

# Radioimmunotherapy with tositumomab and iodine-131 tositumomab for non-Hodgkin's lymphoma

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**Abstract:** With the success of targeted monoclonal antibody therapy in non-Hodgkin's lymphoma, attempts were made to further improve efficacy through the addition of a radioisotope. A goal of radioimmunotherapy is to utilize the monoclonal antibody to deliver radiation to a tumor bed with relatively limited toxicity to the surrounding normal tissues. I-131 Tositumomab is an iodine-131 labeled anti-CD20 murine IgG2a monoclonal antibody and is one of two FDA-approved radioimmunotherapeutic drugs for patients with non-Hodgkin's lymphoma (NHL). For more than a decade now, radiolabeled tositumomab has principally been evaluated in low-grade and transformed low-grade NHL patients with proven efficacy in both the up-front and salvage settings. Studies have included its use as a single agent, in combination with chemotherapy and as part of a conditioning regimen for autologous stem cell transplantation. These data suggest that this agent has an important role in the treatment of patients with B cell lymphoma.

**Keywords:** non-Hodgkin's lymphoma, tositumomab, iodine-131-labeled tositumomab, B-cell lymphoma

## Introduction

The introduction of radioimmunotherapy into the management of B-cell non-Hodgkin's lymphoma has shown substantial promise and clear patient benefit. Early studies utilizing iodine-131-labeled tositumomab (Bexxar®, GlaxoSmithKline, Philadelphia, PA, USA) in the treatment of relapsed and refractory patients have shown durable responses, even in patients who have previously received chemotherapy and rituximab. More recent investigation has demonstrated that radiolabeled tositumomab has substantial activity in previously untreated patients, both as a single agent and in combination with chemotherapy. Additionally, its use as part of a conditioning regimen for autologous stem cell transplantation has been examined. Altogether, the data suggest that radiolabeled tositumomab plays an important role in the management of patients with B-cell lymphoma.

## Treatment regimen

The administration of tositumomab (unlabeled antibody) with iodine-131 tositumomab (labeled antibody) to patients involves a collaborative effort between the oncologist and the nuclear medicine or radiation oncology specialist. Patients receive on day 1 outpatient doses of unlabeled and then trace-labeled tositumomab, followed by dosimetric gamma camera scans at several time points over the next week. The data obtained allow the treating physician to determine the appropriate patient-specific activity of iodine-131 tositumomab to be administered a week later (in the therapeutic dose) in order to deliver a total body radiation exposure of 75 cGy. The dose is attenuated to 65 cGy for patients with platelet counts between 100,000 and 150,000. Patients with cytopenias or extensive bone marrow infiltration with lymphoma (greater than 25%

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of intertrabecular space) are not candidates for radioimmunotherapy due to excessive hematologic risk. Iodine supplementation is provided in the form of saturated solution of potassium iodide or Lugol's solution to block the thyroid and limit toxicity. After the course of treatment is administered, patients are monitored for toxicity through periodic blood count and other laboratory tests, as well as response assessment through standard imaging.

## Early studies

In 1993, Kaminski, Wahl and colleagues from the University of Michigan published phase I data on 10 patients with relapsed or refractory non-Hodgkin's lymphoma (NHL) (Kaminski et al 1993). Half the patients had low grade (indolent) lymphoma and the other half had intermediate-grade (aggressive) lymphoma. Following the administration of unlabeled antibody, radioimmunotherapy escalating whole-body exposures starting at 25 cGy and increasing by 10 cGy increments were given until a maximal tolerated dose not requiring stem cell support was determined. Out of nine evaluable patients, 6 responded (4 CR [complete remission], 2 partial remission [PR]). All four patients with CR entered remission with only one course of radiotherapeutic drug. Remissions lasted 8–11 months. Minimal toxicity was observed, the most common of which was reversible myelosuppression. These early findings of meaningful responses in previously treatment-refractory patients led to the acceleration of further early phase testing which established 75 cGy as the maximally tolerated whole-body radiation dose of <sup>131</sup>I-labeled-anti-CD20 antibody (Kaminski et al 1996). This early work paved the way for further development of radiolabeled tositumomab in NHL.

