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REVIEW

Update on the rational use of tositumomab and iodine-131 tositumomab radioimmunotherapy for the treatment of non-Hodgkin's lymphoma

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Abstract: Targeted radioimmunotherapy in non-Hodgkin's B-cell lymphoma (NHL) offers an efficacious therapy and minimal toxicity compared to conventional chemotherapy. Iodine 131 tositumomab (^{131}I-TST) is a murine monoclonal antibody against the CD20 cell surface protein and is directly covalently conjugated to ^{131}I, a radioactive β and γ emitter. While initially approved for use in relapsed, refractory, or transformed low grade B-cell NHL, investigational uses with promising results include autologous stem cell transplant, intermediate grade NHL, and the frontline management of indolent NHL. This review summarizes the ^{131}I-TST literature on mechanism of action, treatment indications, treatment delivery, efficacy, investigational uses, and future prospects.

Keywords: tositumomab, radioimmunotherapy, non-Hodgkin's lymphoma, Bexxar

Introduction

Non-Hodgkin's lymphoma (NHL) is a common malignancy in the United States in with an estimated 66,000 cases in 2008.[1] Low-grade B-cell NHL is an indolent disease with a long natural history and median survival of 7 to 10 years. As disease relapses, therapeutic options become more toxic and less effective[2] and disease occasionally will transform into higher grade cases of lymphoma.[3] Targeted radioimmunotherapy (RIT) has proven to be an effective weapon against low-grade NHL. Iodine 131 tositumomab (^{131}I-TST) (Bexxar®; GlaxoSmithKline, Brentford, London, UK) was approved by the Food Drug Administration in 2003 for use in relapsed, refractory, or transformed low-grade NHL. This review will discuss the literature pertaining to its use in NHL.

Mechanism of action

The target for TST is CD20, a nonglycosylated 33 to 37 kDa phosphoprotein involved with B-cell proliferation and differentiation. CD20 is expressed on the cell surface of over 90% of normal and malignant B cells. CD20 has four transmembrane domains and appears to function as both a calcium channel and signal transducer.[4] CD20 does not internalize and remains on the cell surface after anti-CD20 antibody binding making CD20 an attractive target for immunotherapy.[5]

Two of the most notable anti-CD20 antibodies in clinical use are rituximab (RTX) and TST. RTX is a chimeric IgG$_1$ antibody directed against CD20 with human κ and γ1 constant domains and a variable domain derived from a mouse monoclonal parent antibody, ibritumomab.[6] TST, formerly known as B1, is a mouse IgG$_{2a}$ monoclonal

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antibody against CD20.[7] Anti-CD20 antibodies appear to kill lymphoma cells through a variety of mechanisms. These include induction of apoptosis through direct signal transduction, complement-mediated cytotoxicity (CDC), and antibody-mediated cellular cytotoxicity (ADCC).[4]

The relative contribution of these different mechanisms to cell kill varies depending on the nature of the antibody. Independent of IgG isotype, two distinct classes of anti-CD20 antibodies exist; type I antibodies that redistribute CD20 into Triton X-100 insoluble lipid rafts, such as RTX, and type II antibodies that do not, such as TST. Type II antibodies mediate homotypic adhesion more than type I antibodies which correlates with their greater ability to induce apoptosis.[8] Redistribution of CD20 into lipid rafts coincides with the cross-linking of CD20, while cross-linking of anti-CD20 antibodies results in the activation of complement.[5] TST does not activate complement.[9] In vitro, apoptosis induction appears to require the cross-linking of CD20 by anti-CD20 antibodies through either antibody-antibody interactions or interaction with Fc receptor bearing cells.[4] In vitro and in vivo data suggest that TST appears to induce apoptosis through additional mechanisms independent of the FC region.[9] Furthermore, TST-induced apoptosis does not involve classic DNA fragmentation, caspase processing, or association with lipid rafts.[7,8,10] Transgenic mice models comparing type I and type II anti-CD20 antibodies found that type II antibodies were superior in duration of B-cell depletion.[7] A summary of the differences between type I and type II antibodies are shown in Table 1. In ADCC, leukocytes bearing the Fc receptor play an integral role. Correlation of clinical outcomes with genetic profiles have shown that patients with follicular lymphoma with a high binding affinity FcγRIIIa polymorphism have a 90% response rate (RR) to RTX at 12 months compared to a RR of 51% for those with a low binding affinity FcγRIIIa polymorphism.[6] Given the current laboratory and clinical evidence, the mechanism of action for anti-CD20 antibodies depends on both individual genetic factors along with cooperation of an intact immune system.

The addition of low-dose-rate radiation to anti-CD20 antibodies improves response in vitro. Increased cell death occurred to a greater extent with the combination of TST and low-dose rate external beam radiation therapy (EBRT) at 0.3 Gy/hour compared to the combination of TST and high-dose-rate EBRT at 2.5 Gy/hour.[10] In vitro, TST combined with EBRT induces a BCL-2 independent method of nonapoptotic cell death. The mechanism by which the additional death from TST occurred is through the mitogen-activated protein kinase/extracellular

signal-regulated kinase (MAPK/ERK1/2) pathway.[10] In clinical use, the low dose rate radiation combined with TST is provided by radioactive ^{131}I.

Isotopes

When TST is directly covalently conjugated to ^{131}I, ^{131}I-TST is better known by its trade name, Bexxar®. ^{131}I is both a β and γ emitter. The β-particle has a mean energy of 191.6 keV, a maximum energy of 0.61 mEv, and a range in tissue of 0.8 mm. The principle γ-ray has an energy of 364.5 KeV. The physical half-life of ^{131}I is 8.1 days.[11, 12] The gamma emission allows Bexxar® to be visualized by a gamma camera and is integral to individual patient dosimetry required for the determination of the proper amount of drug to be administered to achieve the total body dose prescribed.

Antibody alone versus immune targeted radiopharmaceutical

With such impressive preclinical data for some monoclonal antibodies, one wonders about the effectiveness of TST without ^{131}I labeling. A randomized study answering such a question has been reported. Seventy-eight RTX naïve patients with refractory or relapsed low grade NHL were randomized between TST and ^{131}I-TST. Several important measures of response favored ^{131}I-TST: overall response (OR) of 55% vs 19% ($P = 0.002$), complete response (CR) of 33% vs 8% ($P = 0.012$), and median time to progression (TTP) of 6.3 months vs 5.5 months ($P = 0.031$). In the TST arm, 3 patients achieved CR with 2 patients remaining in remission at 48.1 and 56.9 months. Nineteen patients in the TST group who either failed to respond or progressed after TST served as their own controls. Of these 19, 3 were partial responders and 16 never responded to TST. After ^{131}I-TST, 68% (13/19) of these TST failures had a response, with

Table 1 Characteristics of type I and type II anti-CD20 antibodies as determined by preclinical experiments

	Type I antibodies	Type II antibodies
Examples	Rituximab	Tositumomab
Redistribute CD20 into Triton X-100 insoluble lipid rafts	+	−
Homotypic adhesion	+	+++
Induction of apoptosis	+	+++
Complement-dependent cytotoxicity	+	−
B-cell depletion in transgenic mice models	+	+++

42% (8/19) achieving CR. Thus ^{131}I conjugation certainly improves the efficacy of TST, although some patients appear to show impressive responses from the nonradiolabeled antibody.[13]

