Clinical Roundtable Monograph

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Recent Advances in Radioimmunotherapy in the Treatment of Follicular Lymphoma

Moderator

Stephanie A. Gregory, MD
The Elodia Kehm Chair of Hematology
Professor of Medicine
Rush University Medical Center/
Rush University Cancer Center
Chicago, Illinois

Discussants

Mark S. Kaminski, MD
Professor of Internal Medicine
University of Michigan Comprehensive Cancer Center
Ann Arbor, Michigan

John M. Pagel, MD, PhD
Associate Member, Clinical Research Division
Fred Hutchinson Cancer Research Center
Associate Professor, Department of Medicine
Division of Medical Oncology
University of Washington School of Medicine
Seattle, Washington

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Abstract: Follicular lymphoma is the second most common non-Hodgkin lymphoma and the most common indolent lymphoma. It often presents at an advanced stage. Major advances have occurred in the therapy of all B-cell lymphomas with the approval in 1997 of the monoclonal antibody rituximab. However, in general, the disease is not curable. The disease is heterogeneous and there is no standard of care; therefore, therapy should be individualized. One needs to look at both patient and disease characteristics. In the asymptomatic patient with low tumor burden, "watch and wait" is an appropriate choice. However, patients with high tumor burden or symptoms require immediate therapy, usually with chemoimmunotherapy or, on occasion, monotherapy with rituximab. Radioimmunotherapy (RIT) has been used with very promising results as a single agent for frontline treatment; however, single-agent RIT in the upfront setting should be used only as part of a clinical trial. Relapsed disease, likewise, has many options for therapy, but RIT is an effective treatment, especially if used early before the patient has been treated with many regimens. The radioimmunotherapeutics 131I-tositumomab and 90Y-ibritumomab tiuxetan are approved to treat relapsed and refractory lymphoma. RIT has achieved prolonged remissions, which are more likely when patients are treated early rather than as last-line treatment. RIT has also been used as part of the preparative regimen for stem cell transplantation. The 2 main approaches for RIT and stem cell transplantation involve nonablative doses of radiolabeled antibodies combined with high-dose chemotherapy, or high doses of radiolabeled antibodies consisting of myeloablative doses of either 131I-tositumomab or 90Y-ibritumomab tiuxetan combined with high-dose chemotherapy.

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Target Audience

This activity has been designed to meet the educational needs of oncologists, hematologists, and other health care professionals involved in the management of patients with follicular lymphoma.

Statement of Need/Program Overview

Follicular lymphoma is the most common indolent lymphoma. Indolent follicular lymphoma is not curable. Although its presentation and prognosis are variable, it often presents at an advanced stage. Median survival, which is currently about 14 years, has increased with the advent of the newer monoclonal antibodies. There is no standard of care for follicular lymphoma. Management options will vary according to the disease stage. The watch-and-wait approach is appropriate for asymptomatic patients with low tumor burden who may not need treatment. Symptomatic patients needing treatment may benefit from chemotherapy with rituximab. Many novel therapies are in development. Radioimmunotherapy can achieve prolonged remissions, particularly when used further upfront in the course of disease rather than as last-line treatment.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe recent clinical data presented at the American Society of Hematology 2011 Annual Meeting in the assessment and management of follicular lymphoma, including strategies for integrating this information into clinical practice
- Assess the role of maintenance and consolidation therapy in the management of patients with follicular lymphoma based on emerging clinical trial data
- Use evidence-based decision-making to select optimal treatment for patients with follicular lymphoma, including watch and wait, active treatment, maintenance, and consolidation
- Identify ongoing clinical trials that are expected to impact clinical practice
- Define strategies for the integration of new agents into current clinical practice

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Disclosures

Stephanie A. Gregory, MD—Research support (all proceeds go to Rush University Medical Center): Celgene, Emergent, Medimmune, Novartis, and Wyeth/Pfizer. Advisory Boards: Amgen, Genentech (Roche), and Spectrum.
Mark S. Kaminski, MD—Royalty: GlaxoSmithKline. Patent holder: GlaxoSmithKline. Contracted Research: GlaxoSmithKline.
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Introduction to Follicular Lymphoma