## Single-agent radiolabeled tositumomab in relapsed/refractory NHL

Two US-based phase II clinical trials have examined the efficacy of iodine-131 tositumomab in heavily pretreated low-grade and transformed NHL patients (Kaminski et al 2000; Vose et al 2000, Table 1). In 2000, Vose and colleagues published a multicenter phase II study of radiolabeled tositumomab in patients with chemotherapy-relapsed and chemotherapy-refractory low-grade or transformed NHL.

The principal goal of this study was to expand the use of this agent into multiple centers beyond the University of Michigan and to assess its utility more broadly. This population of patients in this trial was heavily pre-treated having received a median of 4 prior chemotherapeutic regimens. Furthermore, more than half of the 45 patients were refractory

to their most recent lymphoma therapy. Despite these adverse prognostic features, the administration of radiolabeled tositumomab to this group resulted in a 57% overall response (32% CR). Importantly, responses were observed in both the low-grade (indolent) and transformed NHL patients. The median overall response duration was 9.9 months and for those who achieved a CR, their median response duration was double (19.9 months). Principal toxicities, as in the phase I studies, were hematologic.

This multicenter experience confirmed the single-center findings from a phase I/II trial of single-agent radiolabeled tositumomab published in the same year by Kaminski et al (2000). As in the multicenter study, nearly half of the 59 patients were refractory to their most recent chemotherapeutic regimen. Likewise, comparable complete remission rates (34%) and median progression-free survivals (12 months) were observed. Long-term adverse effects included asymptomatic TSH elevations in 5 patients, a diagnosis of myelodysplasia (MDS) or acute myelogenous leukemia (AML in 5 patients, and 3 patients with the development of solid tumors (2 transitional cell bladder cancer and 1 with squamous cell carcinoma of the anus). Nearly all patients who developed subsequent malignancies had been exposed to known predisposing chemotherapeutic agents (eg, alkylating agents and cyclophosphamide) prior to receiving radioimmunotherapy, making the role of prior chemotherapy versus that of radioimmunotherapy unclear with respect to the etiology of late toxicity.

Collectively, these two studies demonstrated that treatment-refractory patients who had undergone a median of 3 or 4 prior therapies were still able to respond to radiolabeled tositumomab. Additionally, a UK-based phase II study (Davies et al 2004, Table 1) sought to examine the efficacy of radiolabeled tositumomab earlier in the disease course, at the first or second relapse. As expected, the subjects were overall more favorable than in the multiply-relapsed patients in the Kaminski and Vose studies with the majority of the subjects having low-risk International Prognostic Index scores and two-thirds having only received one prior chemotherapeutic treatment. A similar overall response rate of 76% was observed; however, a higher complete remission rate of nearly 50% was obtained with an overall median remission duration of 1.3 years. These data suggest that perhaps more and lengthier complete remissions could be obtained by administration of radiolabeled tositumomab earlier in the natural history of the disease.

Altogether, these phase II publications suggest that radiolabeled tositumomab can produce responses both in

**Table 1** Single agent tositumomab

Author	Study design	Patient population	Overall response	Median PFS	Median CR	Median survival	MDS	HAMA
<b>Previously untreated follicular lymphoma</b>								
Kaminski et al 2005	Phase II Single institution Open label Single agent tositumomab	Untreated follicular lymphoma patients (n = 76)	OR 95% 75% CR	6.1 years		Not reached at 8 years	None observed at median f/u of 5.1 years	63%
<b>Relapsed or refractory follicular lymphoma</b>								
Vose et al 2000	Phase II Single agent tositumomab	Relapsed/refractory (n = 45) Low grade (n = 37) Transformed (n = 10)	57% (32% CR)	9.9 months (median response duration)	19.9 months	36 months	Not Reported	2.2%
Kaminski et al 2000	Phase I/II Single-center Single agent tositumomab	Relapsed/refractory (n = 59) Low grade (n = 28) Intermediate/High grade (n = 14) Transformed low-grade (n = 17)	71% (34% CR)	12 months	20.3 months	Not reported	8.5%	17%
Kaminski et al 2001	Phase III Non-randomized Multi-center Single agent tositumomab	Refractory Low-grade (n = 36) Transformed low-grade (n = 23) Mantle cell (n = 1)	65% (20% CR)	8.4 months	Not reached at 47 months	Not reported	6.7%	8%
Davies et al 2004	Phase II Open label Two centers in UK Single agent tositumomab	First or second recurrence of indolent Transformed indolent (n = 7) Majority low risk IPI Relapsed (n = 40) Indolent Follicular large cell Transformed B-cell	76% OR (rates similar in indolent and transformed)	0.8 years	Not reached at 2.5 years	Not reached	None at median 2.7 years of follow up	4 out of 41
Horning et al 2005	Prospective Phase II analysis of tositumomab in pts who progressed after rituximab		65% OR 38% CR	10.4 months at 3.3 year median follow up	Not reached at 3.3 years	Not reached	2 out of 40	5%

