



Radioimmunotherapy and autologous stem cell transplantation for the treatment of B-cell lymphomas

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Relapse continues to be the primary cause of treatment failure in patients with non-Hodgkin's lymphomas (NHL) undergoing high-dose therapy and autologous stem cell transplantation. The anti-CD20 radioimmunoconjugates, Y-90 ibritumomab tiuxetan (Zevalin®; Biogen Idec, Inc., Cambridge, MA, USA) and I-131 tositumomab (Bexxar®; Corixa, Seattle, WA; and Glaxo Smith Kline; Philadelphia, PA, USA) have been associated with high response rates, durable remissions and limited toxicity apart from myelosuppression, making them ideal candidates for use in autotransplantation. Tested first as single agents in relapsed patients with indolent and transformed NHL, and then at much higher doses with stem cell support, these agents have now been combined with high-dose chemotherapy prior to autologous stem cell transplant. Radioimmunoconjugates have been used to replace total body irradiation (TBI) in some studies and to augment standard chemotherapy regimens in others. Thus far the results are promising, with combinations of radioimmunoconjugates and chemotherapy producing long-lasting responses in high-risk patients with no more toxicity than that caused by standard conditioning regimens. These results are notable in light of the fact that the dose of radiation delivered to the tumor is 10-fold higher than the dose achievable with TBI. Whether this increase in radiation dose to the targeted lymphoma translates into more durable remissions and an improvement in overall survival requires further investigation.

Key words: radioimmunotherapy, autologous stem cell transplantation, non-Hodgkin's lymphomas.

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The non-Hodgkin's lymphomas (NHL) constitute a diverse group of lymphoid malignancies that range from indolent to highly aggressive in their clinical behavior. High-dose therapy followed by autologous hematopoietic stem cell transplantation (autoSCT) nowadays plays a critical role in the treatment of this heterogeneous group of diseases, in some instances as part of initial treatment, but most commonly as salvage therapy. The cure rate with chemotherapy-only-based transplant conditioning regimens remains less than 50%.¹ Since NHL are known to be sensitive to irradiation, combined modality regimens such as cyclophosphamide and total body irradiation have been studied extensively; however, they have been associated with significant extramedullary toxicity such as pneumonitis.²⁻¹¹ An alternative approach, radioimmunotherapy, in theory delivers a continuous dose of radiation that exponentially decreases over time. One advantage of radioimmunotherapy is that it can treat disseminated disease with only limited effects on normal tissues. Studies have suggested that lymphoma cells may be more sensitive to the low dose-rate radiotherapy associated with radioimmunotherapy than to the high dose-rate radiotherapy associated with external beam radiation.¹² Whereas total

body irradiation (TBI) delivers an equivalent dose of radiation to all organs, radioimmunoconjugates specific for tumor-associated antigens such as CD20, deliver a 10-fold or greater radiation dose to the tumor than to the whole body.¹³ The radiolabeled anti-CD20 antibodies, Y-90 ibritumomab tiuxetan (Zevalin®, Biogen Idec, Inc., Cambridge, MA, USA) and I-131 tositumomab (Bexxar®; Corixa, Seattle, WA, USA; and Glaxo Smith Kline; Philadelphia, PA, USA) both deliver ionizing irradiation to target cells and their immediate neighbors, at higher doses than would be tolerated if administered as TBI.^{14,15} Initially tested as single agents in relapsed patients with indolent and transformed NHL, and then at much higher doses with stem cell support, these agents are now being investigated in combination with high-dose chemotherapy prior to auto-SCT. The data thus far are probably best described as *adolescent*, with all studies at this point being phase I or phase II trials. The various regimens appear to be effective at eliciting responses and do not appear to cause more toxicity than standard conditioning regimens do. This paper will review the current literature investigating radioimmunotherapy with anti-CD20 reagents in the setting of autologous stem cell transplantation for NHL.

