Novel Concepts in Radioimmunotherapy for Non-Hodgkin's Lymphoma

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Tositumomab/iodine-131 tositumomab (Bexxar) and ibritumomab tiuxetan (Zevalin) are radioimmunoconjugates targeting the CD20 antigen. Both agents are approved in the United States for use in relapsed or refractory, indolent or transformed, B-cell lymphoma. These agents are well tolerated and have the highest levels of single-agent activity observed in these histologies. This review will summarize the key trials that led to approval of both I-131 tositumomab and ibritumomab tiuxetan, and then focus on four novel therapeutic concepts in radioimmunotherapy: retreatment, therapy of de novo indolent lymphoma, therapy of aggressive histologies, and incorporation in high-dose therapy programs utilizing autologous stem cell support.

Non-Hodgkin's lymphoma (NHL) is the fifth most common malignancy in the United States, with an inexplicable increase in incidence over the past 2 decades. The majority of NHL cases are of B-cell origin, a collectively heterogeneous group of diseases with a wide variation in clinical phenotype.[1] Classically, effectiveness of therapeutics have varied based on histology, with indolent follicular lymphoma generally regarded as incurable in later stages. Approximately 80% to 85% of patients with follicular lymphoma present with stage III or IV disease, and most will require therapy based on unfavorable risk factors or because of symptoms. After achieving a response in follicular lymphoma, the likelihood of relapse is high. With each subsequent therapy, response rates and duration of response classically diminish.

Antibody Therapy of Lymphoma
Rituximab (Rituxan) is a human-mouse chimeric monoclonal antibody to the CD20 antigen found in over 95% of B cell lymphomas. Approved in 1997 for the treatment of relapsed/refractory follicular lymphoma, this immunotherapeutic agent has had a significant impact on the treatment of indolent lymphoma. In a pivotal trial of 166 patients with relapsed or refractory follicular or low-grade lymphoma, treatment with rituximab at 375 mg/m² every week for 4 weeks showed an overall response of 48%, comparing favorably to single-agent chemotherapy. Indeed rituximab is effective both as a single agent and combined with chemotherapy.[2]

The overall survival of patients with advanced stages of follicular lymphoma has improved in the past several years, which is possibly attributable to the use of rituximab.[3,4] However, a substantial number of patients with indolent lymphomas do not respond to rituximab. Tumor bulk, heterogeneous expression of antigen, and impaired antibody-mediated cytotoxicity have all been postulated to play a role in rituximab resistance.[5] Furthermore, even if a response is obtained, relapse is inevitable, conferring significant morbidity and mortality. The curability of diffuse large B-cell lymphoma is enhanced when rituximab is added to conventional anthracycline-containing chemotherapy.[6-8] However, despite this major advance, many patients presenting with high-risk disease (as defined clinically, immunophenotypically, or molecularly) are not cured.

Radioimmunotherapy
To augment the effectiveness of the CD20 antibody, radioimmunoconjugates have been developed.[9,10] These constructs combine the selectiveness of the CD20 antibody with the additional cytotoxicity of radiotherapy. Even if a tumor is bulky or portions lack CD20 expression, the targeted radiation will cause cytotoxicity—i.e., the "bystander" effect—while limiting undesirable nonspecific radiation (Figure 1).[11] In 2002, yttrium-90 ibritumomab tiuxetan (Zevalin) became the first radioimmunotherapeutic agent (RIT) approved by the US Food and Drug Administration (FDA) for the treatment of relapsed or refractory low-grade lymphoma including transformed phenotypes. Y-90 is primarily a beta-particle emitter with a relatively long path length (5-10 mm), and as such, has been postulated to work better on penetrating bulky tumors. This isotope also has a favorable half-life of only 2.5 days. The Y-90 is bound to a linker tiuxetan, which is then bound to the antibody.
Similarly, tositumomab/iodine-131 tositumomab (Bexxar), approved by the FDA for similar indications, is a murine CD20 antibody that is directly bound to the isotope.[12] The I-131 isotope contrasts with Y-90 in that it has both beta and gamma radiation (with a path length of 0.8 mm). This shorter path has the advantage of minimizing inadvertent radiation to unwanted sites but theoretically may not work as well on bulky disease. The half-life of I-131 is longer, as is the need for posttreatment precautions. Both constructs use a murine antibody to maximize clearance and avoid prolonged radiation.