Rituximab versus tositumomab

Although no head-to head comparisons in randomized trials exist or are likely to be performed in the near future, treatment with RTX of a similar group of patients has yielded similar results to TST. In relapsed low grade NHL, the German Low-Grade Lymphoma Study Group found that RTX yielded an OR of 47%, CR of 17%, and median TTP of 201 days.[14] Similarly, a phase II multi-institutional study of 37 patients with relapsed low-grade NHL treated with RTX yielded an OR of 46% with a median TTP of 10.2 months.[15] A phase III multi-institutional study of 166 patients with relapsed indolent lymphoma treated with 4-weekly doses of RTX gave an OR of 48% and median TTP of 13.0 months.[16] Toxicity from this regimen is predominately acute, with the main side effect being infusional reactions including fevers and chills. Around 20% of patients have hematological abnormalities, mainly thrombocytopenia or leukopenia with very few grade III or IV toxicities.[14,15] These response rates and median TTP for RTX in relapsed low-grade NHL are similar to those of the TST arm reported in the randomized trial comparing TST to ^{131}I-TST discussed above.[13] Radiolabeling of RTX with ^{131}I has also been reported.[17,18] A phase II study of 91 patients yielded an OR of 76% and a CR/complete response unconfirmed (CRu) of 53%. Median duration of response (MDR) for all responders was 10 months, 20 months for patients with CR/CRu, and 7 months for patients with partial response (PR). Hematologic toxicity was less than ^{131}I-TST: 4% with grade IV thrombocytopenia and 16% with grade IV neutropenia. Five patients developed myelodysplastic syndrome (MDS) and 9% developed elevated thyroid-stimulating hormone (TSH) levels. These results and toxicities are comparable to those of ^{131}I-TST in relapsed or refractory NHL as will be discussed later. The estimated cost of in-house iodination was US$1000 above the cost of RTX. Despite laboratory data suggesting superior efficacy of TST over RTX, the clinical response rates and clinical outcomes of patients treated with TST are similar to those of RTX.

Clinical indications and contraindications

^{131}I-TST is FDA approved for the treatment of relapsed or refractory low grade CD20+ B-cell NHL, including disease refractory to RTX, or transformed NHL. Contraindications to treatment include iodine allergy, pregnancy, platelet count <100,000/mL, absolute neutrophil count <1500/mL, Karnofsky performance status < 60, pregnancy, inadequate renal or hepatic function, lymphomatous bone marrow involvement of greater than 25%, or major seropositivity for human anti-mouse antibodies (HAMA). Some studies excluded patients who had disease that progressed in field within a year after 35 Gy EBRT.[13,19,20] Treatment with dose attenuated ^{131}I-TST in patients with greater than 25% bone marrow involvement has been reported and remains investigational.[21]

Dosing and treatment delivery

Due to wide variations in bioclearance of ^{131}I-TST, dosing is individualized for each patient. Although the physical half-life of ^{131}I is approximately 8 days, the median total body effective half-life of ^{131}I-TST in 980 patients as determined by gamma camera counts was 67 hours and ranged between 28 and 115 hours.[11] Total body clearance defined as mean half-life determined by sodium iodide probe or gamma camera are similar.[19] The initial step in therapy involves determining individual patient bioclearance. First, the patient is injected intravenously with a dose of 450 mg TST over 1 hour. This cold (nonradioactive) antibody is thought to saturate both nonspecific binding sites and CD20 binding sites on normal B cells, especially in B cell reservoirs such as the spleen, and thus improve tumor localization of the hot (radioactive) antibody.[22] Next, a dosimetric dose of ^{131}I-TST with 5 mCi ^{131}I conjugated to 35 mg TST is infused over 20 minutes. Three serial gamma camera scans on day 0, days 2 to 4, and days 6 to 7 provide information on whole body clearance and biodistribution. Because both ^{131}I and TST are cleared by the kidneys, these scans must be examined to ensure that abnormal ^{131}I pooling does not happen. Abnormal kidney or lung uptake would be reasons to abort proceeding to the therapeutic dose although this is an extremely rare occurrence. Despite the intuitive appeal of using RIT imaging to determine absorbed dose and the potential for clinical response, human studies have shown extremely poor correlation of imaging intensity and ultimate clinical response.[23] From the serial gamma scans, individual patient clearance can be used to calculate the activity of ^{131}I-TST needed for a therapeutic dose. A figure demonstrating the principle of the "area under the curve" dosimetric analysis and the theoretical reasons for differences in patient bioclearance is depicted in Figure 1. Standard dosing is 75 cGy total body irradiation[24] with dose reductions to 65 cGy for platelet counts between 100,000/mL and 150,000/mL[19] and dose reductions
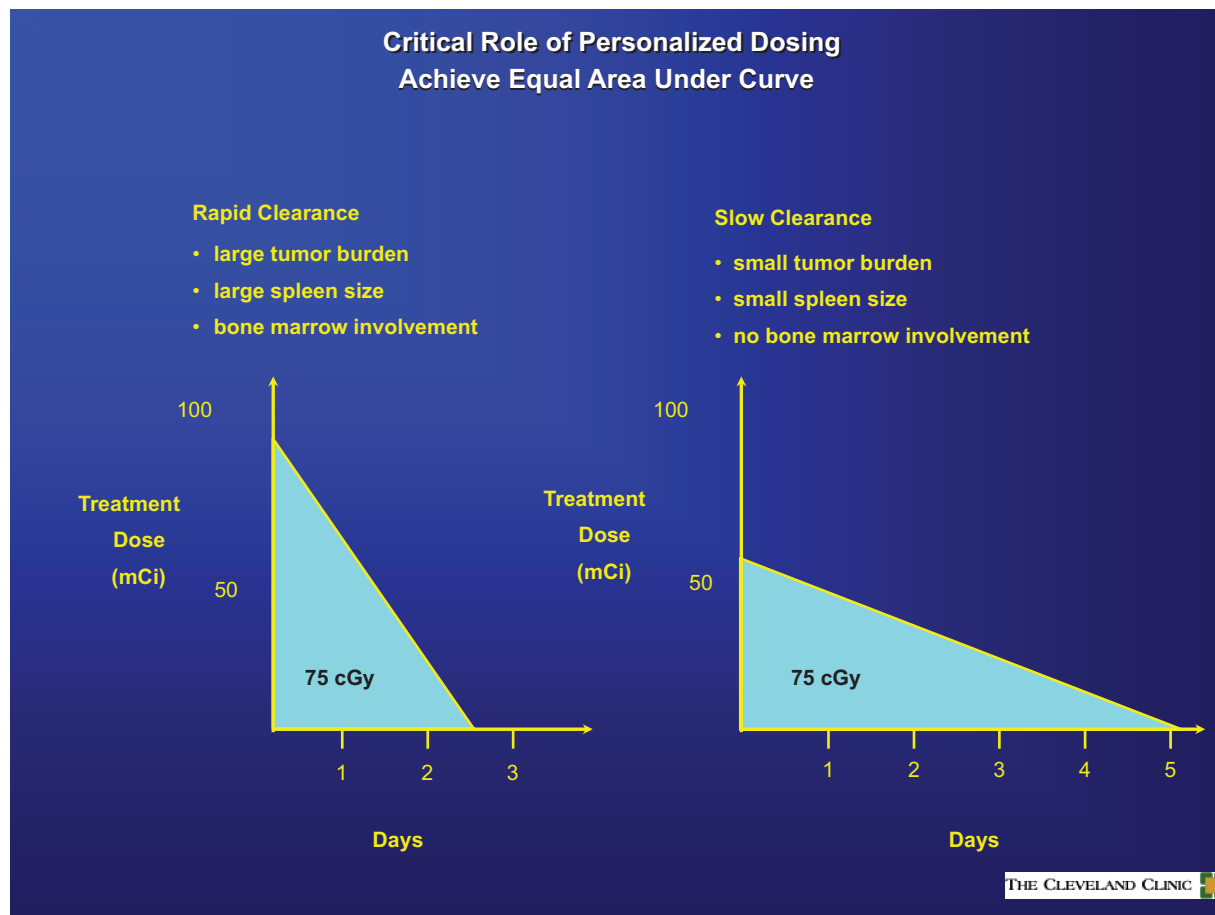
Figure 1 Theoretical reasons for variations in clearance which leads to individualized dosing of ^{131}I activity for each patient.