A review of radioimmunotherapy

Monoclonal antibodies destroy target lymphoma cells through a combination of antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and the induction of apoptosis. Radioimmunotherapeutics that target CD20, CD22, CD37, HLA markers, ferritin, and T-cell antigens have all been studied.¹⁶⁻²³ The addition of a radioactive component (such as yttrium-90 or iodine-131) allows for the emission of radioactive particles that exert a cross-fire effect that treats nearby cells whether or not they are antigen positive.^{24,25} Continuous low dose-rate irradiation is delivered directly to the tumor cell, with relative sparing of surrounding normal organs. There is the potential for dose delivery to be heterogeneous based on tumor bulk and variations in antigen density that may not be overcome by the cross-fire effect mentioned above. Furthermore, the sensitivity of various histologic subsets of CD20⁺ NHL to radioimmunotherapy has been shown to differ although the biological basis for this is not entirely clear. For example, in the pivotal Y-90 ibritumomab tiuxetan vs. rituximab study, patients with follicular lymphomas had better outcomes than patients with other histologies.²⁶ Recent phase I/II data suggest that separate histotypes of NHL may indeed respond differently to radioimmunotherapy followed by auto-SCT. Investigators at the City of Hope showed differences in overall and disease-free survival following radioimmunotherapy and high dose chemotherapy according to histologic subtype. Early grade follicular lymphoma responded better than diffuse large B-cell lymphoma which responded better than mantle cell lymphoma.²⁷

Primarily a gamma emitter, the radioactive component of Bexxar[®] (I-131 tositumomab), I-131, also emits beta radiation, facilitating both treatment and imaging. Although it allows for direct imaging of gamma radiation by a gamma camera it also poses a risk to both healthcare workers and family members. Precautions must be taken to protect the patients' contacts from radiation exposure. Beta emissions pose minimal risk to others and have a longer therapeutic range *in vivo*. An example of a pure beta-emitting radioisotope is yttrium-90, the radioisotope used in Zevalin[®] (Y-90 ibritumomab tiuxetan). Table 1 illustrates some of the different physical properties of the therapeutic β emissions of yttrium-90 and iodine-131.²⁸ Depending on the bulk of the tumor and the neighboring normal tissues, a longer path length may or may not be an advantage. However, unlike gamma emissions, beta emissions cannot be imaged directly. For beta-emitters such as Y-90 ibritumomab tiuxetan, indium-111-labeled antibody with its gamma emissions has been shown to be an effective surrogate which can be used for dosimetry.^{29,30} Both the In-111 and Y-90 radioisotopes are tightly bound to the anti-CD20 monoclonal antibody via the chelator tiuxetan.

The biodistribution of the radioimmunoconjugate can be evaluated using dosimetry, and doses may be tailored to patients individually, based on that patient's

Table 1. Physical properties of I-131 and Y-90.

	I-131	Y-90
β Emission	0.81 MeV	2.3 MeV
Path Length	0.8 mm	5 mm
Half-Life	8.0 days	2.7 days

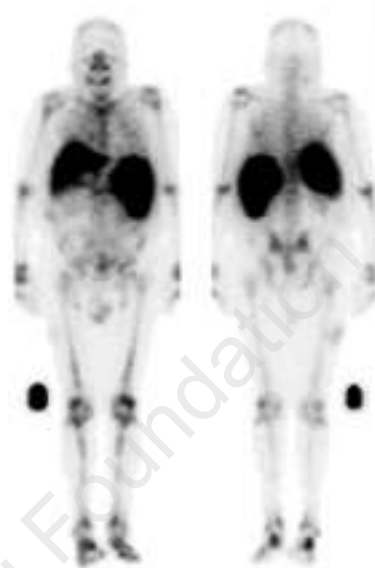


Figure 1. Dosimetry scan (anterior and posterior views) 72 hours after infusion of indium-111 ibritumomab tiuxetan in a patient with mantle cell lymphoma and extensive splenic involvement.