Treatment Regimens
The treatment regimen is administered on an outpatient basis and is similar for both RITs (Figure 2). Initially, a nonradiolabeled antibody is administered to allow for binding of circulating lymphocytes to minimize toxicity and to maximize localization of the RIT to the lymphoma disease sites. Rituximab is used for ibritumomab, and unlabeled tositumomab is used for I-131 tositumomab. Then a "dosimetric," low dose of the RIT is given to determine individual total-body clearance of the constructs.
For I-131 tositumomab, three scans total are performed, using a gamma camera on day 0, then on day 2, 3, or 4, and again on day 6 or 7. The therapeutic dose is calculated to deliver a maximum of 75 cGy total-body radiation; however, the dosimetry to the tumor is about 50 times stronger than the dose delivered to vital organs, owing to RIT specificity. Between days 7 and 14, another dose of unlabeled antibody is given, followed immediately by the therapeutic dose. Specific to treatment with I-131 tositumomab is the need for thyroid protection during therapy. Patients are given potassium iodide or Lugol's solution from day 1 until 14 days after the therapeutic dose is administered.

In the case of Y-90 ibritumomab, total-body scans are performed at 2 to 24 hours, then at 48 to 72 hours, with the therapeutic dose calculated based on a maximum tolerated dose of 0.4 mCi/kg usually administered on day 8 to 10 (dosimetry is not needed). Of note, the yttrium isotope is only used for therapy and not used for imaging (given its lack of gamma emission). Instead, indium-111-labeled antibody is used for these scans, which are performed to ensure normal biodistribution. It is recommended that RIT be avoided in patients who, upon gamma scan, have prolonged uptake in the lungs, urinary tract, or bowel, as this may indicate an aberrant distribution and account for increased toxicity.

Precautions
For either RIT, after the therapeutic dose is administered, appropriate precautions must be undertaken to avoid radiation exposure to others.[11] There are fewer limitations in persons treated with Y-90, but close physical contact should be avoided for the first 24 hours. If treated with I-131, the patient must sleep 6 ft away from his or her partner for at least 7 days. Finally, these patients should avoid contact with children or pregnant women for about 1 week. With both types of RIT treatment, patients must be cognizant of their bodily wastes, which must be restricted to toilets and immediate double-flushing methods. The FDA provides a full list of limitations for RIT patients. Clearly, such treatment requires patient education and input from a team consisting of the medical oncologist, nuclear medicine department, and radiation safety officer. Overall, however, RIT is quite well tolerated, with minimal toxicities.

The initial phase I and II clinical trials of RIT defined the extent of disease activity and toxicity profiles. In 1999, Witzig et al reported on 34 patients with follicular/low-grade NHL, who were treated with Y-90 ibritumomab and showed a response rate of 82%, with 26% complete responses (CRs).[14] The median time to progression of disease was 12.9 months, with a response duration of 11.7 months. On long-term follow-up of those achieving a complete response, the median time to...
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progression and response duration was 45 and 44 months, respectively. Nine patients had a time to progression greater than 3 years, and after 7 years of follow-up, five patients remained in remission. Response in this trial seemed to be associated with tumor burden (i.e., number of nodal sites and size of tumor). Interestingly, neither response to prior chemotherapy nor age was a predictor for response to RIT. This is a novel concept, as normally in follicular lymphoma, each successive failed treatment brings a greater likelihood of failure. The investigators reported predictable infusion reactions, but the major toxicity was hematologic, which was short in duration and reversible. Cell count nadirs occurred at 7 to 9 weeks posttreatment, which is considerably later than when standard chemotherapy is administered. Human anti-mouse antibodies (HAMA) developed in 2% of patients, and there appeared to be no increased risk of myelodysplastic syndrome (MDS).

Kaminski et al conducted the initial trials of I-131 tositumomab in 59 patients with relapsed/refractory NHL.[15] Patients had elevated lactate dehydrogenase (LDH) and large tumor burdens, and some had even relapsed after autologous stem cell transplant (ASCT). Response rate was 71%, with a 34% CR rate. Median progression-free survival was 12 months, and 20.3 months for those achieving a CR. Excluding any intermediate/high-grade subjects, the response rate was even higher at 83%. At long-term follow-up, seven patients remain in CR from 3 to 5.7 years. Again, response to prior therapies had no ability to predict response to RIT. In fact, the median response rate was only 50% with prior therapies, compared to an 83% response to RIT.

