

Editorial

Radioimmunotherapy for Non-Hodgkin's Lymphoma

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The survival of patients with follicular non-Hodgkin's lymphoma has not significantly changed in the past 30 years, and the disease remains essentially incurable (1). The recent introduction of monoclonal antibody-based therapies may change this sobering statistic. Rituximab, an anti-CD20–chimeric monoclonal antibody, was approved by the Food and Drug Administration in 1997 for use in patients with refractory or relapsed low-grade or follicular non-Hodgkin's lymphoma and compares favorably to single-agent chemotherapy (2). However, the vast majority of responses to rituximab are incomplete: at least 50% of patients do not respond, and all patients with follicular non-Hodgkin's lymphoma will experience disease progression at some point after rituximab therapy.

A rational approach to enhance the efficacy of anti-CD20 antibodies involves conjugating them to cytotoxic radionuclides. Because of the inherent radiosensitivity of indolent lymphoma cells, radioimmunoconjugates have the ability to provide direct cytotoxicity even if antibody-dependent cellular cytotoxicity, a major mediator of rituximab activity (3), is impaired. Furthermore, when using radioimmunotherapy, the “crossfire effect,” which delivers radiation to unbound neighboring cells (*e.g.*, inaccessible to antibody due to poor vascularization, or with insufficient antigen expression), results in direct cytotoxicity.

The first radioimmunoconjugate, yttrium-90 ibritumomab tiuxetan (Zevalin, BiogenIdec, Cambridge, MA), was approved by the Food and Drug Administration in February 2002 for the treatment of patients with relapsed or refractory B-cell low-grade or transformed non-Hodgkin's lymphoma, including patients with rituximab-refractory follicular non-Hodgkin's lymphoma. A phase III study compared ⁹⁰Y ibritumomab tiuxetan with rituximab in 143 patients (4). The overall response rate was 80% (complete response 30%) for the ⁹⁰Y ibritumomab tiuxetan group *versus* 56% (complete response 16%) for the rituximab group, statistically demonstrating superiority of the radioimmunoconjugate. However, there was no statistically significant benefit in response duration or survival between the two groups.

Tositumomab is an IgG murine monoclonal antibody that also binds to the CD20 antigen and may be linked covalently with iodine-131 to produce the radioimmunoconjugate ¹³¹I tositumomab (Bexxar, Corixa, Seattle, WA; and Glaxo SmithKline, Philadelphia, PA). As with ⁹⁰Y ibritumomab tiuxetan, ¹³¹I tositumomab is administered over an 8 to 15-day period. To prevent ¹³¹I from concentrating in the thyroid gland, blockade (SSKI, Lugol solution, or potassium iodide tablets) is given for ~30 days beginning the day before commencing therapy. An unlabeled dose of tositumomab is delivered over 1 hour to block circulating B lymphocytes, optimizing the biodistribution of the radiolabeled antibody. This is immediately followed by a dosimetric dose (5 mCi) of ¹³¹I tositumomab to determine the whole-body clearance of the radioimmunoconjugate. A total of three whole-body gamma counts, one immediately after dosimetric dosing, one 2 to 4 days later, and one 6 to 7 days later, are obtained. Because iodine may be dehalogenated by normal tissues at variable rates, dosing of ¹³¹I tositumomab is calculated to limit the whole-body radiation dose to 75 cGy. The actual ¹³¹I activity administered to each patient to achieve this desired total body dose has varied significantly in clinical trials of ¹³¹I tositumomab, emphasizing the importance of patient-specific dosimetry when using this compound.

As with ⁹⁰Y ibritumomab tiuxetan, patients with significant bone marrow involvement by non-Hodgkin's lymphoma (>25%) or with compromised hematopoiesis should not be treated with ¹³¹I tositumomab therapy. Additionally, because of concern over potential pulmonary toxicities, patients with pleural effusions have been ineligible for clinical trials of ¹³¹I tositumomab.