body size, mass, and tumor burden. For I-131-tositumomab, an antibody dose anticipated to deliver the desired total body radiation dose of 0.75 Gy can be calculated. For Y-90 ibritumomab tiuxetan, only one whole body gamma scan, performed 48-72 hours after the imaging dose of In-111 ibritumomab tiuxetan, is now required in the USA to exclude altered biodistribution (Figure 1). In phase I/II trials utilizing the In-111 conjugated antibody for imaging, neither pharmacokinetic parameters nor radiation dose to the red marrow were predictive of hematologic toxicity at non-myeloablative doses.³¹ Similarly, in an analysis of 72 patients treated in a phase III trial comparing rituximab and Y-90 ibritumomab tiuxetan, the depth of the hematologic nadir did not correlate with dosimetric or pharmacokinetic measures, suggesting that marrow suppression, the dose-limiting toxicity, is more likely to be dependent on stem cell reserve.³² Y-90 ibritumomab tiuxetan is now dosed according to the patient's body weight when administered as a single agent for standard therapy. In the context of research protocols involving dose-escalation, however, the antibody distribution and clearance of Y-90-ibritumomab tiuxetan can be calculated and used to determine the probable radiation exposure to secondary organs such as the lungs, liver, and kidneys.³³ When the targeted antigen is not entirely specific to the malignant lymphoma cell but may be present on normal B-lymphocytes as well, a dose of unlabeled antibody is administered prior to the therapeutic dose to saturate potential binding sites on circulating non-malignant cells and thereby improve

Table 2. Administration of radioimmunotherapy.

Treatment Day	I-131 tositumomab	Y-90 ibritumomab tiuxetan
Day 0 Dosimetric dose	Unlabeled Anti-B1 antibody (450mg) is given followed by 5-10 mCi I-131 tositumomab	Rituximab (250 mg/m ²) is given followed by 5 mCi indium-111 ibritumomab tiuxetan
Day 0-7 Imaging for biodistribution	γ emissions imaged and dosimetry performed	
Day 7-14 Therapeutic dose	Unlabeled Anti B1 antibody (450mg) is given followed by the calculated I-131 tositumomab dose to deliver 75cGy (35mg) sometime between day 7 and 14	Rituximab (250 mg/m ²) is given followed by the calculated dose of Y-90 ibritumomab tiuxetan on day 7

targeting. Table 2 illustrates and compares administration of both I-131 tositumomab and Y-90 ibritumomab tiuxetan. The correct timing of re-infusion of stem cells after conditioning with radioimmunotherapy remains to be determined. Some investigators have measured residual radioactivity from serial bone marrow biopsy aspirates to predict when it will be safe to re-infuse stem cells while others have relied on the expected half-life of the radioimmunoconjugate.^{27,33}

Studies using I-131 tositumomab (Bexxar®)

Pioneering studies investigating the use of I-131-labeled antibodies prior to autologous stem cell transplant were performed at the Fred Hutchinson Cancer Research Center in Seattle, Washington. In 1993, Press *et al.* conducted a phase I trial to examine the tolerance and response to increasing doses of I-131-labeled anti CD20 (B1, 1F5) and anti-CD37 (MB-1) antibodies followed by autologous stem cell transplant.³⁴ Biodistribution studies were first performed with escalating doses of antibody trace-labeled with 5 to 10 mCi of I-131. The absorption of radiation by the tumor and normal organs was estimated by quantitative gamma camera imaging and by sampling the marrow and tumor. If these studies predicted that all tumor sites would receive higher doses of radiation than critical organs (liver, lungs, or kidneys) then a single therapeutic infusion of I-131-labeled antibody was prescribed according to a phase I dose-escalation scheme (10 to 30.75 Gy). Therapy using I-131-labeled B1 was limited to doses less than 27.25 Gy to the lung because of cardiopulmonary complications seen in two patients at the 27.25 Gy dose level. A purged autograft was infused if patients became neutropenic (absolute neutrophil count <200 /μL) for two successive days and the total body activity had fallen to a level not expected to injure hematopoietic stem cells. In this study, 16 of 19 patients with refractory or relapsed NHL had complete remissions. The median duration of response was 11 months for patients receiving the B1 anti-CD20 I-131 labeled antibody and 7 months for pooled patients (i.e. all study patients who received a monoclonal anti-