Similar to the Y-90 ibritumomab study, the dose-limiting toxicity in this trial was hematologic.[15] The rate of HAMA in this study was higher, at 17%; this is thought to be due to extra doses of mouse antibody received via unlabeled tositumomab in the I-131 tositumomab protocol, compared to the Y-90 ibritumomab approach, which uses rituximab (a chimera). Only a small number of patients developed thyroid-stimulating hormone (TSH) abnormalities, indicating that prophylaxis worked well. On long-term follow-up, five patients developed MDS, one developed acute myeloid leukemia (AML), and three developed solid tumors. However, the role of RIT in these events is unclear, given that these patients were heavily pretreated, many with alkylating agents. In addition, the effectiveness of retreatment with RIT proved to be efficacious in this study, with a second remission occurring in 56% of cases, again made possible by a favorable side-effect profile.

In both the I-131 tositumomab and Y-90 ibritumomab studies, the activity in transformed low-grade disease seemed similar to that in low-grade phenotypes, although patient numbers have been small. In general, these studies included heavily pretreated patients with favorable performance status and advanced-stage disease. A noteworthy exclusion for RIT studies is patients with > 25% of bone marrow involvement or significant baseline cytopenias.

Overall, these early studies were encouraging, indicating that a single dose of RIT could produce a significant and durable response in previously refractory low-grade/transformed NHL with minimal toxicity and side effects. Also, there seemed to be the potential for activity in intermediate- or high-grade NHL as well as in bulky disease. These studies set the foundation for further investigations, leading to the FDA approval of RIT.

Radioimmunotherapy in Indolent Lymphoma

Pivotal Trials

In a pivotal multicenter phase III study conducted by Kaminski et al in 2001, 60 patients with extensively pretreated refractory indolent NHL and transformed NHL were treated with I-131 tositumomab, achieving an overall response rate of 65% and CR rate of 20%. The median duration of response for complete responders was not reached at 47 months of follow-up.[16] These data compare very favorably with a previous treatment CR rate of 28% and a median duration of response of 6.1 months. Patients in the study represented a difficult-to-treat population; at least two prior chemotherapy agents had failed, nearly all had advanced-stage disease, 65% had a tumor > 5 cm, and 88% had an International Prognostic Index (IPI) score > 2.

Adverse events were minimal, and HAMA was observed in only 8% of patients.[16] Only one patient developed abnormal TSH, and secondary MDS was seen in four patients. Again, it is not clear to what degree I-131 tositumomab contributed to the development of MDS, given that patients were heavily pretreated, often with alkylating agents. Hematologic toxicity was the primary toxicity, but only one patient needed to be hospitalized for neutropenia. (Again, patients with > 25% bone marrow involvement or cytopenias at baseline were excluded from this study.) This study illustrated the safety and efficacy of a single outpatient dose of I-131 tositumomab in poor-prognostic low-grade NHL patients—a vital finding for FDA approval.

A randomized controlled clinical trial compared Y-90 ibritumomab vs rituximab (375 mg/m² weekly for four doses) in 143 patients with relapsed or refractory low-grade follicular lymphoma/transformed NHL.[17] Y-90 ibritumomab proved statistically superior, with an overall response rate of 80%
compared to 56% in the rituximab arm. Similarly, CR was 30% in the RIT group vs 16% in the rituximab group. Time to progression was not significantly different, possibly due to the inadequate power of the trial; however, time to next treatment was longer in the Y-90 ibritumomab group. As expected, the only major toxicity difference between the two regimens was the hematologic toxicity seen in the RIT arm. This study presented evidence that Y-90 ibritumomab is a valuable therapy in heavily pretreated patients with low-grade/transformed low-grade lymphoma and was instrumental in the agent's achieving FDA approval.

Subsequent Safety and Efficacy Studies

As experience with these agents has increased, prolonged safety and efficacy analyses have been performed incorporating large numbers of patients who have been treated. Fisher et al performed an integrated efficacy analysis on five clinical trials encompassing 250 patients treated with I-131 tositumomab.[18] Overall, the population had received a median of four prior therapies, with 50% not responding to their last chemotherapy. Most had advanced-stage low-grade lymphoma, with 60% having bulky disease (≥ 5 cm).

The overall response rate was 56%, with a complete response of 30%. In multivariate analysis, failure to achieve a CR was associated with absence of response to last chemotherapy, elevated LDH, and bulky disease. Perhaps most importantly, 32% of patients were defined as having a durable response with a progression-free survival > 1 year. Surprisingly, 64% of the patients in this subgroup had disease that was considered refractory (no response or response < 6 months), 63% had stage IV disease, and 49% had bulky disease. Attaining a CR proved vital to obtaining a long-term durable response. In patients who achieved a CR, the median progression-free survival has not yet been reached (1.3-11.1 years). Generally speaking, among patients that responded, the length of response was longer than that obtained with previous therapies. This finding again contrasts what has up until now been observed in follicular lymphoma—ie, the inverse relationship between number of previous regimens and CR /duration of response.