In the current issue of “Clinical Cancer Research,” Davis *et al.* present final results of a randomized, multicenter study comparing the efficacy and safety of the ¹³¹I tositumomab regimen to unlabeled tositumomab in patients with relapsed/refractory CD20-positive non-Hodgkin's lymphoma. Importantly, unlabeled tositumomab dosing was not optimized for response evaluation for this study. Seventy-eight patients were enrolled with a median age of 55 years. Seventeen percent of these patients experienced transformation to an aggressive histology before enrollment. Confirmed responses were documented in 55% of patients who received ¹³¹I tositumomab (including 33% complete responses) and 17% of patients who received unlabeled tositumomab (8% complete responses). The median duration of confirmed responses for the ¹³¹I tositumomab-treated patients had not been reached, whereas for the unlabeled tositumomab treated patients, it was 18 months. This study documented the superiority of the radioimmunoconjugate over unlabeled tositumomab in a rituximab-naïve patient population and confirmed the short-term safety profile of ¹³¹I tositumomab.

Based partially on this trial, the ¹³¹I tositumomab regimen was approved by the Food and Drug Administration in June 2003 for the treatment of patients with CD20-positive, follicular

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non-Hodgkin's lymphoma, both with and without transformation, whose disease is refractory to rituximab and has relapsed after chemotherapy. Despite promising clinical results and excellent tolerability, the use of both ^{131}I tositumomab and ^{90}Y ibritumomab tiuxetan has been limited. Several key questions regarding these agents remain, and these unresolved issues likely contribute to the hesitancy of using these agents in the clinic.

1. What Is the True Long-Term Toxicity of These Agents, Particularly the Cumulative Risk of Secondary Myelodysplasia? Because of crossovers, 61 patients eventually were treated with ^{131}I tositumomab in the Davis trial. Despite thyroid protection mandated in the protocol, thyroid supplementation has been started in 3 of 61 ^{131}I tositumomab-treated patients; human antimouse antibody was detected in 13% of ^{131}I tositumomab-treated patients and 25% of unlabeled tositumomab-treated patients. The implications of human antimouse antibody development are unknown, but in theory, this might limit the ability to use other murine monoclonal antibody treatments in the future.

More importantly, thus far, four of these patients (7%) have developed myelodysplasia or secondary acute myelogenous leukemia, with a median follow-up of 42 months. Myelodysplasia is a major long-term toxicity associated with chemotherapy and radiation therapy in patients with non-Hodgkin's lymphoma and is almost universally fatal. In one series of patients treated with low-dose external beam total body irradiation for non-Hodgkin's lymphoma, the 15-year estimated cumulative incidence of myelodysplasia was 17% (5). All of these patients were also treated with cytotoxic chemotherapy, suggesting that combined modality therapy significantly increases the incidence of subsequent stem cell disorders. The highest risks of secondary myelodysplasia have been reported in the setting of autologous stem cell transplantation, where the cumulative incidence may exceed 15% (6). Importantly, a plateau in the incidence curve has not been observed with prolonged follow-up (10 years) of these studies. In a preliminary report of 773 patients treated with ^{131}I tositumomab, 21 patients developed myelodysplasia, with an annualized incidence of 1.45% per year, which compares favorably to patients treated with alkylating agent chemotherapy (7). However, long-term follow-up of this large cohort of patients is clearly required to definitively determine the incidence of this fatal complication and the degree to which radioimmunotherapy contributes to this risk.

2. What Is the Optimal Timing of Radioimmunotherapy in the Treatment of Indolent Non-Hodgkin's Lymphoma? Two recent trials suggest that using radioimmunotherapy earlier in the disease course may provide optimal benefit. At the University of Michigan, 76 patients with previously untreated follicular non-Hodgkin's lymphoma received ^{131}I tositumomab therapy on a phase II study (8). Fifty-six patients (74%) had a confirmed complete response. Forty-five of these patients remained in complete response with a follow-up of 30 to 66 months. The 5-year progression-free survival in this series was estimated to be 62.3%, which compares very favorably to conventional chemotherapy.

