Evidence Mounts for the Efficacy of Radioimmunotherapy for B-Cell Lymphomas

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This issue of *Journal of Clinical Oncology* presents two articles that contribute substantially to the accumulating evidence documenting the important therapeutic role that radioimmunotherapy (RIT) can play in the management of B-cell lymphomas, particularly indolent lymphomas.^{1,2} Radiolabeled monoclonal antibodies were first shown to possess high levels of clinical activity in patients with relapsed or refractory B-cell lymphomas,³⁻⁶ including those refractory to rituximab^{7,8} and chemotherapy.⁹ More recently, several single-arm studies have demonstrated that upfront RIT administered either alone or with chemotherapy to previously untreated indolent non-Hodgkin's lymphoma (NHL) patients produces overall response rates of 90% to 100%, complete response rates of 60% to 95%, and durable remissions.¹⁰⁻¹³

In view of these impressive findings, phase III trials incorporating RIT as part of frontline therapy for indolent NHL were opened both in the United States and Europe. In this issue, Morschhauser et al¹ present impressive evidence from the first of these phase III randomized studies. In this trial, 414 patients in either partial remission (PR) or complete remission (CR) after a variety of chemotherapy induction regimens (chlorambucil; cyclophosphamide, vincristine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]; fludarabine or rituximab combinations) were randomly assigned to either consolidation with RIT (consisting of two doses of rituximab 250 mg/m² followed by yttrium-90 [⁹⁰Y]-ibritumomab tiuxetan) or no consolidation. RIT dramatically improved the median progression-free survival (PFS) in the total patient population (36.5 v 13.3 months with no RIT; $P < .0001$), and this advantage was observed regardless of whether patients were in PR (29.3 v 6.2 months with no RIT; $P < .0001$) or CR (53.9 v 29.5 months with no RIT; $P = .015$) at the time of consolidation. Nearly all subgroups of patients seemed to benefit regardless of prognostic score (Follicular Lymphoma International Prognostic Index score) or chemotherapy induction regimen. Furthermore, RIT consolidation converted 77% of patients who were in PR after induction chemotherapy to CR after RIT. The RIT consolidation regimen was exceptionally well tolerated aside from expected reversible cytopenias (eg, stage 3 or 4 neutropenia in 67% of patients, with stage 3 or 4 infections in 8%).

This study exhibits many important strengths. It is a large, prospective, multinational, intergroup, randomized, phase III trial that seems to have been extremely well organized and rigorously monitored. The two treatment groups were well balanced for important patient characteristics. The study convincingly demonstrated, for the first time to my knowledge, in a randomized fashion that consolida-

tion therapy with ⁹⁰Y-ibritumomab tiuxetan after induction chemotherapy markedly prolongs PFS in patients with previously untreated stage III or IV follicular lymphoma (FL) and prompted the approval of this agent for frontline consolidation therapy by the major regulatory agencies in Europe.

Although the report by Morschhauser et al¹ is clearly a landmark study, some weaknesses are worth noting. The multiplicity of induction chemotherapy regimens allowed and the relatively small sizes of the resultant subgroups make evaluation of end points for each individual regimen problematic because of the limited statistical power within each subgroup. Although single-agent chlorambucil and rituximab plus CHOP (R-CHOP) may both induce apparent clinical CRs in patients with NHL, it is quite conceivable that the depth of CR or magnitude of minimal residual disease remaining after induction is quite different and that this may impact remission duration and PFS. In addition, overall survival is not yet statistically different between the two treatment groups with the current short follow-up period (median follow-up time, 3.5 years). However, the largest unresolved questions relate to interpretations of the findings in the context of current standards of practice for FL involving rituximab. Only 15% of the patients enrolled onto this trial received rituximab as part of induction therapy, and in this small subgroup, there is not yet a statistically significant improvement in PFS in favor of ⁹⁰Y-ibritumomab tiuxetan consolidation. Because administration of rituximab with each cycle of induction chemotherapy has become a worldwide standard based on the documented superiority of this approach over chemotherapy alone,¹⁴⁻¹⁶ it is unclear whether the benefits of consolidation RIT apply to patients treated with modern induction paradigms. Another important unresolved issue is how the application of consolidation RIT would compare with administration of extended rituximab (maintenance) therapy, which has demonstrated impressive efficacy in prolonging PFS in several trials of relapsed FL and in studies of upfront cyclophosphamide, vincristine, and prednisone chemotherapy without rituximab during induction.^{17,18} Randomized studies will eventually be required to investigate the relative benefits of frontline consolidation with RIT, maintenance rituximab, or a combination of the two approaches in patients with FL.

