found that there was an absence of a dose-response relationship between absorbed dose and tumour response. The authors also reported that there was no correlation between total body tumour burden and objective response or toxicity.

Trials of ¹³¹I Tositumomab in Patients with Previously Untreated Non-Hodgkin Lymphoma Study Quality

No randomized controlled trials of ¹³¹I tositumomab in patients with previously untreated NHL were identified. All of the identified studies are single-arm non-comparative phase II trials with sample sizes ranging from 13 to 90 patients (25-29). Two of the trials have been fully published (25,28), and the remaining three trials are only available in abstract form. The median follow-up ranged from 11 to 61.2 months.

Study Characteristics

Study and patient characteristics of the trials of ¹³¹I tositumomab in patients with previously untreated NHL can be found in Table 3. One trial, reported by Kaminski et al (25) treated 76 patients who had advanced stage follicular NHL with ¹³¹I tositumomab at a TBD of 75 cGy. Zelenetz et al (29) treated 13 patients who had mantle cell lymphoma (MCL) with ¹³¹I tositumomab (TBD-NR) followed by standard CHOP, in which, however, the cyclophosphamide dose was 1000 mg/m². Leonard et al (26) treated 38 patients who had advanced low-grade NHL with fludarabine followed by ¹³¹I tositumomab at a TBD of 75 cGy. Link et al (27) treated 30 patients with follicular NHL with cyclophosphamide, vincristine, and prednisone (CVP) followed by ¹³¹I tositumomab at a TBD of 75 cGy. Press et al (28) enrolled 90 patients with stage II-IV follicular NHL into a trial of CHOP followed by ¹³¹I tositumomab at a TBD of 75cGy.

Outcomes

Response rate

Response data for the five trials of ¹³¹I tositumomab in patients with previously untreated NHL can be found in Table 6. In the four trials of ¹³¹I tositumomab alone (25) or ¹³¹I tositumomab after chemotherapy (26-28), the objective response rates ranged from 90% to 100%, and the complete response rates ranged from 67% to 83%. In the trial of ¹³¹I tositumomab followed by CHOP in patients with MCL, the objective response rate was 83% after ¹³¹I tositumomab and 75% after CHOP. The complete response rate was 50% after ¹³¹I tositumomab and 75% following CHOP.

Time-to-progression

Data on time-to-progression can be found in Table 6. Kaminski et al (25) reported median time-to-progression of 73.2 months. Press et al (28) reported that two-year

progression-free survival was 81%. Leonard et al (26) and Link et al (27) both reported that median time-to-progression was not yet reached.

Response duration

Zelenetz et al (29) reported that the median response duration was not yet reached after a median follow-up of 11 months. No other trials reported data on objective response duration. Kaminski et al (25) reported that, of 57 patients in complete response, 40 patients had a complete response for 4.3 years to 7.7 years. Leonard et al (26) reported that the median duration of complete response was not reached after a median follow-up of 52.8 months. However, 72% of 29 patients with a complete response remain in remission.

Table 6. Single arm trials of ^{131}I tositumomab in patients with previously UNTREATED non-Hodgkin's lymphoma: response and survival.

Author, year (ref)	Intervention	N	OR (%)	CR (%)	Median time-to-progression (months)	Median response duration (months)	Median overall survival (months)	Median follow-up (months)
Kaminski, 2005 (25)	^{131}I tositumomab TBD-75cGy	76	95	75	73.2	NR	NYR	61.2
Leonard, 2004 (26) (abstract)	Fludarabine followed by ^{131}I tositumomab TBD-75cGy	35 ^a	100	83	NYR	NR	NR	52.8
Link, 2004 (27) (abstract)	CVP followed by ^{131}I tositumomab TBD-75cGy	30	100	80	NYR	NR	NR	27.6
Press, 2003 (28)	CHOP followed by ^{131}I tositumomab TBD-75cGy	90	90	67	NYR	NR	NYR	27.6
Zelenetz, 2003 (29) (abstract)	^{131}I tositumomab TBD-NR followed by CHOP ^a	12 ^b	75	75	NR	NYR	NR	11

Notes: CHOP – cyclophosphamide, doxorubicin, vincristine, and prednisone; CR – complete response and unconfirmed complete response; CVP – cyclophosphamide, vincristine, and prednisone; N – number of patients included in analysis; NR – not reported; NYR – not yet reached; OR – complete response, unconfirmed complete response, and partial response; ref – reference; TBD – total body dose; w – weeks.