A safety analysis of ibritumomab by Witzig et al included 359 patients spanning five clinical trials.[19] Patients tolerated the outpatient regimen very well; the primary toxicity was a myelosupression nadir at 7 to 9 weeks, with recovery by 1 to 4 weeks. The degree of hematologic toxicity was directly related to extent of bone marrow involvement, requiring less than 25% involvement by lymphoma, a platelet count greater than 150,000, and a neutrophil count greater than 1,500. Likewise, a hypocellular marrow should be excluded. Ibritumomab did cause a transient depletion of B cells for about 6 to 9 months. However this was well tolerated with no significant increase in severe infections or hospitalizations. The rate of human anti-mouse or chimera antibody was around 2% and did not correlate with any significant adverse event. This study outlined a favorable composite safety profile.

Gordon and colleagues have demonstrated that durable responses, similar to those observed by Fisher and colleagues with I-131 tositumomab, may also occur after treatment with ibritumomab tiuxetan.[20] Approximately 24% of responding patients had a time to progression of more than 3 years, including long-term responders with remission durations exceeding 5 years. Myelodysplasia has been of concern as a late toxicity of radioimmunotherapy. At baseline, the patients treated in these clinical trials of both RIT agents mostly had received prior alkylating agents and other aggressive therapies. Integrated analyses have suggested that the risk of MDS in patients treated with either tositumomab or ibritumomab tiuxetan did not exceed the baseline risk due to prior treatments.[21,22]

Activity in Rituximab-Refractory Disease

Witzig et al studied the utility of ibritumomab in follicular lymphoma that had previously proven refractory to rituximab.[23] A total of 57 patients who either did not respond to rituximab or had a short disease-free interval with the agent were enrolled. Approximately 75% had tumors greater than 5 cm and 19%, greater than 10 cm; 90% had stage III/IV disease, and 75% had grade II/III follicular lymphoma. Patients had received a median of four prior treatments. The overall response rate was 74%, with 15% achieving a CR and 94% showing a decrease in tumor size. Median time to progression in responders was 8.7 months. In patients who previously had a response to rituximab, the duration of response was significantly better with ibritumomab (11 vs 3 months, \( P = .001 \)). Similar results in rituximab-refractory lymphoma have been reported for I-131 tositumomab.[24] With a median follow-up of 3.3 years, the median progression-free survival was 10.4 months—24.5 months for responders, and not reached for CR patients.

Novel Concepts in RIT Retreatment

Few patients treated with RIT have been subsequently retreated with RIT. However, evolving
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evidence suggests that retreatment is safe and effective in certain situations. Early studies by Kaminski et al showed that retreatment was efficacious. To confirm these findings, this group conducted a follow-up study, retreating 32 patients who had had a prior response to I-131 tositumomab.[25] Overall, a response was seen in 56% of patients, with 25% of patients attaining a CR. Overall duration of response in those achieving CR was 35 months, which was actually longer than that seen with initial therapy (14.5 months). Five of the eight complete responders continue to be in CR at 22 to 69 months, illustrating that even with retreatment, durable responses are possible. All of the patients who responded had an initial response to the first round of I-131 tositumomab. The duration of response was not significantly different between the first and second treatments.

The toxicity profile was also similar in retreatment compared to initial treatments, with no increase in hematologic or nonhematologic adverse events including thyroid abnormalities and HAMA. However, the authors caution about a slight increase in severe infusion reactions. Five patients went on to develop MDS (16%), but again, these patients were heavily retreated and the contribution of I-131 tositumomab is uncertain.

Further study is required before radioimmunotherapy can be given routinely as retreatment following a prolonged response. In a retrospective analysis, Justice et al reviewed the records of 135 patients treated with ibritumomab tiuxetan who then went on to receive external-beam radiotherapy.[26] Results were reassuring, with minimal toxicity and a favorable response rate of 90% locally.

Upfront Therapy

The above early studies indicate significant and durable responses to RIT in relapsed follicular lymphoma or transformed lymphomas. The next logical hypothesis tested the utility of early (upfront) RIT for follicular lymphoma. The vast majority of experience in upfront radioimmunotherapy in this setting is with I-131 tositumomab. In 2005, Kaminski et al published a phase II clinical trial using tositumomab as upfront therapy for previously untreated follicular lymphoma.[27] A total of 76 patients with stage III/IV disease were enrolled. Around half of this group had disease > 5 cm at diagnosis. Most did not have B symptoms, and all had < 25% bone marrow involvement. Median age was 49, with only seven patients over 60, and 70% had grade 1 disease.