body). The overall median survival exceeded 21 months. Of note, patients with smaller tumor masses (or without splenomegaly) responded better to treatment. The anti-CD20 antibody, B1, was superior to MB-1 as a delivery molecule because it caused less toxicity and had better biodistribution with smaller doses. Substantial patient-to-patient variability in biodistribution, metabolism and circulating half-life of the radioimmunoconjugate confirmed the need for individualized dosing based on each patient's dosimetry. In this ground-breaking study, Press and colleagues demonstrated that radioimmunotherapy with an anti-CD20 reagent is not only feasible and safe, but highly effective.

These encouraging results led to a phase I/II trial investigating I-131-labeled anti-CD20 antibodies (B1) as a single agent at myeloablative doses prior to auto-SCT in patients with B-cell NHL.³⁵ Trace-labeled I-131 B1 antibodies were administered at a dose of 2.5 mg/kg. Serial quantitative gamma camera imaging was used to estimate the total absorbed radiation dose to the tumor, specific organs, and the whole body. Patients with favorable biodistributions (tumor sites had greater radiation than liver, lung, or kidney) were given a single therapeutic infusion of 2.5 mg/kg of I-131-B1 calculated to deliver 25-31 Gy of irradiation to the normal organ receiving the greatest dose of radiation. A purged marrow or peripheral blood autograft was infused when the patient became neutropenic and the residual radioactivity was low enough not to injure stem cells. The maximum tolerated dose to critical normal organs in this study was confirmed to be 27 Gy. Eighteen of 21 patients with relapsed B-cell lymphoma (the majority had follicular lymphoma) achieved objective responses, 16 of which were complete remissions. At a 2-year follow-up, progression-free survival was 62% and overall survival was 93%. These results were comparable to those achieved with other autologous stem cell transplant regimens and found to be superior to those in historical controls receiving conventional chemotherapy. The non-hematologic toxicities were reported to be modest and included abnormal thyroid stimulating hormone (TSH) levels in 20% of patients.

Long-term follow-up data from the two previously mentioned studies were reviewed by Liu in 1998.³⁶ All patients had refractory or relapsed follicular lymphoma that had failed to respond to previous conventional chemotherapy. The major tumor response rate was 86%; 79% of patients achieved complete remissions and 7% had partial remissions. At a median follow-up of 42 months, 22/29 (76%) patients were alive and 14 (48%) still had not progressed. Estimates of overall survival and progression-free survival based on Kaplan-Meier curves at 4 years were 68% and 42%, respectively. Of note, 18 patients experienced equivalent or longer time to treatment failure following myeloablative I-131-anti-CD20 antibody therapy than after any of their prior treatment regimens. Patients with indolent lymphoma, in particular, appeared to benefit most from this approach. The therapy was very well tolerated, with reversible cardiopulmonary toxicity being