to 45 cGy for patients with previous autologous stem cell transplant (ASCT).[25] A typical standard dose without reductions for thrombocytopenia or previous SCT can range between 50 and 200 mCi.[19, 26] On day 7 to 14, the therapeutic dose is administered. Once again, a preceding (cold) dose of 450 mg TST is injected over one hour followed by the therapeutic dose of ^{131}I in mCi conjugated to 35 mg TST over twenty minutes.

Radiation safety guidelines vary by state. Standard dose TST administration is an outpatient procedure. Patients should be counseled that the radiopharmaceutical is excreted in the urine and appropriate precautions should be taken to minimize exposure to others in the first couple of weeks. We refer you to the radiation safety committee of your hospital for information on medical I-131 radiopharmaceutical regulations.

Toxicity

Acute side effects of treatment may include infusional reactions such as fever, rigors, hypotension, diaphoresis, dyspnea, bronchospasm, and nausea. Infusional reactions are more likely to occur during administration of the 'cold' dose but could potentially occur during administration of the radiolabeled antibody.[13,26] Prevention of these reactions is minimized through the use of anti-pyretics and anti-histamines, such as acetaminophen and diphenhydramine, although no randomized studies have determined their effectiveness in preventing infusional reactions. Infusional reactions should be treated by halting the infusion and then restarting at a slower rate. Anaphylactic reactions should be treated by stopping the infusion and then treating with epinephrine, corticosteroids, and anti-histamines.

The most common side effect of ^{131}I-TST is myelosuppression, predominately thrombocytopenia and neutropenia. In the setting of relapsed disease, nadirs typically occur 4 to 7 weeks after infusion and take an additional month to resolve. Grade 3 to 4 thrombocytopenia, <50,000 platelets/mL, or neutropenia, <1000 absolute neutrophil count/mL, occur with a frequency of 53% and 63%, respectively. To monitor for hematologic toxicity, patients should have weekly blood counts for 10 to 12 weeks or until counts return to safe levels.[11]

Because TST is a mouse monoclonal antibody, TST can stimulate the immune system to produce human anti-mouse antibodies (HAMA) which may preclude the use of future monoclonal antibodies. HAMA reactivity usually takes 6 months after treatment to develop. In relapsed or refractory disease, HAMA seroconversion occurs in 10% to 15% of administrations,[25] while in upfront monotherapy the reported rate of HAMA seroconversion is 63%.[27]

Dehalogenation of ^{131}I results in accumulation of radioactive iodine in the thyroid gland and the potential for subsequent hypothyroidism, occurring in roughly 15% of cases at 5 years.[11] Onset of hypothyroidism typically requires 1 to 2 years. To minimize the risk of hypothyroidism, patients are instructed to take Lugol's solution, potassium iodide, or equivalent for a minimum of 24 hours prior to the dosimetric dose and continue until 14 days after the therapeutic dose. Health care providers who handle ^{131}I may be required to have additional radioactive monitoring by their radiation safety officers.

Concerns of serious immunosuppression from ^{131}I-TST have not been realized despite depletion of circulating B cells for 6 months after therapy. Thirty-one patients treated with upfront ^{131}I-TST monotherapy for follicular NHL had serum levels of antibodies against rubella, mumps, varicella zoster, measles, and tetanus measured at baseline, 1 year after therapy, and 2 years after therapy. Few patients lost acquired humoral immunity suggesting that routine revaccination of patients after ^{131}I-TST is unnecessary.[28]

Any patient treated with cytotoxic therapy is at increased risk for MDS/acute myelogenous leukemia (AML). A study investigating the risk of MDS/AML in 995 patients with relapsed NHL treated with ^{131}I-TST found that 3.5% of patients developed MDS/AML with a median follow-up of 6 years from diagnosis and 2 years after ^{131}I-TST. The annualized incidence of AML/MDS was 1.6%/year which is similar to that of patients treated with multiple chemotherapy regimens.[29] In a study of 76 patients treated with upfront ^{131}I-TST monotherapy for follicular NHL, no patients developed MDS/AML with a median follow-up of 7.93 years.[30] Distinguishing the attributable risk of MDS/AML to chemotherapy or ^{131}I-TST is difficult, although it appears that ^{131}I-TST does not significantly increase the risk of leukemia.[29]

^{131}I-TST in relapsed B-cell NHL

In an early phase I/II study from the University of Michigan, 59 patients with relapsed or refractory B-cell NHL were treated with ^{131}I-TST. Fourteen patients had previously undergone ASCT, and 17 patients had de novo intermediate/high risk disease. Fifty percent had responded to their last

chemotherapy regimen. Response was excellent: 71% achieved OR with a median progression free survival (PFS) of 12 months and 34% achieved CR with a median PFS of 20.3 months. Fourteen patients with transformed NHL had similar responses to those with low-grade NHL, but no patients with de novo intermediate/high-grade NHL achieved CR and only 41% had partial responses.[25]

In a multicenter, single-arm trial, 47 patients with relapsed or refractory B-cell NHL were treated with ^{131}I-TST. Patients were required to have failed at least one chemotherapy regimen that included an anthracycline or anthracenedione and their latest progression must have occurred within one year of enrollment. Patients had received a median of four previous chemotherapy regimens with 47% of patients responding to their last regimen. Again, responses were excellent: OR was 57% with a MDR of 9.9 months and CR was 32% with a MDR of 19.9 months. The response rates for patients with transformed and low-grade NHL were similar at 57% and 60%, respectively. MDR for low-grade NHL was 8.2 months and MDR for transformed NHL was 12.1 months.[19]