The overall response rate was 95%, with a 75% complete response rate. The 5-year progression-free survival rate was 59%, with a median progression-free interval of 6.1 years. When applied to complete responders, the 5-year progression-free survival increased to 77%, and 70% remained disease-free at 4.3 to 7.7 years. The 5-year rate of overall survival was 89%. Furthermore, 81% of complete responders were polymerase chain reaction (PCR)-negative for Bcl-2 expression at 6 months, which correlated with a progression-free survival of 5 years. Baseline tumor bulk (> 5 cm) and bone marrow involvement predicted CR, whereas only bone marrow involvement predicted decreased progression-free survival.

Hematologic toxicity with upfront tositumomab was less severe than that seen in studies of previously treated patients. However, the incidence of HAMA was greatly increased to 63%, as compared to 10%. The authors postulate that this may be due to the condition of the host immune system at time of treatment with tositumomab. An influenza-like syndrome that occurred in about 25% of patients seemed to correlate with HAMA. Otherwise these patients were asymptomatic. At 5 years of follow-up, the study revealed no cases of MDS. Subsequent analysis of these patients using the Follicular Lymphoma International Prognostic Index (FLIPI) demonstrated that the majority of these patients were not low risk, and that I-131 tositumomab as a single agent was effective even in high-risk FLIPI groups.[28]

• CHOP/Tositumomab—Tositumomab and CHOP (cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], prednisone) both have considerable activity as upfront therapy in follicular lymphoma, but could combining both regimens be even more effective, providing a synergistic effect? Would RIT work better with some element of cytoreduction first?

The Southwest Oncology Group (SWOG) conducted a phase II clinical trial to answer these questions by using initial CHOP chemotherapy followed by consolidation with tositumomab.[29,30] A total of 102 patients were enrolled with stage III or IV disease—stage II disease was also included if categorized as bulky (> 10 cm or more than one-third the chest diameter). Disease grade was not an exclusion criteria, and 11% had grade 3 follicular lymphoma. The mean age of participants was 52 (up to 84 years old). Following six cycles of CHOP chemotherapy, patients who achieved at least a partial remission and then had < 25% of bone marrow involvement were eligible for tositumomab consolidation.
Overall, patients tolerated the regimen well. Most of the toxicity observed was hematologic (39% grade 4 after CHOP chemotherapy, compared with 12% after tositumomab). At long-term follow-up, the few adverse events included a 9% rate of TSH elevation, with only one case of MDS and no cases of AML. The overall response rate to CHOP followed by tositumomab in patients with previously untreated advanced-stage follicular lymphoma was 90% with 69% complete remissions. What was most provocative about this study was that there seemed to be an improvement in progression-free and overall survival compared to prior studies. At 5-year follow-up, the progression-free survival rate was 67%, with an 87% overall survival rate, suggesting, for the first time in follicular lymphoma patients, an alteration in the natural disease course and a "flattening" of the survival curve (Figure 3). Furthermore, on post hoc analysis, progression-free survival was not affected by higher FLIPI scores.

Based on these encouraging results, SWOG and the Cancer and Leukemia Group B (CALGB) are conducting a phase III randomized controlled clinical trial in patients with advanced-stage, previously untreated follicular lymphoma (S0016), comparing CHOP plus concurrent rituximab vs CHOP followed by I-131 tositumomab. The results of this trial will likely define the optimal upfront regimen in follicular lymphoma.

**Fludarabine/Tositumomab**—Additionally, Leonard et al have reported favorable results using an alternative upfront radioimmunotherapy regimen.[31] A total of 31 patients with late-stage indolent lymphoma were treated with fludarabine (25 mg/m² for 5 days every 5 weeks for three cycles); 6 to 8 weeks later, a single dose of tositumomab was administered. Complete responses were seen in 86% of patients, with 83% attaining a molecular CR. After follow-up of 58 months, the median duration of response has not been reached. The 5-year progression-free survival rate is estimated at 56% (Table 1), but this measure was significantly associated with FLIPI score—79% in patients with low/intermediate-risk scores, as compared with 27% in those with high-risk scores.
Tolerability was similar to that seen in other upfront RIT studies. However, the HAMA rate, at 6%, was lower than previously described (ie, 63% in previously untreated patients receiving I-131 tositumomab). Larger multicenter studies are needed to further evaluate this regimen and others, including CVP followed by I-131 tositumomab.[32]

RIT in Aggressive Histologies

Not infrequently, indolent lymphoma transforms into a diffuse aggressive histology representing a unique therapeutic challenge with significant morbidity and mortality. This clinical scenario is uniformly associated with poor response to standard chemotherapy and even worse overall survival, with a median survival of less than 2 years. The only modality shown to improve outcomes in this setting is allogeneic or autologous stem cell transplant.[33] Transplant-related morbidity and mortality combined with refractoriness to chemotherapy illustrates the need for improved treatment modalities.