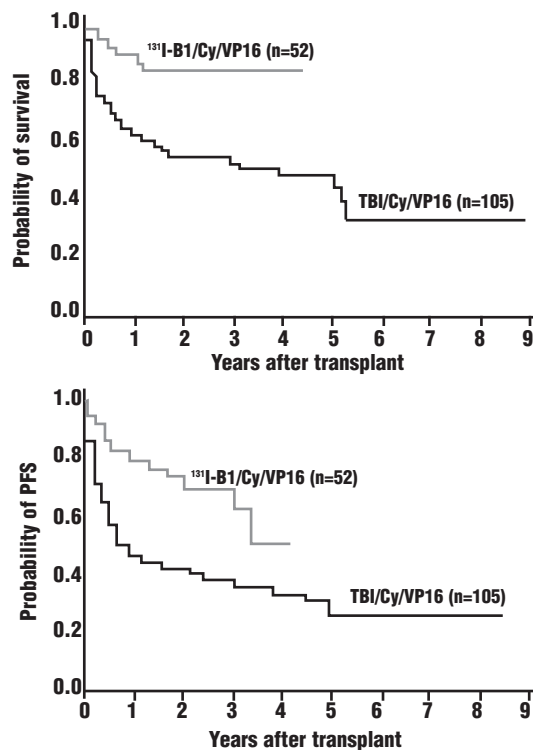


Figure 2. Overall survival and progression-free survival in patients with relapsed B-cell lymphomas with two treatments. Fifty-two patients were treated with I-131 tositumomab, etoposide, cyclophosphamide, and autologous stem-cell transplant (autoSCT) (thin line), and 105 patients treated with external-beam total-body irradiation (1.5 Gy twice a day for 4 days), etoposide (60 mg/kg), cyclophosphamide (100 mg/kg), and autoSCT (thick line). Figure reproduced from ref. 37. Copyright American Society of Hematology, used with permission.

dose-limiting. The most common late toxicity noted was an elevated TSH found in 60% of the patients. Two of the patients developed secondary malignancies but no patients developed a myelodysplastic syndrome.

Although results with dose-escalated I-131-B1 and Auto-SCT were encouraging, half the patients relapsed within 5 years. Whereas most curative strategies for lymphoma require more than a single agent, the combination of I-131-tositumomab and high-dose chemotherapy followed by auto-SCT was investigated by Press and colleagues.³⁷ The investigators hoped to deliver higher radiation doses to CD20 positive lymphoma cells than possible with TBI with less toxicity. A phase I/II trial combining I-131-B1 (now called I-131 tositumomab) at myeloablative doses with high dose etoposide (60 mg/kg) and cyclophosphamide (100 mg/kg) accrued 52 patients with relapsed B-cell NHL (Figure 2). Antibody biodistribution studies were performed in the same manner as in their previous trials. The estimated maximum tolerated dose was determined to be 25 Gy. Overall survival at 2 years was 83% and progression-free survival was 68%. Toxicities were no different in presentation or frequency from those

reported for patients receiving TBI, cyclophosphamide and etoposide. The most serious complication, opportunistic infections, resulted in four treatment-related deaths. Patients in this study were compared to a non-randomized control group of patients who had received a conventional regimen of TBI (1.5 Gy twice a day for 4 days) and high dose etoposide (60 mg/kg) and cyclophosphamide (100 mg/kg). Although susceptible to selection bias (the groups were not randomized and the patients' characteristics differed in terms of stage, extent of prior therapy, histologic subtypes and tumor bulk), outcomes for the radioimmunotherapy group were better. When analyzed according to histologic subgroup (aggressive vs. indolent), the radioimmunotherapy-containing regimen again provided a benefit. In a multivariate analysis designed to compensate for differences in the patients' characteristics between the two groups, the I-131-tositumomab-treated group still had superior outcomes (overall survival and progression-free survival) compared to those in patients who received the TBI-containing program. This was not the main objective of the study but the comparisons are provocative and perhaps foreshadow the results of future phase III trials.

Mantle cell lymphoma is characteristically resistant to standard treatment and relapses occur frequently despite high dose therapy followed by autologous or allogeneic stem cell transplant.³⁸ The Seattle group also investigated their combined modality strategy consisting of I-131 tositumomab, high-dose etoposide (30-60 mg/kg) and high-dose cyclophosphamide (60-100 mg/kg) in poor-risk, relapsed or chemotherapy refractory mantle cell lymphoma patients.³⁹ Two patients each received 20 Gy and 23 Gy, and the rest received 25 Gy to the dose-limiting critical normal organ based on standard biodistribution assessments. The toxicity profile was similar to that of standard autologous transplant conditioning regimens. Response rates were high, with all patients responding and 91% achieving a complete remission. The estimated 3-year overall and progression-free survivals at 3 years from transplantation were 93% and 61%, respectively. At the time of publication, 15 out of 16 patients remained alive and 12 had had no progression of lymphoma by 6 to 57 months post treatment and 16 to 97 months post-diagnosis.