Stephanie A. Gregory, MD

The non-Hodgkin lymphomas (NHLs) are a very heterogeneous group of lymphoproliferative disorders that mostly involve the B cells, although T-cell and natural killer cell lymphomas also exist. Follicular lymphoma is the most common indolent lymphoma, accounting for approximately 22% of NHL cases in North America.[1] The overall number of NHL cases is increasing, with an estimated 70,130 new cases expected in 2012.[2]

Indolent follicular lymphoma, in general, is not curable. Although its presentation and prognosis are variable, it often presents at an advanced stage. Median survival, which is about 14 years, has been increasing with the advent of the newer monoclonal antibodies.[3] The monoclonal antibody rituximab has been a major advance in all of the lymphomas, but it has been especially important in the follicular lymphomas.

Prognostic factors are important and include the Follicular Lymphoma International Prognostic Index (FLIPI; which will be discussed later), a criteria that includes number of nodal sites, levels of lactate dehydrogenase (LDH), age of the patient, stage of disease, and hemoglobin level. Certain biomarkers such as Bcl-2, Bcl-6, and CD10 should always be measured.[4-6] One should also look at cell regulators, such as p53 and related proteins.[7,8] The Fc gamma receptor polymorphisms[9] also play an important role in the response to rituximab and to some of the newer monoclonal antibodies. The tumor microenvironment may also play a role in prognosis.[10]

Diagnostic Criteria

Many patients are asymptomatic when they present with the disease. They may present with painless lymphadenopathy, which may wax and wane before the disease is diagnosed. The indolent nature of follicular lymphoma is why many patients present with advanced disease. Staging workup includes, first and foremost, an excisional lymph node biopsy which should include not only microscopic examination but flow cytometry and histochemical staining for selected markers. In addition, the patient should have routine blood counts, chemistries, uric acid, LDH levels, and β_2 microglobulin tested.[11] Computed axial tomography (CAT) and, on occasion, positron emission tomography (PET) scans are important to evaluate the stage of the disease. Bone marrow biopsies are part of the staging workup. Bone marrow involvement is present in about 60% of newly diagnosed patients. Flow cytometry is performed also on the marrow to look for the characteristic markers of follicular lymphoma (CD19, CD20, and, in particular, CD10+).[11] The disease is often characterized by a translocation between the 14;18 chromosome, which causes a type of an overexpression of the *BCL2* gene.[12] The *BCL2* gene probably prevents the cells from dying, which is considered a possible reason that this disease may not be curable.

Follicular lymphoma, histologically, is graded as 1, 2, or 3. The 2008 World Health Organization Revised European-American Lymphoma (REAL) classification[13,14] subdivides grade 3 into 3a and 3b. Generally, follicular grades 1, 2, and 3a are considered low-grade, whereas 3b is more aggressive and categorized as a diffuse large B cell. Consequently, follicular grade 3 cases are excluded from the evaluations of many clinical trials for low-grade lymphomas.

The prognosis of a patient involves additional factors beyond the stage of the disease. For low-grade lymphomas, the stage does not necessarily indicate prognosis, since most of the patients present with advanced stage. To understand prognosis, the FLIPI criteria were developed.[15] The clinical and laboratory parameters of age, Ann Arbor stage, number of nodal areas, LDH levels, and hemoglobin level are used to divide patients into 3 major subgroups with regard to overall survival: low risk (0–1 risk factors), intermediate risk (2 risk factors), and high risk (3–5 risk factors). The FLIPI system has been an important advent for the prognostic factors in follicular lymphoma. This system has been used in many clinical trials, so patients with low, intermediate, and high risk have been included. Notably, patients in the high-risk FLIPI subgroup do not necessarily need treatment.