• Large-Cell Lymphoma—Zelenetz and colleagues reported on 71 patients whose disease had transformed to large-cell lymphoma.[34] After treatment with tositumomab, the overall response rate was 39% with a CR rate of 25%. Median duration of response was 20 months, with 24% of patients achieving a durable response (> 12 months). Although the response was not as impressive as that seen in follicular lymphoma, response rates compare favorably with numerous previous regimens for transformed disease. In addition to the Zelenetz study, many of the earlier phase I and II clinical trials of RIT included transformed disease. However, the number of patients per study was small, precluding definitive analysis. The CALGB is currently leading an intergroup trial evaluating ibritumomab tiuxetan in the treatment of transformed indolent lymphoma.

Morschhauser and colleagues have presented preliminary results of a phase II trial evaluating ibritumomab tiuxetan for patients with relapsed or refractory diffuse large B-cell lymphoma not appropriate for treatment with autologous transplantation.[35] Two cohorts of patients were evaluated: those previously treated with chemotherapy alone, and those previously treated with chemotherapy and rituximab. For the entire study population, the overall response rate was 44%; in the second cohort, this incidence was only 19%. Progression-free survival was approximately 6 months in patients who relapsed within 1 year of initial therapy.

Because of this favorable activity, several groups are evaluating RIT as consolidation after standard chemotherapy and rituximab for patients with de novo diffuse large B-cell NHL. SWOG S0433 is enrolling patients over age 60 with diffuse large B-cell lymphoma, and administering a single course of I-131 tositumomab in patients who respond to standard R-CHOP (rituximab plus CHOP) therapy. Similar studies are ongoing in Europe and at Memorial Sloan-Kettering Cancer Center using ibritumomab tiuxetan consolidation. Additionally, both SWOG and the Eastern Cooperative Oncology Group (ECOG) are conducting studies incorporating ibritumomab tiuxetan into therapeutic strategy for early-stage diffuse large B-cell lymphoma.

• Mantle Cell Lymphoma—Mantle cell lymphoma combines the chemoresistant properties of an indolent lymphoma with a more aggressive clinical pattern, representing a unique challenge in
therapeutics. Early studies of RIT included limited numbers of patients with mantle cell lymphoma, revealing mixed results. However, a phase II ECOG study of R-CHOP followed by ibritumomab showed promising results.[36] Most patients in this trial had advanced disease, with a median age of 60. After four cycles of R-CHOP, there was only a 14% CR rate and 58% partial response rate. In contrast, after ibritumomab, the response rate increased to 84%, with a CR rate of 45%. This study suggests a significant benefit for the addition of radioimmunotherapy to standard chemotherapy in mantle cell lymphoma.

More recently the Polish Lymphoma Research Group presented preliminary data on the treatment of 30 mantle cell lymphoma patients, 13 of whom were previously untreated. Patients received fludarabine, cyclophosphamide, and mitoxantrone for three to six cycles, followed by ibritumomab consolidation.[37] Overall, 22 of 29 patients achieved a CR, with 10 of 13 who were newly diagnosed achieving a CR. Thirteen patients continue in CR at 8 to 20 months.

Role of RIT in Transplant Therapy

• Conditioning Regimens—Although chemotherapy followed by stem cell transplantation has proven largely ineffective in mantle cell lymphoma, Gopal et al illustrated a role for RIT combined with high-dose chemotherapy followed by autologous stem cell support.[38] Sixteen patients with measurable relapsed or refractory mantle cell lymphoma were treated on phase I/II trials. The following high-risk features were observed in this population: median of three prior therapies, all had stage IV disease, half had high/intermediate IPI scores (with half having an elevated LDH), and about 30% had B symptoms. Approximately 44% of patients had been refused transplant outside of these trials.