A cautionary note must be added concerning the administration of large quantities of unlabeled cold anti-CD20 antibodies immediately before radiolabeled anti-CD20 antibodies based on a recent publication by Gopal et al.¹⁹ On the other hand, it is clear that a priming dose of unlabeled anti-CD20 antibody administered before

the radioactive anti-CD20 antibody is necessary to optimize radiolabeled antibody concentrations in tumor sites,^{4,20} presumably by partially saturating easily accessible B cells in the blood and the spleen and permitting sufficient radiolabeled antibody to bypass these sites and penetrate less accessible compartments (eg, lymph nodes, large tumor masses). Yet, there is clearly a point beyond which extra cold antibody is deleterious as a result of blocking of CD20 antigenic epitopes. Gopal et al¹⁹ found that serum from patients with distant exposures to rituximab blocked binding of iodine-131 (¹³¹I)-tositumomab (anti-CD20) antibodies at concentrations as low as 7 μ g/mL in vitro. Pre-clinical studies in three mouse xenograft models (Granta, FL-18, and Ramos) also demonstrated that rituximab pretreatment significantly reduced B-cell NHL targeting and tumor control by CD20-directed RIT but not by radiolabeled antibodies targeting unrelated cell surface antigens. These findings suggest that, in some clinical circumstances, ambient rituximab concentrations may impair the clinical efficacy of CD20-directed RIT. If verified, one approach might be to omit rituximab from the last one or two of cycles of therapy before RIT, as recently proposed by Jonathan Friedberg of the Southwest Oncology Group in a phase II study (S0801) that uses R-CHOP induction for four cycles followed by two cycles of CHOP without rituximab, then consolidation with ¹³¹I-tositumomab, and finally 4 years of maintenance rituximab. Alternatively, one could choose to target an alternative B-cell surface antigen with RIT, such as CD19, CD22, or CD45 (with stem-cell rescue).^{19,21,22} Further information on the role of upfront RIT in indolent NHL will soon be available from a large US intergroup study coordinated by the Southwest Oncology Group (S0016) that has randomly assigned untreated FL patients (grades 1, 2, and 3) to either six cycles of R-CHOP or six cycles of CHOP followed by ¹³¹I-tositumomab consolidation. To date, 535 of 550 planned patients have been enrolled onto this trial.

In the second RIT study reported in this issue, Devizzi et al² report on 30 patients with B-cell NHL (FL, *n* = 12; diffuse large B-cell lymphoma [DLBCL], *n* = 10; mantle cell lymphoma, *n* = 3; other histologies, *n* = 5) treated with five sequential cycles of chemotherapy followed by high-dose ⁹⁰Y-ibritumomab tiuxetan and peripheral-blood autologous stem-cell transplantation (ASCT). The chemotherapy component of this regimen consisted of three cycles of a CHOP-like or a dexamethasone, high-dose cytarabine, and cisplatin–like regimen, one cycle of high-dose cyclophosphamide (4 to 7 g/m²), and one cycle of high-dose cytarabine (12 to 24 g/m²). The RIT regimen was intended to be myeloablative, and patients underwent rescue by infusion of autologous peripheral-blood stem cells on days 7 and 14 after RIT. At enrollment, five patients were chemotherapy naïve, seven patients had de novo refractory lymphoma, eight patients had experienced relapse after one prior chemotherapy regimen, and 10 patients had experienced relapse after more than one prior regimen. The five chemotherapy-naïve patients were considered high risk, including three patients with DLBCL, one patient with grade 3B FL, and one patient with Richter's transformation. Nineteen of the patients were considered to have too many comorbidities to undergo standard ASCT. Six of the patients were older than 65 years, and six had recent severe pulmonary infections. In vivo purging was successful in rendering 92% of the grafts polymerase chain reaction negative. Thirteen patients were treated at a ⁹⁰Y-ibritumomab tiuxetan dose of 0.8 mCi/kg (twice the dose approved by the US Food and Drug Administration for nonmyeloablative therapy), and 17 patients were treated at a dose of 1.2 mCi/kg (three times

the approved dose). With a median follow-up time of 30 months, the overall survival rate is 87%, and the event-free survival rate is 69%. High-dose RIT was well tolerated at both dose levels, with moderate cytopenias of short duration being the most common adverse effects. The double stem-cell infusion seemed successful in ameliorating both the extent and duration of cytopenias. Indeed, half of the patients did not develop grade 4 neutropenia or require platelet transfusions. Only three patients required hospitalization, all for febrile neutropenia. None of the 30 patients were reported to have any nonhematologic toxicities of any grade other than grade 1 to 2 nausea/vomiting in four patients.