The high-doses of I-131 tositumomab used in the above-mentioned trials preclude out-patient treatment. With the goal of combining standard outpatient dosing of I-131 tositumomab with high-dose BEAM chemotherapy and auto-SCT, Vose and associates at the University of Nebraska conducted a phase I trial in which they escalated the radioimmunoconjugate up to the standard 75 cGy total body dose.⁴⁰ Twenty-three patients with relapsed or refractory lymphoma received increasing total body doses of I-131 (0.30 to 0.75 Gy). The authors noted no significant toxicities with the higher dose of I-131 compared to those in other patients receiving high-dose BEAM chemotherapy alone. The investigators reported event-free and overall survivals of 39% and 55%, respectively, at a median follow-up of 38 months. A phase II trial com-

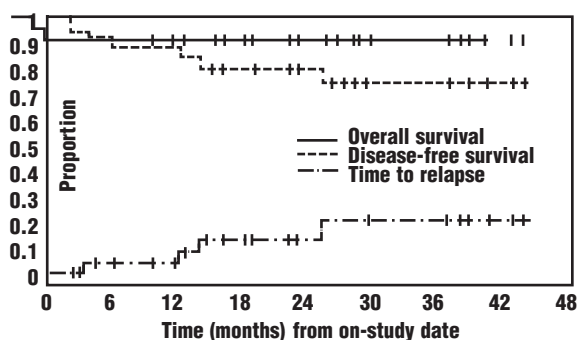


Figure 3. Twenty-four of 31 patients treated with high-dose Y-90 ibritumomab tiuxetan in combination with high-dose etoposide and cyclophosphamide followed by autoSCT are alive in remission at a median follow-up of 22 months (range, 2 - 44). The Kaplan-Meier estimated 2-year relapse-free and overall survivals are 78% (95% confidence interval [CI], 61%-96%) and 92% (95%[CI], 82%-100%), respectively.

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bining I-131 tositumomab at the 75 cGy total body dose with high-dose BEAM and autoSCT is ongoing.

Although no phase III data directly comparing radioimmunotherapy with conventional autoSCT are yet available, Gopal and colleagues compared outcomes of 27 patients with follicular lymphoma enrolled in phase I and II trials of I-131-tositumomab with outcomes of 98 historical controls.⁴¹ The patients treated with high dose radioimmunotherapy received 17 to 31 Gy to normal critical organs, while those treated with conventional high-dose therapy received either total body irradiation plus chemotherapy or chemotherapy alone. After adjusting for variables that either were associated with outcome or influenced the association of treatment with outcome in a multivariate analysis, patients receiving radioimmunotherapy had a significant reduction in risk of dying (HR=0.3, $p=0.04$) and disease progression or death (HR=0.5, $p=0.03$) compared to the control group. The estimated overall and progression-free survivals for patients receiving radioimmunotherapy compared to conventional autoSCT were 67% vs. 53% and 48% vs. 29%, respectively. Treatment-related mortality was lower with high-dose radioimmunotherapy than with conventional autoSCT (3.7% vs. 11%). Hematologic toxicities, including cytopenias and frequency of neutropenic fever, were similar in both groups. The likelihood of developing myelodysplastic syndrome or acute myeloid leukemia at 8 years was slightly lower in the high dose-radioimmunotherapy group (0.76 vs. 0.86 for the high-dose chemotherapy group). Although these results must be interpreted with caution, they are encouraging. Phase III trials will be required to confirm the superiority of high-dose radioimmunotherapy over conventional autoSCT.