**Abbreviations:** CR, complete remission; IPI, International Prognostic Index; OR, odds ratio; PFS, progression-free survival; MDS, development of myelodysplasia.

patients with a first or second relapse, but also in the treatment-refractory and multiply-relapsed setting.

In light of the now ubiquitous use of the anti-CD20 monoclonal antibody rituximab in the treatment of B-cell lymphomas, a key issue became the utility of anti-CD20 radioimmunotherapy in patients who had previously been treated with an unlabeled agent with the same target. Horning and colleagues published an important prospective phase II study examining the efficacy of radiolabeled tositumomab in patients who had progressed after rituximab therapy (Horning et al 2005, Table 1). Forty follicular or transformed follicular NHL patients who had received a median of 4 prior treatment regimens were studied. Thirty-five of patients had no response or a response duration of less than 6 months to prior rituximab and therefore are considered to be rituximab-refractory by standardly accepted criteria. Treatment of these subjects with radiolabeled tositumomab generated a 65% overall response (38% CR) and a 10.4 month progression-free survival (PFS) at 3.3 years of median follow up. Overall response rate, duration of response and median PFS were unchanged by stratification for prior response to rituximab. Importantly, this work demonstrated a role for radiolabeled tositumomab in patients who had progressed after treatment with rituximab, regardless of their previous response to it.

A pivotal phase III study of single-agent tositumomab in refractory NHL has also been conducted (Kaminski et al 2001, Table 1) that by design assessed its activity in the chemotherapy-refractory patient population. This multicenter trial of 60 chemotherapy-refractory low-grade or transformed low-grade (indolent) lymphoma patients was conducted in a non-randomized fashion with comparisons being made to enrolled patients' responses to their last qualifying chemotherapy (LQC) regimen. The overall response rate was 65% (20% CR) and was statistically better than the overall response to the LQC. Similarly, the complete remission rate was significantly higher (3% vs 20%,  $p < 0.001$ ) and the median response duration nearly doubled (6.5 vs 3.4 months,  $p < 0.001$ ) in comparison to the prior chemotherapy. The non-randomized (patient as their own control) nature of the study poses potential biases, however, a chemotherapy control arm would be impractical given the heterogeneity of the patient population. These data suggest that radioimmunotherapy can reverse the trend of shorter remissions with each sequential therapy that has been well-reported in indolent lymphoma (Johnson et al 1995).

A larger integrated efficacy analysis of 250 patients with relapsed or refractory low-grade and transformed NHL who were treated with a single course of radiolabeled tositumomab demonstrated high response rates (47%–68%) that were

durable (> 1 year) in one third of patients (Fisher et al 2005). Within this durable response population, 77% achieved a CR and 23% a PR. With a median follow-up of 5 years, the PFS for those who had achieved a CR had not yet been reached. The fact that patients with recurrent/resistant disease can have durable remissions with radioimmunotherapy is important in establishing its value. It was this data set that formed the basis of the 2003 regulatory approval of iodine-131 tositumomab by the US Food and Drug Administration for the treatment of patients with CD20 positive, follicular, NHL, with and without transformation, whose disease is refractory to rituximab and has relapsed following chemotherapy.

### **Single-agent radiolabeled tositumomab in untreated follicular NHL**

Given the high response rates observed in refractory patients, several investigators sought to study the efficacy of tositumomab as initial therapy in advanced stage follicular lymphoma (Kaminski et al 2005a, Table 1). A single therapeutic dose of tositumomab was administered by Kaminski and colleagues to 76 patients of which 95% had a response (75% CR). With a median follow-up of 5.1 years, the actuarial 5-year PFS was 59% with median PFS of 6.1 years. The 5-year rate of overall survival was 89%. Follicular Lymphoma International Prognostic Index (FLIPI) score was not predictive of overall response or PFS; however an overall survival difference was observed when low- and intermediate-risk patients were compared with high risk patients. These data may suggest that the benefit of up-front treatment with radiolabeled tositumomab may be more useful in the lower-risk IPI patients and perhaps should be considered as initial therapy specifically for such patients. This landmark trial demonstrated that one course of treatment (over one week) with radiolabeled tositumomab can produce durable remissions in previously untreated patients with advanced follicular lymphoma. What remains to be seen is how this treatment regimen compares in the long term (with respect to efficacy and toxicity) to other commonly employed regimens such as chemotherapy plus rituximab.