Even when faced with poorly responsive disease, ^{131}I-TST still offers a potential for long-term disease control. A study of 60 patients who had a failed a minimum of two qualifying regimens with the last qualifying regimen (LQR) failure within 6 months of study enrollment showed a benefit with ^{131}I-TST. LQR included fludarabine or chlorambucil monotherapy, cyclophosphamide-based regimens, or variety of other combination regimens. Response to LQR was worse than those in the two previously mentioned studies, with only 28% patients achieving a response and only 3% with a CR. Patients included in this trial were running out of options as the median number of previous chemotherapy regimens was four and by trial definition they had to have failed within 6 months of their LQR. Response rates to ^{131}I-TST in this patient population were impressive: OR of 65% and CR of 20%. Even in transformed disease, where prognosis is especially poor, ^{131}I-TST had an OR of 39%. The MDR for patients was 6.5 months for all ^{131}I-TST responders. For patients in CR after ^{131}I-TST, MDR had not been reached with a median follow-up of 47 months. In this study where a patient's response to their LQR served as his own control, ^{131}I-TST clearly outperformed conventional chemotherapy.[26]

Given these impressive responses in heavily pretreated patients, one wonders if ^{131}I-TST given earlier in the natural history of a patients NHL might lead to higher response rates and prolonged remissions. An open label phase II study from the United Kingdom attempted to answer this question. Forty-one patients with recurrent indolent and transformed

B-cell NHL and had progressed after one or two previous chemotherapy regimens were treated with ^{131}I-TST. The OR of 76% and CR of 49% were better than the previous studies of patients who were more heavily pretreated. The overall MDR was longer at 1.3 years. The most striking difference is in the 49% of patients who achieved CR: their MDR had not yet been reached with 11 patients still in remission at 2.6 to 5.2 years at the time of publication. Again, OR for indolent NHL and the 7 patients with transformed NHL was similar at 77% and 71%, respectively.[20] It appears as though earlier treatment with ^{131}I-TST yields better results with ^{131}I-TST, although the optimal treatment strategy to maximize longevity and minimize toxicity in patients with indolent NHL remains to be determined.

One feature that all of the above mentioned studies have in common is that they all excluded patients who received prior immunotherapy. Because advanced stage follicular lymphoma is an indolent, apparently incurable disease, the goal of therapy is to provide effective treatment while minimizing toxicity. Since RTX approval for B-cell NHL, RTX therapy is considered standard of care in the frontline management of this disease (National Comprehensive Cancer Network guidelines). We have already discussed how RIT appears to provide greater benefit than immuno-therapy alone. Given some of the obvious similarities in mechanism of action between immunotherapy and RIT, one wonders whether patients who are no longer susceptible to immunotherapy may still respond to RIT. Indeed, such a trial has already been reported. A multicenter phase II TST trial included 40 patients with indolent, follicular large cell, or transformed B-cell NHL who had progressed after RTX. Patients had been heavily pretreated with a median of four prior regimens. Twenty-four patients had failed to respond to RTX and an additional 11 had response durations less than 6 months after RTX. Despite their failure to RTX treatment, response to ^{131}I-TST was excellent with an OR of 65% and CR of 38%. Responders had a median PFS of 24.5 months with some patients remaining in remission at 3.4, 3.7, and 4.0 years at the time of the report. Curiously, previous response to RTX had no impact on either response or duration of response with ^{131}I-TST. We have previously noted that the clinical efficacy of unlabeled TST is inferior to ^{131}I-TST. Also mentioned earlier was the difference in mechanism of action in vitro between RTX and TST, with TST unable to activate complement and instead having a greater ability to activate apoptotic pathways through CD20 binding. Therefore, one should not be surprised that ^{131}I-TST therapy is effective in disease refractory to RTX.[31]

A summary of the responses of ^{131}I-TST in relapsed, refractory, or transformed low-grade B-cell NHL is given in Table 2. An integrated analysis of these trials containing 250 patients has examined factors predictive of long-term duration of response. For all 250 patients, 5-year PFS was 17% after a median follow-up of 5.3 years. A durable response was defined as a TTP greater than one year. Eighty-one patients achieved a durable response with a MDR of 45.8 months, and 44% of durable responders were still in remission at 2.5 to 9.5 years. In complete responders, the MDR was not reached. Multivariate analyses found the following factors to predict for failure to achieve CR: absence of response to last chemotherapy, elevated lactate dehydrogenase (LDH), and bulky disease greater than 5 cm. Factors predictive of a shorter duration of response included elevated LDH, age greater than 65 years, and no response to last chemotherapy. However, the durable response population did include patients with these poor prognostic factors.[32]

One might consider the effectiveness of ^{131}I-TST after previous treatment with ^{131}I-TST. Kaminski has reported retreatment of thirty-two patients with ^{131}I-TST. The initial OR, CR, and MDR were 94%, 56%, and 13.6 months, respectively. After a median of 21 months, patients were given an additional dose of ^{131}I-TST. Dosing was the standard 75 cGy total body with a dose reduction to 65 cGy for platelet counts between 100,000/mL and 150,000/mL. Patients who had grade IV hematologic toxicity during their previous treatment had dose reduction by an additional 10 cGy. After the second treatment, OR, CR and MDR were 56%, 25%, and 15.2 months, respectively. Although response rates were poorer on second treatment, some patients still responded and even had long-term control. Hematologic toxicity was similar to initial treatment. Five patients, who had been treated with between 2 and 8 chemotherapy regimens, developed MDS/AML.[33]

Although patients receiving ^{131}I-TST in relapsed or refractory disease have a poor prognosis, ^{131}I-TST does not preclude the use of subsequent therapy. As ^{131}I-TST therapy becomes integrated earlier into the treatment paradigm for indolent NHL, conventional salvage regimens once given prior to ^{131}I-TST may instead be given later. If ^{131}I-TST achieves improved responses compared to conventional regimens but precludes additional therapy because of bone marrow suppression, overall survival after ^{131}I-TST may remain unchanged or even become worse. In one review of patients treated on six trials, relapses occurred in 68 of 155 patients treated with ^{131}I-TST. Blood counts before and after ^{131}I-TST were similar with the exception of platelets which had decreased from a median of 193,000/mL to 130,000/mL.

Table 2 Summary of major published trials of ^{131}I-Tositumomab for relapsed, refractory, or transformed low-grade B-cell non-Hodgkin's lymphoma (NHL)

Study design	N	OR (%)	CR (%)	PFS (TTP) [MDR] (months)
Phase I/II single center trial; prior stem cell transplant allowed; includes 17 patients with de novo intermediate/ high-grade NHL; no prior RTX[25]	59	71	34	12 for all responders
Phase II multicenter nonrandomized trial; at least one prior anthracycline or anthracenedione based chemotherapy regimen with disease progression within 1 year; no prior RTX[19]	47	57	32	5.3 [9.9]
Phase III multicenter nonrandomized trial; at least two prior chemotherapy regimens with either no response or relapse within 6 months of completing their last regimen; no prior RTX[26]	60	65	20	8.4 for all responders [6.5]
Phase II open label single arm trial; only 1 or 2 previous chemotherapy regimens; no prior RTX[20]	41	76	49	0.8 years [1.3 years]
Multicenter randomized trial comparing ^{131}I-TST to unlabeled TST; no prior RTX[13]	78	55	33	(6.3) [not reached]
Mutlicenter phase II trial; failure after prior RTX[31]	40	65	38	10.4 [24.5]

Abbreviations: OR, overall response; CR, complete response; PFS, progression-free survival; TTP, median time to progression for all patients in study; MDR, median duration of response in responders; RTX, rituximab; ^{131}I-TST, ^{131}I tositumomab.