The Southwest Oncology Group recently reported the outcome of a novel chemoradioimmunotherapeutic approach, combining standard induction chemotherapy [cyclophosphamide-

Adriamycin-vincristine-prednisone (CHOP)] followed by consolidation with ^{131}I tositumomab. This phase II trial included 90 patients with previously untreated advanced-stage, follicular non-Hodgkin's lymphoma (9). The overall response rate to the entire treatment regimen (chemotherapy + ^{131}I tositumomab) was 90%, including 67% complete remissions. The 2-year progression free survival was estimated to be 81%, which is better than observed historically with chemotherapy alone or chemimmunotherapy.

As expected, in contrast to the studies in relapsed and refractory disease, more patients develop human antimouse antibody after early ^{131}I tositumomab therapy. Thus far, there have been no reports of myelodysplasia after this therapy when given to previously untreated patients. CHOP, followed by ^{131}I tositumomab for patients with previously untreated advanced-stage follicular non-Hodgkin's lymphoma, is being compared with the CHOP-rituximab regimen in an ongoing phase III trial conducted by the Southwest Oncology Group and the Cancer and Leukemia Group B. A positive outcome of this study may change standard of care for *de novo* follicular non-Hodgkin's lymphoma; however, it will require many years of follow-up before we have definitive results.

3. What Is the Role of Radioimmunotherapy in the Treatment of More Aggressive Histologies of Non-Hodgkin's Lymphoma, Potentially in Combination with Chemotherapy and Novel Biological Agents? The median survival after histologic conversion from indolent to aggressive lymphoma in most series is <2 years. Zelenetz *et al.* (10) analyzed 71 patients with histologic transformation of indolent lymphoma treated with ^{131}I tositumomab on five different clinical trials. The overall response rate to a single treatment with ^{131}I tositumomab in this setting was 39%, with a median response duration of 20 months. Twenty-four percent of these patients had response durations of >1 year. Given the relatively low toxicity profile of the ^{131}I tositumomab regimen compared with autologous stem cell transplantation (11), the radioimmunotherapy approach holds significant promise for patients with transformed disease.

Both ^{131}I tositumomab and ^{90}Y ibritumomab tiuxetan are currently under evaluation for *de novo* aggressive non-Hodgkin's lymphoma. The Southwest Oncology Group is planning a trial with ^{131}I tositumomab as consolidation for patients > 60 years of age with large B-cell lymphoma responding to standard CHOP chemotherapy with rituximab.

4. What, if Any, Is the Role of Myelablative Radioimmunotherapy and Autologous (or Allogeneic) Stem Cell Support in the Treatment of Non-Hodgkin's Lymphoma? Given the ability to perform patient-specific dosimetry and the potential for *in vivo* purging of residual bone marrow lymphoma, ^{131}I tositumomab may be an ideal agent to use as a component of myeloablative high-dose therapy with autologous stem cell support. Press *et al.* (12) in Seattle, Washington, have combined ^{131}I tositumomab with etoposide and cyclophosphamide followed by autologous stem cell transplantation in 52 patients with relapsed B-cell lymphomas. The estimated overall survival and progression-free survival of all treated patients at 2 years was 83 and 68%, respectively, with this approach. A cohort of 16 patients with mantle cell lymphoma, a disease generally resistant to high-dose therapy with autologous rescue,

had particularly promising preliminary results (13). Additional studies with these combinations in various non-Hodgkin's lymphoma histologies are ongoing, with preliminary results superior to conventional conditioning regimens.

5. Can One Safely Retreat Patients with Radioimmunotherapy, and What Is the Efficacy of Re-treatment? This is unknown, and currently, the subject of early-stage trials.

Therefore, ^{131}I tositumomab represents one of the most active single agents for the treatment of recurrent indolent and transformed B-cell non-Hodgkin's lymphoma. Most states now permit administration of ^{131}I tositumomab on an outpatient basis, and availability is widespread. There is no data comparing the outcome of the two commercially available radioimmun-conjugates (a proposed trial may commence soon), but the activity of these two compounds appears to be remarkably similar when comparing the phase II and pivotal trials results. The role of radioimmunotherapy needs to be defined before the optimal agent can be defined. Until we have sufficient data to answer these key questions, the therapeutic promise of these agents will not be fully realized.

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