### **Radiolabeled tositumomab in combination with chemotherapy**

The Southwest Oncology Group (SWOG) performed a phase II trial studying the combined effect of CHOP followed by radiolabeled tositumomab in 90 previously untreated, advanced stage follicular lymphoma patients (Press et al 2006, Table 2). The treatment course consisted of standard CHOP chemotherapy

every 21 days for 6 cycles. Patients who received at least a partial response to CHOP were then consolidated with radiolabeled tositumomab 4–8 weeks later. Ninety percent achieved remission (69%CR, 23%PR). The 5-year overall survival rate for patients in this study was 87% and PFS rate was 67%. Comparing outcomes with historical CHOP alone data from SWOG (Dana et al 1993), CHOP plus radiolabeled tositumomab demonstrated a 23% higher estimated 5-year PFS (67% vs 44%,  $p=0.001$ ) and overall survival (87% vs 64%,  $p=0.0003$ ). These data are particularly impressive, given the fact that they were obtained in a cooperative group, community-based setting, rather than a single institution trial. These findings have led to an intergroup, randomized trial of CHOP-tositumomab versus CHOP-rituximab in previously untreated follicular lymphoma patients.

Our own group has also examined radiolabeled tositumomab in combination with chemotherapy (Leonard et al 2005, Table 2). We conducted a phase II, single-institution study of 35 previously untreated follicular lymphoma patients given an abbreviated course of fludarabine (three cycles) followed six to eight weeks later by radiolabeled tositumomab. The patients generally had high risk disease (45% with high risk FLIPI). The overall response rate after completing fludarabine was 89% (9% CR). However, after completion of the entire regimen (fludarabine + radiolabeled tositumomab) the overall response was 100% with 86% of patients achieving a complete remission. After a median follow up of 58 months, the median response duration and median progression free survival had not yet been reached suggesting durable responses are possible with this regimen.

We have additionally evaluated CVP chemotherapy followed by radiolabeled tositumomab in untreated follicular

lymphoma (Link et al 2004). All enrolled patients ( $n = 30$ ) completed full therapy. This regimen produced an overall response rate of 100% and a CR rate of 80%. Among patients who achieved less than a CR with CVP, 60% achieved a CR after radioimmunotherapy. With a median follow-up of 2.3 years, 77% of patients continued in response. This study suggests that the combination of CVP + radiolabeled tositumomab is a promising therapeutic regimen for patients with previously untreated, advanced-stage, follicular NHL.

The results of these trials combining standard chemotherapy with radioimmunotherapy as up-front therapy in follicular lymphoma patients suggest that partial tumor reduction by chemotherapy may be converted to complete and durable responses by the subsequent administration of radioimmunotherapy. However, it remains to be seen whether the addition of chemotherapy to radioimmunotherapy has any advantage over radioimmunotherapy alone. A randomized trial of chemotherapy + radioimmunotherapy versus radioimmunotherapy would be ideal to answer this question. In the meantime, the SWOG and CALGB (Cancer and Leukemia Group B) are conducting a randomized study in of CHOP + concurrent rituximab vs CHOP followed by I-131 tositumomab in order to assess the role of radioimmunotherapy as part of initial treatment in follicular lymphoma.