Recently, the FLIPI has been revised to create FLIPI-2, which takes into account the addition of rituximab to chemotherapy. The FLIPI-2 criteria also consider bone marrow involvement, the size of the lymph node, and β_2-microglobulin levels. Its principal endpoint is progression-free survival (PFS; Table 1).

Physicians are encouraged to evaluate these prognostic factors. The LDH levels of all patients with follicular lymphoma should be tested, as elevated LDH is very unusual, especially at diagnosis. If LDH levels are elevated, there may be a concern that the lymphoma has transformed.[16] Transformation to a diffuse large B-cell lymphoma portends a worse diagnosis in the follicular lymphomas. The rate of this transformation is 3% per year; over the lifetime of a patient, the incidence is approximately 30%. Autopsy specimens, however, suggest that the transformation rate is probably much higher.[17] Importantly, a patient with follicular lymphoma can have a localized transformation. The possibility of transformation should be considered for any

Table 1. FLIPI-2 Risk Assessment

Five Parameters of FLIPI-2
β_2-microglobulin higher than upper limits of normal
Longest diameter of largest lymph node >6 cm
Bone marrow involvement
Hemoglobin level <12 g/dL
Age >60 years
Advantages
More accurate version
Considers immunochemotherapy as a widely used treatment option
Future treatment guidelines will most likely be based on staging, genetic profiles, and immune response signatures

Data from Federico M et al. *J Clin Oncol.* 2009;27:4555-4562.[53]

Table 2. Treatment Initiation: GELF Criteria

All of the Following
Involvement of >3 nodal sites, each >3 cm in diameter
A nodal or extranodal tumor mass with a diameter of >7 cm
B symptoms
Splenomegaly
Cytopenias (white blood count <1.0 x 10^9, platelets <100,000)
Leukemic phase (>5.0 x 10^9/L malignant cells)

GELF=Groupe pour l'Etude de Lymphome Folliculaire. Data from Brice P et al. *J Clin Oncol.* 1997;15:1110-1117.[54]

patient with a rapidly enlarging tumor mass, any symptoms (including systemic), or a rising LDH level.[18] Because of the possibility of transformation, each time a patient with follicular lymphoma relapses, a re-biopsy should be performed. Patients with transformation may be treated with an anthracycline-containing regimen[19] and, if a suitable candidate, proceed to a stem cell transplant.[20]

Therapy for Low Tumor Burden Follicular Lymphoma

Recommended therapies for follicular lymphoma are listed in the National Comprehensive Cancer Network (NCCN) guidelines.[11] However, each patient's personal characteristics and disease characteristics must be considered. A young patient who is physically fit will be treated much differently than an elderly patient with many comorbid conditions. Disease characteristics include the stage of the disease, the rapidity of the onset of the disease, and whether or not the patient has symptoms. Patient preference also may play a role in how patients are treated. Patients with follicular lymphoma should not be overtreated, as their life expectancy is long, multiple relapses will occur, and secondary myelodysplasia/acute leukemia are complications of overtreatment.

Importantly, follicular lymphoma does not always require treatment. "Watch and wait" is a common approach used for the newly diagnosed patient with follicular lymphoma who is asymptomatic and has a low tumor burden. The level of tumor burden is defined by the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria (Table 2).[21] A patient with low tumor burden is asymptomatic, and does not have symptomatic splenomegaly, cytopenias, more than 3 nodal areas measuring more than 3 centimeters, or any node measuring more than 7 centimeters. For a patient with a low tumor burden, the watch-and-wait approach is appropriate. This approach involves regular office visits and occasional CT scans.