After ^{131}I-TST, 65% of patients went on to receive additional chemotherapy including regimens of anthracyclines, platinum, fludarabine, and SCT. Of the 35% who did not receive additional chemotherapy for a variety of reasons, 88% had hematologic parameters permitting additional therapy. Thus, the majority of patients who receive ^{131}I-TST can still receive additional therapy after relapse.[34]

Dose escalation with autologous stem cell transplant

After failing multiple chemotherapy regimens, a common alternative for treatment of low-grade NHL is high dose systemic therapy followed by ASCT. The goal of therapy is to eradicate all malignant cells while preserving the patient's own ability to regenerate blood cells through the reinfusion of one's own procured stem cells once the cytotoxic period has passed. In a carefully monitored environment accustomed to the perils of ASCT, patients can achieve responses unattainable by conventional dosing.

One of the earliest reports of the use of ^{131}I-TST was with autologus bone marrow support at the University of Washington/Fred Hutchinson Cancer Research Center (UW/FHCRC). Twenty-four patients with B-cell NHL were treated on a dose escalation study with ^{131}I conjugated

to either TST, another anti-CD20 antibody called 1F5, or an anti-CD37 antibody named MB-1. Dosing was patient specific, with dose limits based on critical normal organs rather than the total body equivalent dose. In comparison to total body external beam irradiation (TBI) where all body structures receive a similar radiation dose, this strategy allowed a ten-fold increase of tumor to total body dose and 2- to 3-fold increase of tumor to critical organ dose.[35] A follow-up phase II study investigating only high dose ^{131}I-TST in 25 patients with B-cell NHL confirmed that 27 Gy was the maximally tolerated dose (MTD) that could be delivered to either the lung or kidneys. Splenomegaly and tumor burden greater than 500 mL predicted for an unfavorable biodistribution precluding the administration of the therapeutic dose. Activity of ^{131}I ranged from 345 to 785 mCi which gave estimated tumor doses of 27 to 92 Gy. In comparison, a total body dose of 75 cGy from ^{131}I-TST corresponds to an average tumor dose of 10 Gy.[25] Two patients died prior to neutrophil counts reaching 500/μL, one of lymphoma and one of sepsis.[36] With a median follow-up of 42 months, 29 patients treated at UW/FHCRC with high dose ^{131}I-TST yielded impressive results: OR of 86%, CR of 79%, 4-year OS of 68%, and 4-year PFS of 42%. Long-term toxicity included 63% incidence of

elevated TSH, seroconversion of HAMA in 35%, and no cases of MDS/AML. No patients were transfusion dependent at year 1.[37]

Building on this prior experience, the UW/FHCRC performed another phase I/II trial to evaluate the potential gain of substituting ^{131}I-TST for TBI in their ASCT program. Fifty-two patients were treated with ^{131}I-TST followed by etoposide (60 mg/kg) and cyclophosphamide (100 mg/kg). Stem cells were not replenished until forty-eight hours after infusion of etoposide and cyclophosphamide at which time total-body radioactivity levels were below 0.02 mSv/h at 1 m. Critical organ dosimetry for each individual patient determined the activity of ^{131}I to be infused; the MTD was 25 Gy to the lungs or kidneys. At two years, PFS and OS were estimated to be 83% and 68%, respectively. Four treatment-related fatalities occurred. Major long-term complications included hypothyroidism in 56%, 1 case of MDS, and 4 patients who developed pneumonitis at 2 to 8 months that subsequently responded to outpatient corticosteroids. When compared to a group of 105 patients treated at UW/FHCRC during the 1990s with an ASCT after etoposide, cyclophosphamide, and TBI, patients treated with the ^{131}I-TST regimen had significantly improved 2-year OS and PFS. On multivariate analysis designed to compensate for confounding factors, the hazard ratios for OS and PFS for the ^{131}I-TST regimen compared to the TBI regimen were both 0.3 ($P = 0.004$, $P = 0.002$).[38]

A multivariate analysis performed at UW/FHCRC compared ASCT regimens of high dose radioimmunotherapy (HD-RIT) to conventional high dose therapy (C-HDT), including chemotherapy or chemotherapy and TBI, in relapsed FL. The 27 patients treated HD-RIT had worse international prognostic scores, yet outcomes were improved compared to the 125 patients treated with C-HDT. The estimated 5-year OS and 5-year PFS for HD-RIT were 67% and 48%, respectively, and for C-HDT were 53% and 29%, respectively. One hundred-day treatment-related mortality was higher for C-HDT at 11% than for HD-RIT at 3.7%. The long-term risks of MDS/AML were equivalent between the two groups. HD-RIT provided both safer and more effective therapy than C-HDT in this nonrandomized retrospective review.[39]

Mantle cell lymphoma is an aggressive form of NHL. Applying the previous protocol of ^{131}I-TST followed by etoposide and cyclophosphamide to 16 patients with relapsed mantle cell NHL, excellent results were obtained at the UW/FHCRC. Toxicity was comparable to the previous study. With a median follow-up of 19 months, estimated 3-year OS and PFS were 93% and 61%, respectively.

Three patients were alive without disease progression at 4 years. Again, these results compare favorably to historical controls.[40]

Finally, researchers at the UW/FHCRC have used high dose ^{131}I-TST in 24 patients older than 60 years old with relapsed or refractory B-cell NHL. The MTD was determined to be 27 Gy to critical organs. Results were excellent: OR 67%, CR/CRu 54%, 3-year OS of 59%, and 3-year PFS of 51%. Two patients developed MDS/AML, 10 patients developed hypothyroidism, and 2 patients developed grade III pneumonitis at 3 and 12 months after ASCT that responded to outpatient corticosteroids. Most importantly, there were no treatment-related deaths compared to the 5% to 10% expected from conventional chemotherapy ASCT regimens in this age group.[41]

Not all investigators have attempted ultra-high dose ^{131}I-TST as the primary preparation for ASCT regimens utilizing RIT. The University of Nebraska added standard-dose ^{131}I-TST to their BEAM (carmustine, etoposide, cytarabine, melphalan) regimen for relapsed NHL. The 23 patients on this phase I protocol had aggressive chemotherapy resistant NHL: grade III follicular lymphoma, DLBCL, or mantle cell lymphoma. ^{131}I-TST was given on day −12, BEAM given on days −6 to −1, and stem cells were infused on day 0. The MTD of ^{131}I-TST was found to be 75 cGy. Toxicity was similar to patients previously treated with BEAM, and no patients died within the first 100 days of transplant. Response was excellent: 57% CR/CRu and 65% OR. The 3-year event-free survival was 39% and 3-year OS was 55%. In a similar group of patients treated with previous regimens, expected 3-year survival rates are 10% to 20%. These impressive results have encouraged the authors to begin a phase II study at their institution.[42]

Results of ASCT protocols for patients with B-cell NHL treated with ^{131}I-TST are listed in Table 3. An ongoing phase III study by the National Heart, Lung, and Blood Institute compares two ASCT conditioning regimens in relapsed diffuse large B-cell NHL (DLBCL): rituximab plus BEAM chemotherapy versus ^{131}I-TST followed by BEAM chemotherapy. The primary end-point in this study is PFS. Results of this study should help determine the role of ^{131}I-TST in ASCT for relapsed DLBCL.