## Radiolabeled tositumomab in autologous stem cell transplantation

A commonly used conditioning regimen for relapsed lymphoma patients undergoing autologous stem cell transplantation (ASCT) includes total body irradiation (TBI) followed

**Table 2** Tositumomab in combination with chemotherapy

Author	Study design	Patient population	Overall response	Median PFS	Median CR	Median survival	MDS	HAMA
Press et al 2003, 2006	Phase II SWOG 9911 CHOP+tositumomab	Previously untreated follicular NHL ( $n = 90$ ) 21% high-risk FLIPI	91% OR (69% CR)	5 year est PFS 67%		5 year est OS 87%	1.1%	Not reported
Leonard et al 2005	Phase II Single institution Open label Prospective 3 cycles of fludarabine followed by tositumomab	Previously untreated FL patients	100% OR 86% CR	Not reached at median follow up of 58 months			One patient developed MDS at 58 months post-therapy	6%

**Abbreviations:** CR, complete remission; FLIPI, Follicular Lymphoma International Prognostic Index; HAMA, human anti-mouse antibody formation; NHL, non-Hodgkin's lymphoma; OR, odds ratio; PFS, progression-free survival; MDS, development of myelodysplasia.

by high dose chemotherapy. Although TBI is efficacious as a preparative regimen, its organ toxicity in addition to myelotoxicity is a major limitation. Several groups have sought to limit the toxicity of TBI, or enhance its efficacy, by replacing it with radioimmunotherapy (RIT). The rationale for this approach is that targeted delivery of radiation preferentially to lymphoma sites might enable physicians to give higher dose of radiation without undue toxicity to normal body sites and perhaps increase the number and durability of remissions from ASCT.

In 2000, Press and colleagues evaluated radiolabeled tositumomab administered in conjunction with 60 mg/kg of etoposide and 100 mg/kg of cyclophosphamide followed by ASCT (Press et al 2000, Table 3). Fifteen percent of patients experienced grade III or IV toxic effects. All four treatment-related deaths were due to opportunistic infections. Compared with non-randomized controls who received TBI in combination with etoposide and cyclophosphamide, patients who received radioimmunotherapy as part of their preparative regimen had higher overall and PFS, suggesting a benefit overall to the use of RIT. This group also examined high-dose chemo-radioimmunotherapy (HD-RIT) followed by ASCT in relapsed mantle cell lymphoma patients (Gopal et al 2002, Table 3). They observed an estimated 3-year overall survival and PFS of

93% and 61%, respectively. These responses were observed even in patients with chemo-refractory disease, suggesting that high dose iodine-131 tositumomab (with or without chemotherapy) with stem cell support may be a valuable treatment strategy in some settings.

Vose and colleagues examined the combination of radiolabeled tositumomab with high-dose carmustine, etoposide, cytarabine and melphalan (BEAM) followed by ASCT in chemotherapy-refractory of multiply-relapsed B-cell NHL patients (Vose et al 2005, Table 3). Overall survival and PFS at 2 years was 83% and 68%, respectively. Time to engraftment and non-hematologic toxicity was similar to historical control patients receiving BEAM alone. The maximum tolerated dose of radiolabeled tositumomab was higher in this phase I study at 75 cGy total body dose. This suggests that radioimmunotherapy can be given in combination with chemotherapy prior to ASCT and that tolerability is largely dependent upon the toxicities of the chemotherapeutic component of the conditioning regimen.

A comparison of over 100 consecutive follicular lymphoma patients who underwent autologous stem cell transplantation with either HD-RIT using radiolabeled tositumomab or conventional high-dose therapy suggested that HD-RIT patients experienced a significant improvement in overall survival and PFS (Gopal et al 2003). However, a

**Table 3** Tositumomab prior to autologous stem cell transplantation

Author	Study design	Patient population	Overall response	Median PFS	Median CR	Median survival	MDS	HAMA
Press et al 2000	Phase I/II Tositumomab +chemo prior to ASCT	Relapsed (n = 55) Follicular gr I/II (n = 34) Follicular grade III (n = 4) Mantle cell (n = 6) Transformed (n = 6) De novo DLBCL (n = 2)	87%	68% PFS at 2 years		83% OS at 2 years	1.9%	15%
Gopal et al 2002	Retrospective Tositumomab + chemo prior to ASCT	Relapsed/refractory Mantle cell (n = 16)	100% (91% CR)	61% estimated 3 year PFS		93% estimated 3 year OS	Not reported	Not reported
Vose et al 2005	Phase I Tositumomab + high dose BEAM followed by ASCT	23 chemotherapy refractory or multiply relapsed B-cell NHL patients 61% DLBCL, 17% follicular grade 3, 22% mantle cell	65% OR (57% CR)			OS 55% at 38 months of follow up	2 out of 23 (median f/u 38 months)	35%

**Abbreviations:** ASCT, autologous stem cell transplantation; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; HAMA, human anti-mouse antibody formation; NHL, non-Hodgkin's lymphoma; OR, odds ratio; OS, overall survival; PFS, progression-free survival; MDS, development of myelodysplasia.

randomized comparison of TBI versus radioimmunotherapy is obligatory to determine differences, if any, in efficacy and toxicity. Currently, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) is conducting a phase III, multi-center trial comparing progression-free survival after autologous hematopoietic stem cell transplantation using a standard rituximab plus BEAM transplant regimen versus a regimen adding radiolabeled tositumomab to BEAM in patients that have persistent or recurrent diffuse large B-cell lymphoma.