^aThree of 38 enrolled patients did not receive treatment with ^{131}I tositumomab and were not included in the analysis of the data.

^bOne of 13 enrolled patients did not receive treatment with ^{131}I tositumomab and was not included in the analysis of the data.

Survival

Kaminski et al (25) reported a five-year overall survival of 89%, and Press et al (28) reported a two-year overall survival of 97%. The remaining three trials did not report data on overall survival.

Quality of life

None of the trials reported data on quality of life.

Adverse events

Adverse events were reported in all five trials of ^{131}I tositumomab in patients with previously untreated NHL (Table 7). Kaminski et al (25) and Press et al (28) reported that grade 3/4 thrombocytopenia occurred in 17% and 11% of patients, respectively, and grade 3/4 neutropenia occurred in 34% and 13%. Leonard et al (26) and Link et al (27) reported that grade 4 thrombocytopenia occurred in 29% and 23% of patients, respectively, and grade 4 neutropenia occurred in 34% and 33% of patients. Grade 3/4 anemia was reported by Kaminski et al (25) and Press et al (28), and occurred in no patients and 2% of patients, respectively, with

grade 4 anemia occurring in 3% of patients in the trial reported by Leonard et al (26). Grade 3 infection occurred in 2% of patients in the trial reported by Press et al (28), and febrile neutropenia occurred in no patients and 42% of patients in the trials reported by Kaminski et al (25) and Zelenetz et al (29). Kaminski et al (25) reported that no patients were hospitalized due to infection. No other trials reported on the rate of hospitalization. Four trials reported on HAMA response, which occurred in 0% to 63% of patients (25-27,29). The number of patients with elevated thyroid stimulating hormone (TSH) was reported in three trials and occurred in 7%, 12%, and 12% of patients (25,26,28). The rate of MDS/AML was reported for three trials with MDS/AML occurring in 0% to 3% of patients (25,27,28).

Table 7. Single arm trials of ^{131}I tositumomab in patients with previously UNTREATED non-Hodgkin's lymphoma: adverse events.

Author, year (ref)	Intervention	N	Thromb (G3/4) (%)	Neut (G3/4) (%)	Anemia (G3/4) (%)	Infection (G1-4) (%)	Febrile neut (%)	HAMA (%)
Kaminski, 2005 (25)	^{131}I tositumomab TBD-75cGy	76	17	34	0	NR	0	63
Leonard, 2004 (26) (abstract)	Fludarabine followed by ^{131}I tositumomab TBD-75cGy	35 ^a	29 (G4)	34 (G4)	3 (G4)	NR	NR	6
Link, 2004 (27) (abstract)	CVP followed by ^{131}I tositumomab TBD-75cGy	30	23 (G4)	33 (G4)	NR	NR	NR	0
Press, 2003 (28)	CHOP followed by ^{131}I tositumomab TBD-75cGy	82 ^b	11	13	2	2 (G3)	NR	NR
Zelenetz, 2003 (29) (abstract)	^{131}I tositumomab TBD-NR followed by CHOP ^a	12 ^c	NR	NR	NR	NR	42	16

Notes: CHOP – cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP – cyclophosphamide, vincristine, and prednisone; G – grade; HAMA – human anti-mouse antibody; N – number of patients included in analysis; Neut – neutropenia; NR – not reported; ref – reference; TBD – total body dose; Thromb – thrombocytopenia; w – weeks.

^aThree of 38 enrolled patients did not receive treatment with ^{131}I tositumomab and were not included in the analysis of the data.

^bEight of 90 enrolled patients were not evaluable for toxicity.

^cOne of 13 enrolled patients did not receive treatment with ^{131}I tositumomab and was not included in the analysis of the data.

Predictive Factors for Treatment with ^{131}I Tositumomab

Only Kaminski et al (25) reported on predictive factors. Univariate analyses were performed using the Chi-square and log-rank tests, and multivariate analyses were conducted using logistical regression. Nodal diameters of $\geq 5\text{cm}$ were associated with decreased response rates, and bone marrow involvement was also associated with decreased response rates. In multivariate analyses, only bone marrow involvement had a significant effect on progression-free survival.