Treatment after autologous stem cell transplant

Patients who receive ASCT typically have high burdens of refractory disease. After ASCT, their bone marrow reserve becomes depressed and restricts the use of further

Table 3 Results of autologous stem cell transplant protocols involving ^{131}I tositumomab in non-Hodgkin's lymphoma

Center	N	Histology	Chemo	^{131}I-TST	OR	CR	Outcome
Washington[37]	29	66% LG, 34% IG	None	27 Gy to lung or kidney	86%	79%	4-year PFS 42%
Washington[38]	52	65% FL G1-2, 8% FL G3 12% MC, 16% DLBCL	CE	25 Gy to lung or kidney	87%[a]	77%[a]	2-year PFS 68%
Washington[40]	16	MC	CE	25 Gy to lung or kidney	82%[b]	73%[b]	3-year PFS 61%
Nebraska[42]	23	61% DLBCL, 17% FL G3, 22% MC	BEAM	75 cGy total body	65%	57%	3-year EFS 39%
Washington[41]	24	38% DLBCL, 33% MC, 25% FL, 4% MZ	None	25–27 Gy to lung or kidney	67%	54%	3-year PFS 51%

[a]Excludes 18 patients with no measurable disease after the mobilization regimen; [b]Excludes 5 patients with no measurable disease after the mobilization regimen.
Abbreviations: ^{131}I-TST, ^{131}I tositumomab; OR, overall response; CR, complete response; LG, low grade; IG, intermediate grade; PFS, progression-free survival; FL, follicular lymphoma; G, grade; MC, mantle cell lymphoma; DLBCL, diffuse large B cell lymphoma; CE, cyclophosphamide and etoposide; BEAM, carmustine, etoposide, cytarabine, melphalan; EFS, event-free survival; MZ, marginal zone lymphoma.

cytotoxic therapy. The initial studies in relapsed, refractory, or transformed NHL largely excluded patients with prior SCT with exception of the Michigan phase I/II study that included 14 patients.[25] The ^{131}I-TST for patients with previous ASCT was found to be 45 cGy total body equivalent dose. Response rate for these 14 patients was 50% with a median PFS of 4.7 years. For patients who have received prior ASCT, dose-reduced ^{131}I-TST is a viable option with a chance for response and even long-term control.

^{131}I-TST in the frontline management of B-cell NHL

Because RIT requires the cooperation from the immune system and ^{131}I-TST used earlier in the course of a patient's disease provides better outcomes, one wonders about the efficacy of ^{131}I-TST in a patient untainted by previous chemotherapy or immunotherapy. A phase II trial at the University of Michigan treated 76 patients with stage III or IV grade I to II follicular lymphoma (FL) with ^{131}I-TST as initial management.[27,30] Response was excellent: 75% CR, 95% OR, and median PFS of 6.1 years. With a median follow-up of 7.93 years, 8-year PFS was 50%, 8 and 10-year OS were 86%, and median PFS for complete responders was 9.2 years. Hematologic toxicity was less than that in relapsed disease: no patients developed grade IV thrombocytopenia, 17% developed grade III thrombocytopenia, and 34% developed grade III/IV neutropenia. No patients developed MDS/AML. HAMA developed in 63% of patients. While HAMA seroconversion did not

predict for PFS, the 23 patients with HAMA greater than five times the lowest level of detection had a significantly worse 5-year PFS of 35% compared to the other patients at 70% ($P = 0.003$). Both bone marrow involvement and bulky disease greater than 5 cm were negative predictors of CR, while only bone marrow involvement negatively predicted for PFS. Fifty-six percent of patients had a diagnosis of follicular lymphoma for over 1 year prior to enrollment; critics would argue that these patients had indolent disease and would have responded favorably to any therapy. Nevertheless, responses in this trial were excellent and deserve further consideration.