Studies using yttrium-90 ibritumomab tiuxetan (Zevalin®)

Initial studies investigating dose-escalated Y-90 ibri-

tumomab tiuxetan in the transplant setting combined increasing doses of radioimmunotherapy with either BEAM or etoposide and cyclophosphamide.^{33,42} In a phase I study design reported by Winter *et al.* which is similar to that used by Press and colleagues, the radioimmunotherapy dose within each cohort is individualized based on dosimetry to provide a cohort-defined radiation dose to critical organs (10-13 Gy). Toxicity has been similar to that seen with BEAM and autoSCT. Patient-specific doses calculated to deliver a cohort-defined absorbed radiation dose to critical organs have been variable, suggesting that dosing based on weight and not dosimetry is likely to result in a wide range of absorbed dose to critical organs. Twelve patients have safely received doses of 0.5 mCi/kg or greater combined with high-dose BEAM. Accrual continues at the 15 Gy dose level.

Nademanee from the City of Hope recently published data from a phase I/II trial combining high dose Y-90 ibritumomab tiuxetan with high dose etoposide (40-60 mg/kg) and cyclophosphamide (100 mg/kg).²⁷ Patients were given escalating doses of radiation based on dosimetry during phase I. The maximum tolerated radiation dose to normal critical organs was estimated to be 10 Gy. During the phase II part, 31 patients with follicular, diffuse large B-cell, and mantle cell lymphomas, including seven in first complete or partial remission, were treated with a target dose of 10 Gy of Y-90 ibritumomab tiuxetan (37-105 mCi). At a median follow up of 22 months, the 2-year estimated overall survival was 92% and the disease-free survival was 78% (Figure 3). One patient failed to engraft, but otherwise toxicities were similar to those associated with standard transplant regimens. These results are also comparable to data presented by Press *et al.* using I-131 tositumomab with the same doses of etoposide and cyclophosphamide.³⁷ Interestingly though, the total radiation dose delivered to patients in Nademanee's trial was 1000 cGy whereas it was 2500 cGy in Press's study. Figure 3 presents illustrative survival curve.

Since individualized dosing based on dosimetry requires experienced nuclear medicine physicians and a significant time commitment, weight-based dosing at the standard non-transplant dose of 0.4 mCi/kg combined with high-dose BEAM has been investigated. Fung *et al.*, also from the City of Hope, combined high-dose BEAM chemotherapy with a standard dose of 0.4 mCi/kg of y-90 ibritumomab tiuxetan prior to autoSCT.⁴² All 12 patients (median age of 61 years) had poor-risk aggressive B-cell lymphoma. Therapy was well tolerated with only 2 of the 12 patients reporting grade III/IV gastrointestinal toxicity. At 9 months, 11 out of 12 patients were without clinical evidence of lymphoma. The median dose of yttrium-90 ibritumomab tiuxetan was 32 mCi. Patients were scanned after a tracer dose of Indium 111 ibritumomab tiuxetan, to make sure those with poor biodistribution were not allowed to continue and be placed at increased risk of toxicity.

To determine the non-hematologic maximum tolerated dose of y-90 ibritumomab tiuxetan, Flinn *et al.*

Table 3. Summary of study results.

Study	RIT (+/- Chemotherapy) prior to autoHSCT	Dose of RIT	Overall survival	Progression-free survival
Liu, 1998	I-131	0.35, 1.7, 7 mg/kg (280-785 mCi)	68% at 4 years	42% at 4 years
Press, 2000	I-131 and etoposide/cyclophosphamide	25 Gy	83% at 2 years	68% at 2 years
Gopal, 2002	I-131 and etoposide/cyclophosphamide	20-25 Gy	93% at 3 years	61% at 3 years
Fung, 2003	Y-90 and BEAM*	0.4 mCi/kg	11/12 of patients without progression at 9 months	
Winter, 2004	Y-90 and BEAM*	10-13 Gy	60% at 3 years	47% at 3 years
Nademanee, 2005	Y-90 and etoposide/cyclophosphamide	10 Gy	92% at 2 years	78% at 2 years
Flinn, 2004	Y-90	14-24 Gy	Too early to tell	
Vose, 2005	I-131 and BEAM	0.3-0.75 Gy (Total body dose)	55% at 38 months	39% at 38 months

*BEAM: BCNU, etoposide, cytarabine, melphalan.

have dose-escalated the radioimmunoconjugate with stem cell support.⁴⁵ Thus far, five patients have received 14-18 Gy to the liver, while three patients have received 24 Gy (20-122 mCi). No hepatotoxicity has been observed. The major toxicity has been hematologic, although the two patients evaluated at the 24 Gy dose level engrafted promptly. The results with single agent radioimmunotherapy and autoSCT are encouraging with high response rates, although the number of patients is small and the follow-up is short.