Dosimetry and Imaging

All of the trials that enrolled patients with previously untreated NHL used dosimetry and imaging in the trial protocol, as it is part of the ^{131}I tositumomab regimen. Four full publications (32-35) that included patients who were enrolled in the trial reported by Kaminski et al (25) provided data on tumour dosimetry. The latest of those four publications, Koral et al (35), provided updated data on the 33 patients included in the other three publications, as well as data for an additional 19 patients. The authors reported that, for patients with previously untreated follicular NHL who received ^{131}I tositumomab, the patients with tumours that received the highest radiation doses were more likely to achieve a complete response; however, the correspondence was not statistically significant (hybrid single photon emission computed tomography [SPECT] method, $p=0.18$; conjugate-view method, $p=0.25$) (35).

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 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 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 CML who were refractory to interferon alpha. With the emergence of higher quality comparative evidence on both those agents, the evidence summaries have been replaced with evidence-based guidelines with more specific recommendations for the use of those 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, 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. It is in this context of a heavily pre-treated disease that the DSG considered the evidence to support the use of ^{131}I tositumomab.

Based on currently available evidence for ^{131}I tositumomab, the DSG has reached the following initial conclusions regarding the role of ^{131}I tositumomab in NHL:

1. The Hematology DSG does not recommend the use of ^{131}I tositumomab in previously untreated patients as there are no randomized controlled trials that compare ^{131}I tositumomab to standard therapy.
2. There are no randomized controlled trials comparing ^{131}I tositumomab to rituximab or that compare ^{131}I tositumomab to chemotherapy in patients with previously treated NHL. Therefore, there is no evidence to support the use of ^{131}I tositumomab prior to the use of rituximab.
3. ^{131}I tositumomab demonstrated significant anti-lymphoma activity in six single arm trials in patients with NHL that was relapsed or refractory to chemotherapy without rituximab and two single arm phase II trials in patients with NHL that was relapsed or refractory to rituximab with or without chemotherapy. One trial used each patient as their own paired control comparing duration of response to the patient's last qualifying chemotherapy regimen (7). The Hematology DSG felt that ^{131}I tositumomab is a reasonable option in pre-treated patients who have failed or are refractory to chemotherapy and rituximab. Given the limited available options in this heavily pre-treated population, the use of ^{131}I tositumomab may offer benefit when other treatments (including rituximab) have failed.
4. It is the opinion of the Hematology DSG that patients with other relapsed or refractory CD20+ indolent NHL histologies, including MCL, , who have been previously treated with rituximab, may also benefit from treatment with ^{131}I tositumomab. However, the DSG agreed that this benefit may not extend to patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).
5. The evidence for ^{131}I tositumomab in patients with transformed NHL is limited to subgroup data from single arm phase II trials. However, given that there are limited treatment options available to this group of patients and that there is evidence of

significant activity in this subgroup, the availability of ^{131}I tositumomab offers potential benefit.

6. Members of the DSG agreed that ^{131}I tositumomab should be administered according to published dosing strategies and based on each patient's pharmacokinetics as described in the package insert. A detailed description of dosing can be found in Vose et al (13). Dose reductions should occur if platelets are $100\text{--}150 \times 10^9/\text{L}$. ^{131}I tositumomab should not be administered if platelets are less than $100 \times 10^9/\text{L}$, ANC is less than $1.5 \times 10^9/\text{L}$ or bone marrow involvement is greater than 25%.
7. Members of the DSG agreed that dosimetry studies are required prior to drug administration.
8. The evidence for ^{131}I tositumomab as part of a conditioning regimen prior to ASCT is limited to two single arm trials (20,21). There is insufficient evidence to support the use of ^{131}I tositumomab as part of a conditioning regimen prior to ASCT.
9. For the majority of this heavily pre-treated patient population, therapeutic options have been exhausted. Radioimmunoconjugate therapy is a treatment option in patients who have progressed or become refractory to multiple chemotherapy agents. At this time, no comparative data exist to guide a recommendation addressing the use of one radioimmunoconjugate over another (i.e. ^{131}I tositumomab (Bexxar) or ^{90}Y ibritumomab tiuxetan (Zevalin)). Therefore, the Hematology DSG is unable to make a recommendation regarding the use of one agent prior to the other. Patient preference and institutional resources should be taken into consideration when selecting radioimmunoconjugate therapy.

ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the National Institute of Health Clinical Trials database (<http://clinicaltrials.gov/>) were searched for reports of new or ongoing trials that involved ^{131}I tositumomab for patients with lymphoma. Nine trials were closed to recruitment as of November 21, 2005. The Hematology DSG identified five single arm trials that were active as of November 21, 2005. Details of those trials can be found in Appendix 2. In addition, the following randomized trials were active as of November 21, 2005:

Protocol ID	Title and details of trial
SWOG-S0016, NCT00006721, CLAGB-50102	Phase III Randomized Study of Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) With Either Rituximab or Iodine I 131 Tositumomab (Monoclonal Antibody Anti-B1) in Patients with Newly Diagnosed Follicular Non-Hodgkin's Lymphoma. Outcomes: progression-free survival, overall survival, response, toxicity. Projected accrual: 775 patients within 5.5 years. Notes: CHOP-only arm closed to recruitment on December 15, 2002. Summary last modified: November 17, 2005. Accessed: November 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=68321&version=HealthProfessional&protocolsearchid=1985489 .
CCBX001-049, NCT00078598	A Study of Rituximab Versus Iodine I 131 Tositumomab Therapy for Patients With Non-Hodgkin's Lymphoma. Outcomes: response and safety. Projected accrual: 506 patients. Summary last modified: not reported. Accessed: November 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=360910&version=HealthProfessional&protocolsearchid=1985505 .

CCBX001-053, Comparative Trial Between Bexxar and Zevalin. Outcomes: efficacy and safety. NCT00078676 Projected accrual: not reported. Summary last modified: not reported. Accessed: November 21, 2005. Available at: <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=361581&version=HealthProfessional&protocolsearchid=1985524>.

CONCLUSIONS

¹³¹I tositumomab 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 ¹³¹I tositumomab is generalizable to other relapsed or refractory CD20+ indolent NHLs, including MCL, previously treated with rituximab. However, this benefit may not extend to patients with CLL/SLL. ¹³¹I tositumomab should be administered according to published dosing strategies, and based on actual patient body weight. Dose reductions should occur if platelets are 100 to 150. ¹³¹I tositumomab should not be administered if platelets are less than 100, ANC is less than $1.5 \times 10^9/L$ or bone marrow involvement is greater than 25%, or prior to myeloablative therapy with stem cell support. Dosimetry is required to determine the dose to be administered. There is no available evidence to guide a recommendation regarding the use of ¹³¹I tositumomab prior to or after ⁹⁰Y ibritumomab tiuxetan.

CONFLICT OF INTEREST

The members of the Hematology DSG disclosed potential conflicts of interest relating to the topic of this systematic review. No potential conflicts of interest were declared.

JOURNAL REFERENCES

A manuscript based on this report has been published by Current Oncology (<http://www.current-oncology.com/>):

- Cheung MC, MacEachern JA, Haynes AE, Meyer RM; Members of the Hematology Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. ¹³¹I-Tositumomab in lymphoma. Curr Oncol. 2009;16(5):32-47.

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For a complete list of the Hematology DSG members and the Report Approval Panel members, please visit the CCO Web site at <http://www.cancercare.on.ca/>

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Contact Information

For further information about this series, please contact:

Dr. K. Imrie, Co-Chair, Hematology Disease Site Group, Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5; TEL (416) 480-5145; FAX (416) 480-6002;

or

Dr. C.T. Kouroukis, Co-Chair, Hematology Disease Site Group, Juravinski Cancer Centre, 699 Concession Street, Hamilton, Ontario, L8V 5C2; TEL (905) 387-9711 ext. 62484; FAX (905) 575-6340.

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Appendix 1. Literature search strategy used in MEDLINE.