## Re-treatment with tositumomab

Given previously observed response durability in subsets of patients who had received radiolabeled tositumomab, the question of whether re-treatment with this agent could produce a second and safe response upon disease progression in some patients. To address this question, 32 patients with low-grade, follicular, or transformed low-grade B-cell lymphoma who relapsed after a response to radiolabeled tositumomab (and who recovered hematologic parameters) were enrolled into a phase II single-arm, open-label, multi-center study (Kaminski et al 2005b). Patients were required to have achieved at least a partial response for a duration of at least three months following initial treatment radioimmunotherapy. The majority of patients (84%) had low grade follicular lymphoma. The subjects had received a median of 4 previous treatments and 22% of the patients had received rituximab. Overall response was 56% (25% with CR or clinical complete response) with an overall median response duration of 15.2 months. There was no significant difference in median duration of first and second response and toxicity was comparable to that observed after initial therapy. Altogether, this study showed that patients who relapse following an initial response to tositumomab can have a second response that is as durable with acceptable toxicity. Patient selection, based on hematologic reserve and effectiveness of the prior course of radioimmunotherapy, may be important in optimizing the use of retreatment.

## Toxicities

The adverse-effect profile of tositumomab use includes grade IV cytopenias (minority of patients), rare but serious and even fatal hypersensitivity reactions, hypothyroidism, the development of human-antimouse antibodies (HAMA), and secondary malignancy. Infusion of tositumomab must be done under conditions in which treatment for anaphylaxis can be initiated promptly. Administration of potassium iodide is implemented prior to and after treatment to reduce the incidence of second-

ary hypothyroidism. The development of HAMA appears to be related to the degree of immunosuppression. Patients who have undergone prior treatment with chemotherapy tend to have low rate of HAMA development which is often clinically undetectable (only on blood serology) (Table 1), whereas patients treated with tositumomab in the first-line setting developed HAMA in 63% of cases.

The most concerning of the toxicities related to the administration of tositumomab is the potential for the development of secondary malignancy, most notably MDS and AML. Secondary MDS and AML have long been recognized as potential complications of treatment for NHL even before the era of radioimmunotherapy (Armitage et al 2003). With the prolonged survival observed in patients treated with tositumomab, it is unclear whether the development of subsequent MDS/AML is related to the radioimmunotherapy or to the longer period of observation after chemotherapy in patients who are living longer. Bennett and colleagues examined this question in a review of 1071 patients treated with radiolabeled tositumomab (Bennett et al 2005). A 6.3% 5-year cumulative incidence of MDS/AML was observed in patients who received radiolabeled tositumomab in the relapsed/refractory setting. However, with a median follow up of 5 years, no cases of MDS/AML were observed in patients who received tositumomab as initial therapy. Longer follow up is needed, but these initial data suggest that radiolabeled tositumomab is safe and that the development of secondary MDS/AML may be attributable to both the duration and amount of prior chemotherapy as well as to effects of the radioimmunotherapy itself.

## Conclusions

The last decade has seen much investigation into the role of radioimmunotherapy in the treatment of NHL. Radiolabeled tositumomab clearly is able to produce durable and lengthy complete remissions with progression-free and overall-survival benefits in relapsed and treatment-refractory patients, including those who have progressed after rituximab. This suggests that it may be utilized as a way to overcome resistance or to get lengthier remissions in patients with responsive disease but short prior remissions. Its role in the up-front setting is promising although comparisons to alternative regimens are awaited. Whether I-131 tositumomab should be used as a single-agent or in combination with chemotherapy needs to be further studied. Challenges in understanding the role of radioimmunotherapy in NHL are the lack of randomized data and unclear comparisons to other agents. Additional questions relate to the integration of radioimmunotherapy

with other approaches, and whether it should be used early in the course of the disease, at first or second relapse, or later once resistance to other drugs has emerged. Further investigation in the form of randomized control trials will hopefully clarify the role of radioimmunotherapy in the management of patients with NHL.