One potential criticism of this study was the exclusion of patients with bulky disease. Overall, however, patients did not have favorable risk factors. Because the trials involved dose escalation, not all patients received the same amount of RIT or chemotherapy, but most received the maximum tolerated dose of I-131 tositumomab (25 Gy). A majority received the higher doses of chemotherapy-60 mg/kg of etoposide and 100 mg/kg of cyclophosphamide. This was followed by autologous stem cell rescue.

Adverse events were similar to those undergoing a traditional conditioning regimen prior to autologous stem cell transplant. Results were very encouraging, with an overall response rate of 100% and a CR rate of 91%. The 3-year overall survival rate was 93%, with a 3-year progression-free survival of 61%. The molecular response rate was 60%. These results compare favorably to previous results of autologous transplant in mantle cell lymphoma.

Autologous transplant often involves total-body irradiation (TBI), which results in higher than desired doses to vital structures with potential underdosing of lymphoma aggregates. RIT represents a rational alternative to TBI, providing a more targeted radiotherapy prior to transplant. Furthermore, RIT allows for in vivo purging of residual lymphoma in the bone marrow.

Press et al reported the use of I-131 tositumomab combined with etoposide and cyclophosphamide followed by stem cell rescue in patients with relapsed NHL as part of a phase I/II clinical trial.[39] Most patients had advanced (stage III/IV) disease; 42% had B symptoms and 60% had low/intermediate-risk disease, whereas 37% had high/intermediate risk. Follicular lymphoma was the most common subtype (72%), with 28% having an aggressive phenotype (mantle cell, transformed disease, or diffuse large B-cell lymphoma). This study included eight patients with primary refractory disease, many of whom had been rejected by other transplant programs. Overall, patients were heavily pretreated with a median of three previous regimens. The maximum tolerated dose of I-131 tositumomab was 25 Gy (maximum of 20 Gy to solid organs). I-131 tositumomab administration was followed by cyclophosphamide at 100 mg/kg and etoposide at 60 mg/kg, then by autologous stem cell transplant.

Overall toxicities were similar to traditional conditioning regimens using TBI. However, on historical comparison, there were fewer deaths with the I-131 tositumomab regimen (17.6% vs 7.6%). One case of MDS was reported. The study revealed an 87% response rate and a 77% CR rate. Progression-free survival at 2 years was 68%, and 69% of patients had a molecular response after transplant (PCR-negative). Compared to historical patients who underwent traditional conditioning with TBI/etoposide/cyclophosphamide, this approach produced a significant improvement in overall and progression-free survival posttransplant. Furthermore, patients receiving I-131 tositumomab had more aggressive histologies, greater tumor bulk (> 5 cm), higher-stage disease, and were more heavily pretreated than observed in traditional conditioning protocols. On further analysis, the superiority of conditioning with I-131 tositumomab in terms of progression-free survival and overall survival was seen in both aggressive and indolent lymphomas.
• **Larger Trial**—In a more recent study by Gopal et al, 125 patients with refractory/relapsed follicular or transformed disease received either high-dose tositumomab (27 patients on clinical trials) or conventional high-dose chemotherapy plus external-beam radiotherapy (98 patients in reference group) followed by autologous stem cell transplant.[40] Patients in the standard chemotherapy group received a variety of conditioning regimens; the most common was TBI and high-dose cyclophosphamide/etoposide. The investigators observed a 93% overall response rate with an 85% CR rate in the cohort conditioned with tositumomab.

In terms of overall survival, the group treated with high-dose tositumomab showed statistically superior results compared to those of conventional conditioning regimens. The survival benefit was superior even excluding the 100-day posttransplant, nonrelapse mortality, which was higher in the traditionally treated group but did not account for the observed difference ($P = .03$). Progression-free survival was also superior in the RIT group compared to the high-dose chemotherapy cohort ($P = .06$). The cohort receiving RIT had a statistically higher LDH and IPI score, adding further strength to the superiority of the RIT conditioning regimen. Toxicities in the two groups were similar.

Transplant-related mortality was higher in the high-dose chemo/radiotherapy group (11.2% vs 3.7%), but this difference was not significant.

In summary, based on observations at the Fred Hutchinson Cancer Center, high-dose RIT appears to be an efficacious and safe regimen for conditioning prior to autologous stem cell transplant in patients with relapsed or refractory follicular lymphoma, with improved overall survival and progression-free survival compared to traditional conditioning regimens. A randomized, prospective clinical trial would be optimal to confirm this finding. Nevertheless, evidence is mounting for the utility of RIT, not only as upfront therapy for follicular lymphoma, but also as a conditioning regimen for stem cell transplant.