These results confirm and extend the remarkable tolerability and efficacy of high-dose RIT with ASCT reported using either ¹³¹I-tositumomab²³⁻²⁵ or ⁹⁰Y-ibritumomab tiuxetan.^{26,27} Unique features of the current trial include integration of high-dose ⁹⁰Y-ibritumomab tiuxetan into the sequential intense chemotherapy regimen developed in Milan and the use of a double infusion of peripheral-blood stem cells. As in previous high-dose RIT trials, the results to date are extremely encouraging, although the median follow-up time is still relatively short, especially since more than half of the patients had indolent lymphoma and seven patients were treated as part of upfront induction. As with all studies, there are some methodologic limitations of the current trial. First, the heterogeneity of the small patient population enrolled confounds interpretation of the efficacy results because the disparate histologies (DLBCL, FL, mantle cell lymphoma, small lymphocytic lymphoma) and clinical settings (de novo, primary refractory, and relapsed) have variable natural histories. Second, the median follow-up time is short (30 months), and it is likely that the efficacy results will become less impressive with longer observation and that delayed toxicities (myelodysplasia and second malignancies) may emerge. Third, the definition of maximum-tolerated dose (MTD) used in this study is dubious. Rather than basing the MTD on actual observed adverse events, as is standard in clinical trials, dose escalation was truncated in this study because of mathematical calculations estimating that 11 of 17 patients in the 1.2-mCi/kg cohort exhibited an estimated absorbed dose close to the published dose-limiting radiation threshold (*D_L*) of the heart wall, liver, kidney, or lungs. As the data from this trial clearly show, these *D_L* values, which are based on high-dose rate external-beam irradiation,²⁸ may not apply to studies of RIT. Basic radiation research has established that an important determinant of the magnitude of damage inflicted by irradiation of a tissue depends on the amount of ionizing radiation delivered per unit of time (the dose rate).²⁹ Conventional fractionated external-beam radiotherapy results in the delivery of radiation at a relatively high dose rate (eg, 0.75 to 2 Gy/min) for short periods of time, separated by intervals of hours or days with no irradiation. In contrast, RIT delivers radiation at an exponentially declining low dose rate (usually < 0.003 Gy/min) that is several orders of magnitude lower than that of external-beam radiotherapy and delivers this irradiation continuously for days or weeks as the bound isotope decays.^{29,30} Some tissues, including most critical normal organs, are more affected by the dose rate effect than other tissues (eg, bone marrow, lymphoma) that are sensitive to irradiation even when it is delivered at a low dose rate. It is this dose rate effect that permits RIT to be so effective for hematologic malignancies while causing minimal nonhematologic toxicity. With these principles in mind, it is inappropriate, in my view, to apply *D_L* limits derived from high-dose rate external-beam irradiation to studies of RIT without experimental

validation because they will likely overestimate the amount of normal tissue toxicity, as exemplified by this study. Instead, MTDs in clinical trials should be based on actual observed data rather than theoretical extrapolations. The absence of any nonhematopoietic toxicities of any grade (except four patients with mild nausea out of 30 patients), despite the presence of serious pre-existing comorbid cardiopulmonary conditions in many of the patients, clearly indicates that there is still a lot of room for potential dose escalation for the RIT component of this regimen. Despite this quibble, it is clear that the current regimen is effective and well tolerated, and it must be admitted that the high cost of RIT may limit further dose escalation more than toxicities.

One unresolved debate is whether high-dose RIT studies performed in the setting of ASCT should rely on individualized dosimetry or whether the simpler approach of weight-based dosing (mCi/kg of body weight), as used in the Devizzi et al² study, will suffice. Because of great variability from patient to patient in the estimated absorbed dose estimates to critical normal organs at a given antibody dose, most investigators who have conducted high-dose RIT studies in which the doses were pushed to true dose-limiting non-hematologic toxicities have believed that basing radionuclide dosing on individualized dosimetry is safest and optimizes both efficacy and toxicity profiles.²³⁻²⁷ However, Devizzi et al² have clearly shown in their report that it is possible to double or triple the current standard dose of ⁹⁰Y-ibritumomab tiuxetan using the simpler weight-based dosing paradigm, without encountering dose-limiting nonhematologic adverse events. In their hands, individualized dosimetry was not necessary and did not predict toxicities, presumably because they are still well below the true MTD defined by conventional evidence-based criteria.

Together, these two studies confirm and extend prior data demonstrating the tremendous potential of RIT for the treatment of B-cell NHL at diagnosis and after relapse at both conventional and myeloablative doses. Despite the overwhelming body of evidence that has accumulated, however, RIT remains underused in the United States and other countries. The reasons for this underuse have been widely debated but seem to be related, at least partially, to logistic issues involved in transfer of care from the hematologist/oncologist to the nuclear medicine physician, concerns about inadequate reimbursement by Medicare for RIT, and exaggerated emphasis on delayed effects such as marrow damage and secondary malignancies. It is hoped that studies such as those in this issue will encourage wider appreciation and use of RIT.

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