1. Bexxar.mp.
2. tositumomab:.mp.
3. 1 or 2
4. exp lymphoma/
5. lymphoma:.mp.
6. 4 or 5
7. 3 and 6
8. exp practice guidelines
9. practice guideline.pt.
10. practice guideline?.tw.
11. exp meta-analysis/
12. metaanal:.tw.
13. meta-anal:.tw.
14. metanal:.tw.
15. data pool:.tw.
16. systematic review?.tw.
17. systematic overview?.tw.
18. quantitative review?.tw.
19. quantitative overview?.tw.
20. quantitative synthes#s.tw.
21. exp randomized controlled trials/
22. randomized controlled trial.pt.
23. exp random allocation/
24. exp double blind method/
25. exp single blind method/
26. random:.tw.
27. exp controlled clinical trials/
28. controlled clinical trial.pt.
29. exp clinical trials/
30. clinical trial.pt.
31. exp clinical trials, phase ii/
32. clinical trial, phase ii.pt.
33. exp clinical trials, phase iii/
34. clinical trial, phase iii.pt.
35. exp multicenter studies/
36. multicenter stud:.tw.
37. clinical trial:.tw.
38. exp comparative study/
39. controlled trial:.tw.
40. or/8-39
41. 7 and 40
42. limit 41 to (humans and English language)

Appendix 2. Ongoing single-arm trials.

Protocol ID	Title and details of trial
CCBX001-048, NCT00062894	Pharmacokinetic Study of Previously Untreated, Relapsed, or Transformed Follicular Non-Hodgkin's Lymphoma with Fission-Derived Iodine I 131 Tositumomab. Outcomes: tumour dosimetry and biodistribution. Projected accrual: 12 patients. Summary last modified: not reported. Accessed: November 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=352416&version=HealthProfessional&protocolsearchid=1985562 .
SWOG-S0433, NCT00107380	Phase II Study of Iodine I 131 Tositumomab in Combination With Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Older Patients With Previously Untreated Bulky Stage II or Stage III or IV Diffuse Large B-Cell Non-Hodgkin's Lymphoma. Outcomes: progression-free survival and response. Projected accrual: 80 patients within 15 months. Summary last modified: November 2, 2005. Accessed: November 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=415955&version=HealthProfessional&protocolsearchid=1985582 .
UNMC-051-00, COULTER- IND-3323, NCT00006695	Phase II Study of Iodine I 131 Monoclonal Antibody Anti-B1, Followed By High-Dose Carmustine, Etoposide, Cytarabine, and Melphalan, and Autologous Peripheral Blood Stem Cell Transplantation in Patients With Relapsed or Refractory Non-Hodgkin's Lymphoma. Outcomes: response, time-to-treatment failure, safety. Projected accrual: 50 patients over 5 years. Summary last modified: October 18, 2004. Accessed: November 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=68308&version=HealthProfessional&protocolsearchid=1985606 .
FHCRC- 1734.00, NCT00098566	Phase II Long-Term Follow-up Study of Patients With Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma Previously Treated With Iodine I131 Tositumomab Followed By Autologous Bone Marrow or Stem Cell Transplantation. Outcomes: progression-free survival, overall survival, toxicity, quality of life. Projected accrual: 47 patients. Summary last modified: June 13, 2005. Accessed: November 21, 2005. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=398806&version=HealthProfessional&protocolsearchid=1985613 .
NCT00240565	Tositumomab And Iodine I 131-Tositumomab In Patients With Relapsed Indolent Non-Hodgkin's Lymphoma. Outcomes: response, progression-free survival, overall survival, adverse events, quality of life. Projected accrual: 90 patients. Summary last modified: October 2005. Accessed: November 21, 2005. Available at: http://clinicaltrials.gov/ct/show/NCT00240565?order=1 .



Evidence-based Series #6-19: Section 3

Iodine-131 Tositumomab in Lymphoma: Guideline Development and External Review - Methods and Results

The Hematology Disease Site Group

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

Report Date: January 18, 2007

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, 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 in the province 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 the use of iodine-131 (¹³¹I) tositumomab in patients with lymphoma, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Report Approval Panel

Prior to the submission of this evidence-based series report for external review, the report will be reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

External Review by Ontario Clinicians

The systematic review on ¹³¹I tositumomab 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 June 1, 2006)

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:

- ¹³¹I tositumomab 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 who should be prioritized for therapy with ¹³¹I tositumomab are those with follicular non-Hodgkin's lymphoma who are refractory to chemotherapy and rituximab and to patients 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 ¹³¹I tositumomab 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, and ¹³¹I tositumomab cannot be routinely recommended in this group of patients.
- There is insufficient evidence to support the use of ¹³¹I tositumomab in patients with

refractory or relapsed low-grade or follicular non-Hodgkin's lymphoma <u>prior</u> to the use of rituximab. Based on the available evidence, dosimetry (calculation of actual radiation absorbed to specific organs) is required to determine the dose to be administered.
Qualifying Statements ^{131}I tositumomab should be administered according to published dosing strategies and based on each patient's pharmacokinetics as described in the package insert. A detailed description of dosing can be found in Vose et al (3). Dose reductions should occur if platelets are $100\text{-}150 \times 10^9/\text{L}$. ^{131}I tositumomab should not be administered if platelets are less than $100 \times 10^9/\text{L}$, absolute neutrophil count is less than $1.5 \times 10^9/\text{L}$, or bone marrow involvement is greater than 25%.

Methods

Feedback was obtained through a mailed survey of 112 practitioners in Ontario who treat hematological malignancies (hematologists, medical oncologists, and radiation oncologists). 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 June 23, 2006. 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

Fifty-one responses were received out of the 112 surveys sent (46% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 49% 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.	24 (96)	1 (4)	0
There is a need for a guideline on this topic.	23 (92)	1 (4)	1 (4)
The literature search is relevant and complete.	25 (100)	0	0
The results of the trials described in the report are interpreted according to my understanding of the data.	23 (92)	2 (8)	1 (3)
The draft recommendations in the report are clear.	19 (76)	2 (8)	4 (16)
I agree with the draft recommendations as stated.	20 (80)	2 (8)	3 (12)
This report should be approved as a practice guideline.	19 (76)	3 (12)	3 (12)
	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	18 (75)	3 (12)	3 (12)

^a Percentages may not add to 100% due to rounding.

^b One practitioner did not answer this question.

Summary of Written Comments

Twelve respondents (48%) provided written comments. The main points contained in the written comments were:

1. One practitioner noted that although mantle cell lymphomas (MCL) make up a small population of lymphoma patients, many patients experience multiple relapses. The evidence for MCL is limited, however the available evidence is comparable to other indolent non-Hodgkin's lymphomas (NHL). The practitioner stated that a discussion regarding MCL, as well as an opinion of its use, should be added to the evidence-based series.
2. Three practitioners were concerned that the target population was poorly described. Specifically, it should be made clear that the recommendations apply to patients with recurrent chemotherapy-refractory generalized CD20+ lymphomas. One of these practitioners also stated that the duration of remission should be defined. In addition, patients who are poor candidates for intravenous cytotoxic chemotherapy should be considered.
3. One practitioner was concerned that the recommendations were too vague. Specifically, the statement "should be made available to selected patients" is not helpful. Should ¹³¹I tositumomab be used as first-, second-, or third-line salvage therapy?
4. One practitioner noted that involved field radiation is a more effective treatment for local control of localized presentations or limited relapse. No mention of the use of involved field radiation appears in the document.
5. Two practitioners noted that the evidence informing the recommendations is limited.
6. One practitioner was concerned that many community oncologists in Ontario would have difficulty accessing dosimetry for patients to determine the dose of ¹³¹I tositumomab. A network of radiation oncologists in Ontario who could be consulted for treatment with ¹³¹I tositumomab would be useful.
7. Three practitioners noted that the use of this therapy depends upon whether it is funded for use in Ontario. Without funding for ¹³¹I tositumomab, the guideline is of limited use.

Modifications/Actions

1. The Hematology DSG recognizes the limited options available for MCL. We identified only seven trials with reporting on 33 patients in total. Only one trial (4) provided separate data for MCL patients, however it was only for 13 who had previously untreated MCL. Given the limited evidence available, MCL was not discussed separately in the guideline document, however, the DSG does consider it reasonable to generalize the results to MCL and this histology is included in the second bullet point of the recommendation.
2. In response, the DSG has changed the wording of the second bullet to restrict the population to patients with CD20+ indolent lymphomas. There is insufficient evidence to identify a threshold duration of response to rituximab before considering ¹³¹I tositumomab
3. In the absence of randomized trials, insufficient evidence exists to better define a specific population to be treated with ¹³¹I tositumomab.
4. This evidence-based series does not address the role of involved field radiation therapy for patients with lymphoma. Furthermore, no trials were identified that compared the use of ¹³¹I tositumomab to external radiation therapy. Therefore involved field radiation therapy was not included in this evidence-based series.
5. The DSG agrees that there is limited evidence for the use of ¹³¹I tositumomab in patients with lymphoma. For patients with previously untreated lymphoma, the DSG agreed that there was insufficient evidence to recommend the use of ¹³¹I tositumomab in first-line therapy or prior to the use of rituximab. However, for patients with relapsed or refractory