Conclusions

Future research in radioimmunotherapy in the transplant setting will likely focus on efforts to improve the activity of radioimmunoconjugates. New radio-antibody structures are being evaluated, such as I-131 rituximab which is based on a chimeric anti-CD20 antibody rather than the murine antibody used in I-131-tositumomab.⁴⁴ Other antibodies that have been radio-labeled and studied in the clinical setting include epratuzumab (humanized anti-CD22 IgG; Immunomedics, Inc.) and Oncolym (anti-HLA-DR10; Peregrine Pharmaceuticals, Inc.).^{46,47} Preliminary studies dose-escalating I-131-labeled epratuzumab have demonstrated a 33% response rate in heavily pretreated NHL patients. Alternative radioisotopes such as alpha-emitters which have emission path lengths that span only several cell diameters are under investigation. It is thought that their more precise almost unicellular delivery of radiation may be ideal for micrometastatic disease or infiltrated bone marrow to reduce collateral toxicity to hematopoietic stem cells,

and in the case of stem cell transplant, marrow stroma. Lastly, the new frontier in radioimmunotherapy technology is the use of pre-targeting to overcome the limitations of slow blood clearance of the radiolabeled antibody. This strategy separates *targeting* by the antibody from the subsequent delivery of the radionuclide.⁴⁷ Bi-specific monoclonal antibodies have been created that attach to the target cell and to a metal chelator which can be administered subsequently after the bi-specific antibody has cleared from the blood to deliver a radioactive particle. The benefit is that less radiation is retained in the bloodstream because the slow clearance of radiolabeled IgG is avoided and thus less treatment-related toxicity results.⁴⁷

Autologous stem cell transplantation has an important therapeutic role in patients diagnosed with aggressive or refractory NHL. With improved supportive care, relapse has emerged as the primary cause of treatment failure. Pre-transplant conditioning regimens composed of a combination of total body irradiation and high-dose chemotherapy may be the most efficacious, but also the most toxic. Radioimmunoconjugates, such as I-131 tositumomab and Y-90 ibritumomab tiuxetan, have engendered considerable interest in the transplant community because of their capacity to deliver higher doses of radiation to the tumor site than to normal tissues, without increasing treatment-related toxicity. In all the above-mentioned studies (Table 3), the investigators reported that treatment-related toxicity was no different from that associated with conventional high-dose chemotherapy. These results are notable in light of the fact that the dose of radiation delivered to the tumor is 10-fold higher than that possible with TBI.¹³ The possibility of an increase in the incidence of secondary acute myeloid leukemia (AML) and myelodysplasia (MDS) associated with radioimmunotherapy and autoSCT must be considered, especially in patients who have been heavily pretreated with chemotherapy. Bennett *et al.* reported data from over 1,000 patients treated with I-131-tositumomab showing that the incidence of secondary AML and MDS was no different than that expected for patients heavily pretreated with other chemotherapy for NHL.⁴⁸ Furthermore, none of the 76 previously untreated patients treated with Bexxar® (I-131 tositumomab) alone have developed AML or MDS to date (5 years). The risk of secondary leukemia and myelodysplasia may be as high as 10-15% following conventional autoSCT for NHL, and the addition of radioimmunotherapy has the potential to further increase the risk, so this issue will need to be monitored closely.^{49,50} Clinicians and researchers enthusiastically await phase III studies comparing standard regimens and radioimmunotherapy in a randomized head-to-head comparison. A multicenter trial comparing rituximab/ BEAM and Bexxar® (I-131 tositumomab)/ BEAM prior to autoSCT in patients with persistent or recurrent diffuse large B-cell lymphoma is in development.

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