An alternative to monotherapy with ^{131}I-TST in the upfront management of FL is the use of conventional chemotherapy followed by consolidation ^{131}I-TST. Ninety patients with bulky stage II or stage III-IV FL were enrolled on SWOG S9911 which was a single-arm phase II study of 6 cycles of CHOP (cyclophosphamide, hydroxydaunomycin, oncovin, and prednisone) followed by consolidation ^{131}I-TST.[43] After CHOP × 6, 39% of patients achieved radiologic CR. After ^{131}I-TST, CR improved to 69% and the OR was 91%. At a median follow-up of 5 years, 5-year OS was 87% and 5-year PFS was 67%. Compared to historical controls of patients treated with CHOP on 2 prior SWOG trials, patients treated with consolidation ^{131}I-TST had an absolute improvement of 23% in both OS and PFS (Figures 2 and 3). The incremental benefit of ^{131}I-TST over RTX will be determined by Intergroup Study S0016 that has randomized 500 patients with bulky stage II-IV FL between CHOP-R × 6 and CHOP × 6 followed
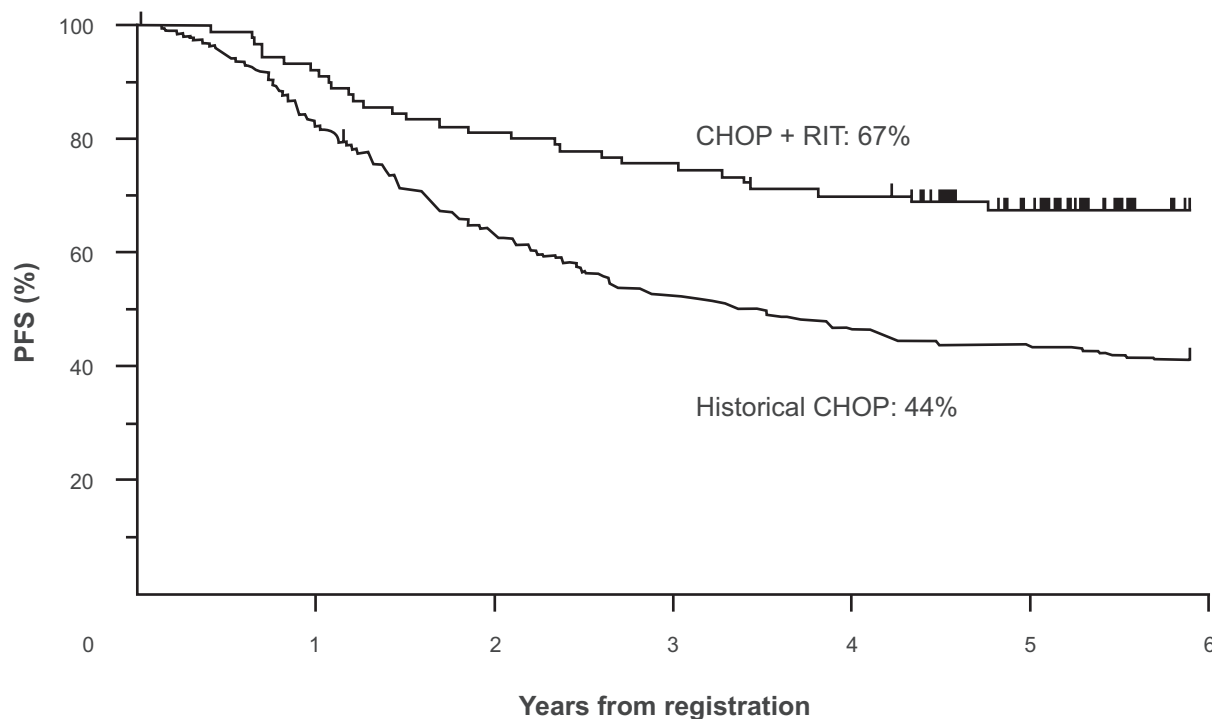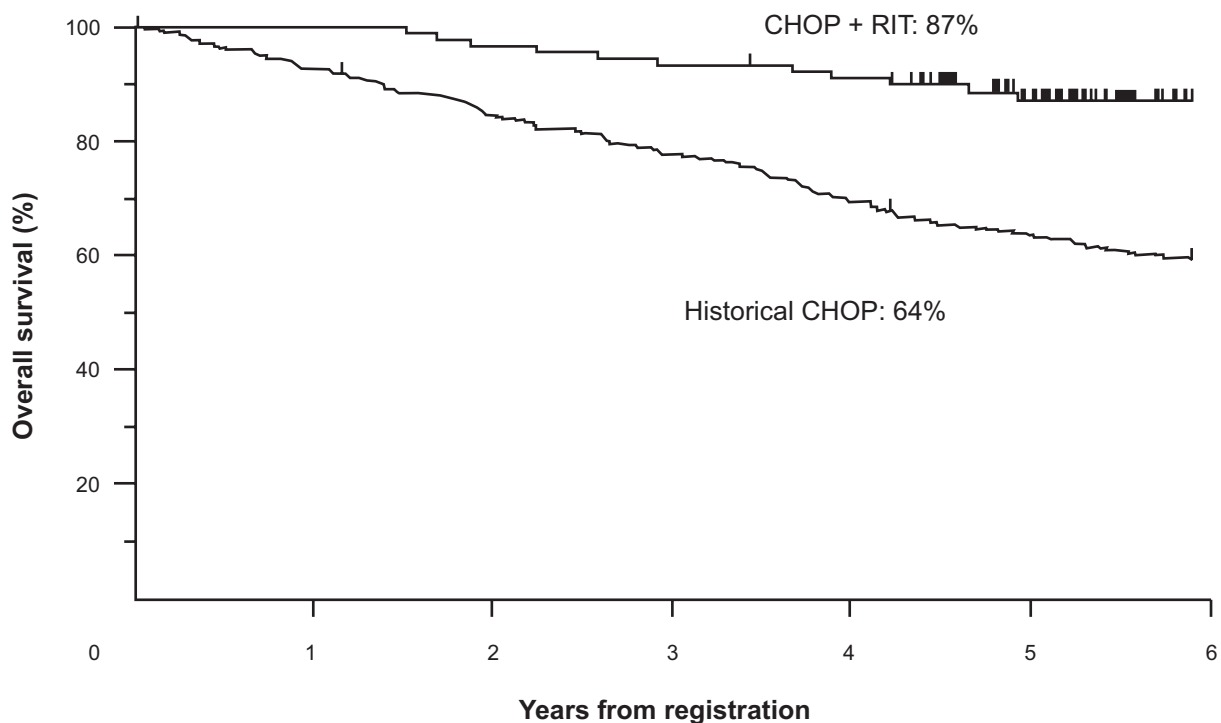
Figure 2 Comparison of progression-free survival (PFS) of 90 patients with bulky stage II to stage IV follicular non-Hodgkin's lymphoma treated with 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy followed by tositumomab I-131 (radioimmunotherapy [RIT]) with the PFS of 356 similar patients treated on previous Southwest Oncology Group studies of CHOP without anti-CD20 antibodies (historical CHOP). Five-year estimates of PFS for each regimen are shown. Reprinted with permission from Press OW, Unger JM, Braziel RM, et al. Phase II Trial of CHOP chemotherapy followed by tositumomab/iodine-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: five-year follow-up of Southwest Oncology Group Protocol SW9911. *J Clin Oncol.* 2006;24(25):4143–4149.[43] Copyright © 2006 American Society of Clinical Oncology.

by consolidation ^{131}I-TST. Enrollment has completed and we eagerly await results.

An open-label phase II single center study of 35 patients with newly diagnosed stage III to IV small lymphocytic, follicular, or monocytoid B-cell NHL involved treatment with 3 cycles of fludarabine followed by consolidation ^{131}I-TST. After fludarabine, OR was 89% and CR was 9%. After ^{131}I-TST, OR was 100% and CR was 86%. With a median follow-up of 58 months, estimated 5-year PFS was 56% and median PFS was not reached but will be at least 4 years. Two interesting caveats to this study included bone marrow involvement as well as HAMA reactivity. The authors thought that bone marrow tumor debulking could decrease the hematologic toxicity of ^{131}I-TST. Before fludarabine, 26 patients had bone marrow involvement and 6 of these patients had greater than 25% bone marrow involvement. After fludarabine, 7 of 18 assessed patients continued to have bone marrow involvement. Five of the 6 patients with greater than 25% bone marrow involvement had disease regress to less than 25% involvement, allowing them to receive full standard dose ^{131}I-TST. The sixth patient received dose-reduced ^{131}I-TST at 45 cGy total body. After ^{131}I-TST, only 2 patients continued to have bone marrow involvement.

While patients still had bone marrow suppression from ^{131}I-TST, fludarabine did remove the exclusion criteria of 25% bone marrow involvement in 5 out of 6 patients. Finally, the authors postulated that pretreatment with fludarabine could potentially improve outcomes through immunosuppressing the production of HAMA. HAMA are known to be associated with an unpleasant flu-like syndrome and potentially interfere with the therapeutic activity of ^{131}I-TST. In this study, the rate of HAMA formation was 6% which is lower than the 10% conversion in relapsed disease and 63% conversion in initial monotherapy.[44]

Finally, a phase II, open-label multicenter study has been reported in abstract form. In this trial, 30 patients with newly diagnosed bulky stage II or stage III/IV FL were treated with 6 cycles of CVP (cyclophosphamide, vincristine, and prednisone) followed by consolidation ^{131}I-TST. All patients initially responded to CVP × 6, with 50% achieving CR. After ^{131}I-TST consolidation, an additional 9 patients converted from PR to CR giving a final CR of 80%. At a median follow-up of 2.3 years, median PFS was not reached and 77% of patients remained in remission. Grade IV neutropenia and thrombocytopenia occurred in 33% and 23% of patients, respectively. One patient developed AML, and no patients developed HAMA.[45]

Figure 3 Comparison of the overall survival (OS) of 90 patients with stage II to IV follicular non-Hodgkin's lymphoma treated with 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy followed by tositumomab I-131 (radioimmunotherapy [RIT]) on the current trial (S9911) with the OS of 356 similar patients treated on previous studies with CHOP without anti-CD20 antibodies (historical CHOP). Five-year estimates of OS for each regimen are shown. Reprinted with permission from Press OW, Unger JM, Braziel RM, et al. Phase II Trial of CHOP chemotherapy followed by tositumomab/iodine-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: five-year follow-up of Southwest Oncology Group Protocol SW9911. *J Clin Oncol.* 2006;24(25):4143-4149.[43] Copyright © 2006 American Society of Clinical Oncology.