CD20+ low-grade NHL after treatment with rituximab, there are very few treatment options. Therefore the DSG concluded that the use of ^{131}I tositumomab would be a reasonable treatment option for this patient population as few other options exist.

6. The DSG recognizes that ^{131}I tositumomab is a complex therapy and it may not be feasibly administered in all cancer centers. A process to identify centers that are able to provide this therapy and route for referral, while very appropriate lie outside of the scope of this document.
7. The DSG agrees that funding of ^{131}I tositumomab is required before practitioners in Ontario can use it in patients. The evidence-based series was submitted to the Drug Quality and Therapeutics Committee (DQTC) for review in 2005. Please see the section entitled "Policy Review" below for further details.

Policy Review

Evidence-Based Report #6-19 *Iodine-131 Tositumomab in Lymphoma* was submitted to the Drug Quality and Therapeutics Committee (DQTC) for review in 2005.

Implications for Policy

In Ontario, 2,400 people are diagnosed annually with lymphoma. Follicular and other indolent lymphomas account for approximately 40% of those diagnoses. ^{131}I tositumomab is 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 patients eligible for ^{131}I tositumomab 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 50-100 patients per year.

The population of interest includes patients with multiply relapsed follicular and other indolent lymphomas. Often these patients have advanced disease and are not considered curable with currently available therapies. The goal of treatment in these patients is to provide symptom relief and hopefully an extended duration without needing treatment (i.e., a long response duration) prior to the next inevitable relapse. ^{131}I tositumomab represents an additional line of treatment for the disease. Currently, no specific treatment would be considered standard therapy, although possibilities would include rituximab monotherapy, combination chemotherapy (anthracycline-based or purine analog-based) with or without rituximab, and radiation. High-dose therapy with stem cell support may be appropriate in select younger patients with excellent functional status but is used less often in multiply relapsed disease or in the elderly.

It should be noted that recent evidence suggests a role for rituximab in upfront (first-line) therapy; thus, its role as a monotherapy in relapse may diminish with evolving clinical practice. The current Ontario Drug Benefit structure does not fund rituximab in the setting of retreatment if previously combined with chemotherapy. Retreatment with a prior chemotherapy combination is a well-accepted strategy in the management of indolent lymphoma, if an extended response duration was previously attained. However, only scarce and mainly retrospective data exists on the feasibility of retreatment with the combination of rituximab and chemotherapy. Therefore, as more physicians adopt rituximab into upfront management, the need for alternative options to manage a relapse from rituximab-refractory disease will grow.

No additional drug regimens would be used more often, directly as a result of ^{131}I tositumomab administration. However, hospitalizations due to infections have been associated with 2% to 15% of ^{131}I tositumomab doses; thus, antibiotics and supportive care would be anticipated for a proportion of patients who experience cytopenia-related complications.

Peer-Review Feedback

The systematic review will be submitted to a peer-reviewed journal for possible publication.

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Contact Information

For further information about this series, please contact:

Dr. K. Imrie, Co-Chair, Hematology Disease Site Group, Toronto-Sunnybrook Regional Cancer Centre,
2075 Bayview Avenue, Toronto, Ontario, M4N 3M5; TEL (416) 480-5145; FAX (416) 480-6002;

or

Dr. C.T. Kouroukis, Co-Chair, Hematology Disease Site Group,
Juravinski Cancer Centre, 699 Concession Street, Hamilton, Ontario, L8V 5C2;
TEL (905) 387-9711 ext. 62484; FAX (905) 575-6340.

*For information about the PEBC and the most current version of all reports,
please visit the CCO Web site at <http://www.cancercare.on.ca/> or contact the PEBC office at:*

Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681

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