• **Alternative Regimens**—Given the effectiveness of high-dose RIT alone as a conditioning regimen, standard-dose RIT has also been combined with standard high-dose chemotherapy prior to autologous stem cell transplant in lieu of total-body radiotherapy. Vose and colleagues reported a phase I clinical trial using standard BEAM (high-dose carmustine [BCNU], etoposide, cytarabine [Ara-C], melphalan [Alkeran]) with outpatient I-131 tositumomab as part of conditioning regimen.[41] A total of 23 patients with refractory or relapsed CD20+ NHL enrolled, 48% of whom had primary refractory disease, which portends a particularly poor prognosis. Most patients had diffuse large B-cell lymphoma, but a proportion had follicular lymphoma.

Beginning on day 19, patients received a dosimetric dose of tositumomab, followed by a therapeutic dose on day 12; total-body doses ranged from 0.3 to 0.75 Gy. Patients then received standard BEAM on days 6 through 1, followed by autologous stem cell transplant. At day +100, the CR rate was 57%. The 3-year overall survival rate was 55%, and event-free survival was 39%, which compares favorably to historical controls at 1% to 20% in this population. Toxicity was similar to that of BEAM alone, although 35% developed asymptomatic HAMA. A larger protocol is implementing a 0.75 Gy total-body dose of I-131 tositumomab at the University of Nebraska, and the BMT Clinical Trials Network is currently conducting a randomized trial comparing BEAM plus rituximab to BEAM plus I-131 tositumomab.

In an alternative regimen, Nademanee et al reported on 31 patients with advanced-stage NHL, most of whom had experienced failure of first CR. In addition, 16% had induction failures, with approximately 39% having follicular lymphoma and 45% diffuse large B-cell histology.[42] Patients were treated with Y-90 ibritumomab on day 14 (dosimetry beginning day 21), then high-dose etoposide (40-60 mg/m$^2$) on day 4, and cyclophosphamide (100 mg/m$^2$) on day 2, followed by autologous transplant. The Y-90 ibritumomab dose was capped at 100 mCi and designed so that the maximum dose absorbed by vital organs was 1,000 cGy. The 2-year overall survival rate is estimated at 92%, with a relapse-free survival of 78% at 22-month follow-up. Toxicity was similar to that observed in historical controls using traditional regimens. Importantly, there was no delay to engraftment and, specific to RIT recipients, no cases of HAMA were documented. This study also demonstrated the tolerability and effectiveness of RIT when added to traditional conditioning regimens.

In a nonrandomized retrospective analysis at the City of Hope, Y-90 ibritumomab plus chemotherapy was compared to a standard TBI-plus-chemotherapy regimen. The results suggested a survival advantage for patients treated with RIT prior to transplant.[43] These findings will need to be repeated in a randomized controlled trial.
• **Allogeneic Stem Cell Transplant**—RIT has also been employed in allogeneic transplant. Gopal et al conducted a phase II clinical trial of Y-90 ibritumomab in reduced-intensity allogeneic transplant. A total of 14 patients with a wide variety of CD20+ subtypes were treated with ibritumomab followed by fludarabine at 30 mg/m² and TBI (2 Gy).[44] Patients were unique in that five had greater than 25% bone marrow involvement, five had undergone a previous autotransplant, and all were considered chemoresistant. The study showed three complete responses and four partial responses. At a follow-up of 6 months, 64% are alive with 50% progression-free. Further follow-up for these studies is essential to determine the benefit over current standard therapy in terms of overall survival and ultimate morbidity.

**Future Directions and Conclusions**

Rituximab has had a tremendous impact on the treatment of CD20+ NHL, potentially changing the natural history of follicular lymphoma. However, a substantial proportion of patients spanning the various histologic subtypes of NHL still fail to respond or relapse after rituximab therapy. Radioimmunotherapy is an emerging option for this group of patients, and in fact, has the highest single-agent activity observed in lymphoma therapy. Recent studies have suggested that RIT works best earlier in the treatment continuum and may have particular utility as upfront therapy in follicular lymphoma, especially when combined with chemotherapy. Active multicenter clinical trials continue to enroll patients to determine the optimal timing of RIT in indolent NHL and to confirm observations of activity in aggressive subtypes. RIT has also proven to be a safe and effective agent for conditioning regimens in autologous transplant regimens for B-cell NHL. Hopefully, mature results of these clinical trials will define the optimal use of RIT and increase the numbers of patients who benefit from these highly active agents.

**Disclosures:**

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