A summary of the phase II studies investigating the upfront management of FL with ^{131}I-TST, either as monotherapy or consolidation therapy after conventional chemotherapy, is summarized in Table 4. None of the studies listed in Table 4 have incorporated RTX into the induction regimen. RTX therapy is now considered standard of care in the frontline management of most types of B-cell CD20+ lymphoma. Induction therapy with RTX-containing cytotoxic chemotherapy regimens followed by consolidation therapy with RIT may yield superior results. Theoretically, treatment with RTX prior to RIT may reduce the incremental benefit of ^{131}I-TST because of similarities in mechanism of action discussed previously. Furthermore, residual RTX remains in patients' serum for three to six months after treatment and could potentially block CD20 binding sites.[46] Preclinical studies using human lymphoma cell lines, patient-derived specimens, and mouse xenograft models have shown that prior RTX therapy reduces CD20 binding, tumor-specific localization, and tumor control for ^{131}I-TST.[46] Despite this preclinical data, ^{131}I-TST has been shown to be clinically effective in RTX-refractory relapsed low grade B-cell NHL as discussed previously.[31] Future clinical studies should help determine whether inclusion of RTX in induction chemotherapy regimens abrogates the incremental

therapeutic gain of consolidation ^{131}I-TST found in the studies listed in Table 4.

Diffuse large B-cell lymphoma

The Michigan phase I/II study included 17 patients with de novo intermediate/high grade NHL. No patients achieved CR and 41% achieved PR suggesting that ^{131}I-TST may have some activity in higher grade NHL.[25] Because the toxicity from ^{131}I-TST is low and does not overlap temporally with conventional chemotherapy, ^{131}I-TST could potentially improve outcomes as part of a multimodality combination regimen. Several of the ASCT protocols mentioned previously included patients with DLBCL and showed improved outcomes compared to historical controls (Table 3). SWOG protocol S0433 is a phase II study for DLBCL. Patients with bulky stage II to IV DLBCL will receive CHOP-R followed by ^{131}I-TST. Longer follow-up and randomized trials should determine the role of consolidation RIT in DLBCL.

Future directions: measuring outcomes

The International Working Group (IWG) response criteria for malignant lymphoma were revised in 2007 to reflect

Table 4 Phase II studies investigating the use of ^{131}I tositumomab in the initial management of low grade B-cell NHL

Center	Patients	Regimen	CR after chemo	CR after ^{131}I-TST	5-yr PFS
Michigan[27]	76 stage III-IV	^{131}I-TST	N/A	75%	59%
Iowa, Michigan, Cornell[45]	30 bulky stage II-IV	CVP × 6 + ^{131}I-TST	50%	80%	
Cornell[44]	35 stage III-IV	Fludarabine × 3 + ^{131}I-TST	9%	86%	
SWOG S9911[43]	90 bulky stage II-IV	CHOP × 6 + ^{131}I-TST	39%	69%	67%

Abbreviations: CR, complete response; PFS, progression-free survival; ^{131}I-TST, ^{131}I tositumomab; CVP, cyclophosphamide, vincristine, prednisone; CHOP, cyclophosphamide, hydroxydaunomycin (doxorubicin or adriamycin), oncovin (vincristine), and prednisone.

improvements in response analysis from the development of radiologic and pathologic technologies: positron emission tomography (PET), immunohistochemistry, and flow cytometry. PET eliminated the previous category of CRu.[47] None of the trials mentioned in this review utilized PET in response evaluation. The new IWG guidelines could potentially alter the scoring of response rates as well as change treatment management. In ^{131}I-TST, correlation of FDG PET with clinical responses suggests that declines in FDG uptake predicts for prolonged clinical remissions.[48,49] Incorporation of PET imaging in future trials could help determine their utility.

Molecular response data obtained from the polymerase chain reaction (PCR) of bone marrow aspirates or peripheral blood was not included in the new IWG response criteria.[47] The classic cytogenetic translocation associated with follicular lymphoma is t(14:18) which involves juxtaposition of the BCL-2 gene next to the immunoglobin heavy chain locus.[50] In low-grade NHL, several investigators have incorporated PCR for the BCL-2 gene rearrangement into clinical protocols. In the Michigan initial monotherapy study, bone marrow PCR analysis was available at baseline from 73 patients, 39 of which were positive for the BCL2 gene rearrangement. Of the 20 patients with the rearrangement at baseline and were in CR at six months, 16 had converted to PCR negative and 13 of these patients remained in CR with a median follow up of over 5 years. In contrast, 3 of the 4 patients who were in CR at 6 months but did not become PCR negative had relapsed.[27] In SWOG S9911, bone marrow specimens were assessed for the BCL-2 rearrangement using PCR. Sixty-five of the 90 patients had detectable levels of the BCL-2 rearrangement at baseline. Of the patients with data available for analysis, 18% converted to PCR negative status after CHOP while an additional 63% converted to PCR negative status after ^{131}I-TST. PCR remission was not correlated with clinical outcomes such as PFS or OS, although the power to detect a difference was low.[43] In the study of fludarabine followed by ^{131}I-TST, 13 patients had positive bone marrow PCR for the BCL-2 translocation. After ^{131}I-TST, 10 of the 13 patients had negative bone marrow PCR at 12 months and their 5-year PFS of 70% was significantly better than the 3 patients who were not PCR negative at twelve months.[44] Just as radiologic and bone marrow cytology CR to ^{131}I-TST predicts for prolonged remissions, these data on molecular responses also suggest that molecular CR may be a positive prognostic sign after treatment with ^{131}I-TST. Incorporation of molecular response in future trials could help answer this question.

Unanswered questions and new opportunities

^{131}I-TST clearly shows dramatic disease control activity against low grade B cell lymphoma. However, in an era where other biologically active targeted therapies such as RTX have been shown capable of almost single handedly increasing disease control rates for the same group by 5% to 10% when added to various conventional chemotherapy regimens,[51] one must ask whether the small but perhaps significant incremental risks posed by high dose radiopharmaceutical exposure are justified. Certainly, as long as RIT agents such as ^{131}I-TST and ^{90}Y-ibritumomab tiuxetan remain one set of effective options among many palliative therapies, their use will remain subject to individual beliefs and opinions shaped by mixtures of medicoscientific data, economic incentives and disincentives,[52] and various training biases. Arguments that the palliative effectiveness of these agents far exceeds any other single agent with similar low toxicity levels are unlikely to be persuasive enough to change strongly reinforced beliefs.

Hochster recently reported on the impact of post-chemotherapy maintenance therapy using 2 years of cyclic RTX therapy.[53] They found that 3-year OS was increased significantly compared to observation, prompting observations by other commentators that perhaps serial approaches to lower the tumor load using various effectors strategies may be able to bring the level of clonogenically active tumor deposits down to a minimal level at which ablative therapy such as SCT or RIT could produce permanent control (true

biological cure).[54] While this hypothetical strategic path to cure is still a future target, it does not seem illusory based on the recent positive datasets. If ^{131}I-TST finds itself a core part of a truly curative regimen for disseminated low grade lymphoma, then this may signal good news not only for patients with low grade follicular lymphoma but also those with more aggressive varieties of lymphoma in which the cellular circuitry might be similarly affected by judicious and creative application of the principles derived from the multi decade study of the therapeutic potential of well targeted immune-cell radiotherapy.[55]

Disclosures

The authors declare no conflicts of interest.

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