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## References

- Armitage JO, Carbone PP, Connors JM, et al. 2003. Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. *J Clin Oncol*, 21:897-906.
- Bennett JM, Kaminski MS, Leonard JP, et al. 2005. Assessment of treatment-related myelodysplastic syndromes and acute myeloid leukemia in patients with non-Hodgkin lymphoma treated with tositumomab and iodine I-131 tositumomab. *Blood*, 105:4576-82.
- Dana BW, Dahlberg S, Nathwani, et al. 1993. Long-term follow-up of patients with low-grade malignant lymphomas treated with doxorubicin-based chemotherapy or chemoimmunotherapy. *J Clin Oncol*, 11:644-51.
- Davies AJ, Rohatiner AZS, Howell S, et al. 2004. Tositumomab and iodine I-131 tositumomab for recurrent indolent and transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol*, 22:1469-79.
- Fisher RI, Kaminski MS, Wahl RL, et al. 2005. 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*, 23:7565-73.
- Gopal AK, Gooley TA, Maloney DG, et al. 2003. High-dose radioimmunotherapy versus conventional high-dose therapy and autologous hematopoietic stem cell transplantation for relapsed follicular non-Hodgkin lymphoma: a multivariable cohort analysis. *Blood*, 102:2351-7.
- Gopal AK, Rajendran JG, Petersdorf SH, et al. 2002. High-dose chemoimmunotherapy with autologous stem cell support for relapsed mantle cell lymphoma. *Blood*, 99:3158-62.
- Horning SJ, Younes A, Jain V, et al. 2005. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. *J Clin Oncol*, 23:712-19.
- Johnson PW, Rohatiner AZ, Whelan JS, et al. 1995. Patterns of survival in patients with recurrent follicular lymphoma: a 20-year study from a single center. *J Clin Oncol*, 13:140-7.
- Kaminski MS, Estes J, Zasadny KR, et al. 2000. Radioimmunotherapy with iodine <sup>131</sup>I tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. *Blood*, 96:1259-66.
- Kaminski MS, Radford JA, Gregory SA, et al. 2005. Re-treatment with I-131 tositumomab in patients with non-Hodgkin's lymphoma who had previously responded to I <sup>131</sup> tositumomab. *J Clin Oncol*, 23:7985-93.
- Kaminski MS, Tuck M, Estes J, et al. 2005. I-131-tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med*, 352:441-9.
- Kaminski MS, Zasadny KR, Francis IR, et al. 1993. Radioimmunotherapy of B-cell lymphoma with [I]anti-B1 (anti-CD20) antibody. *N Engl J Med*, 329:459-65.
- Kaminski MS, Zasadny KR, Francis IR, et al. 1996. Iodine-131 - anti-B1 radioimmunotherapy for B-cell lymphoma. *J Clin Oncol*, 14:1974-81.
- Kaminski MS, Zelenetz AD, Press OW, et al. 2001. Pivotal study of iodine I-131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol*, 19:3918-28.
- Leonard JP, Coleman M, Kostakoglu L, et al. 2005. Abbreviated chemotherapy with fludarabine followed by tositumomab and iodine I-131 tositumomab for untreated follicular lymphoma. *J Clin Oncol*, 23:5696-704.
- Link B, Kaminski MS, Coleman M, Leonard JP. 2004. Phase II study of CVP followed by tositumomab and iodine I-131 tositumomab (Bexxar therapeutic regimen) in patients with untreated follicular non-Hodgkin's lymphoma (NHL). *J Clin Oncol*, 22:6520a.
- Press OW, Eary JF, Gooley T, et al. 2000. A phase I/II trial of iodine-131-tositumomab (anti-CD20), etoposide, cyclophosphamide, and autologous stem cell transplantation for relapsed B-cell lymphomas. *Blood*, 96:2934-42.
- Press OW, Unger JM, Braziel RM, et al. 2006. Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: Five-year follow-up of Southwest Oncology Group protocol S9911. *J Clin Oncol*, 24:4143-9.
- Vose JM, Bierman PJ, Enke C, et al. 2005. 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*, 23:461-7.
- Vose JM, Wahl RL, Saleh M, et al. 2000. Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol*, 18:1316-23.