Many clinical trials have included patients with low tumor burden who did not require treatment. An early study by Colombat and associates treated 50 patients with single-agent rituximab and achieved promising responses, including a 73% response rate 1 month after treatment.[22] A follow-up study of 7 years found that approximately 25% of patients (7 of 46) still did not require any additional treatment.[23] In an important trial reported by Ardeshna and colleagues, 3 groups of patients with low tumor burden were randomized to observation, rituximab for 4 weeks, or rituximab for 4 weeks followed by 2 years of maintenance rituximab (Table 3).[24] The arms receiving rituximab had significantly longer PFS (P<.001 for each rituximab arm vs observation arm). Although the study authors concluded that the patients had a delay of time before they first needed chemotherapy, the patients were receiving therapy in some form, and they were immunosuppressed by the treatment. Many oncologists are not convinced that asymptomatic patients should be treated with rituximab. Rituximab is a newer therapy. Old trials have taught us that when a watch-and-wait approach has been compared to a chemotherapy regimen, the chemotherapy did not make any difference in overall survival.

Upfront Treatments

For patients who truly do need treatment upfront, the NCCN guidelines offer many combinations, and no one combination is the standard of care.[11] Most treatments today are combined with rituximab, which is certainly a frontline treatment (Table 4). The many category 1 NCCN recommendations include bendamustine plus rituximab; rituximab plus cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone or prednisolone (R-CHOP); and rituximab

Table 3. Observation Versus Single-Agent Rituximab

	Rituximab→2-Year Maintenance	Rituximab→ Observation	Watch and Wait
Patients	192	84	187
Median Time to New Therapy	NR	NR	33 months
Overall Response Rate (%)	85	78	9

Data from Ardeshna KM et al. *Blood*. 2010;116(21): Abstract 6.[24]

plus cyclophosphamide, vincristine, and prednisone or prednisolone (R-CVP). Radioimmunotherapy (RIT) has been used as a frontline treatment for patients. RIT is a category 2B recommendation, so, in general, use of single-agent RIT should be limited to patients in clinical trials.

An interesting study compared the combination of bendamustine and rituximab to R-CHOP.[25] The bendamustine-rituximab combination had improved complete responses (CRs; 40.1% vs 30.8% for R-CHOP; *P*=.0323) and PFS (54.8 months vs 34.8 months for R-CHOP; *P*=.0002). This study found fewer toxicities with bendamustine-rituximab than with R-CHOP, including lower rates of alopecia (15% for bendamustine-rituximab vs 62% with R-CHOP). These results have led many physicians to choose bendamustine-rituximab as the frontline treatment for advanced-stage symptomatic patients with follicular lymphoma. Also, many newer agents are being combined with bendamustine in clinical trials for patients with relapsed and refractory disease.

Maintenance rituximab after chemotherapy combined with rituximab for advanced-stage follicular lymphoma was approved on the basis of the PRIMA (Primary Rituximab and Maintenance) study.[26] This trial examined the combination of rituximab with chemotherapy. Most of the patients received R-CHOP, and the second most common therapy was R-CVP. The trial led to the approval of 2 years of rituximab maintenance given every 2 months, compared to observation alone. The patients on maintenance rituximab had a marked improvement in PFS of 74.6%, with a median follow-up of 36 months (vs 57.6% for the maintenance arm; *P*<.0001).

The FIT (First-Line Indolent) trial examined chemotherapy for advanced-stage patients with follicular lymphoma who needed treatment.[27] The patients received a variety of chemotherapy regimens, but only 15% of 414 patients received rituximab with their chemotherapy. Many had not received rituximab because, when the trial started, the standard of care was mostly chemotherapy alone, rather than the combination of rituximab and chemotherapy. The patients who responded were randomized to receive either RIT with yttrium-90 (90Y)-ibritumomab tiuxetan as consolidation or observation without therapy. The responses favored the 90Y-ibritumomab tiuxetan consolidation approach. A follow-up with a median of 66.2 months found that patients in complete remission at the end of their chemotherapy who went on to the consolidation therapy had a 57% rate of 5-year PFS and had not yet reached the median at 92 months.[28] When blood samples from some of the patients receiving consolidation therapy were evaluated by polymerase chain reaction (PCR), 90% of the treated patients converted from Bcl-2 PCR-detectable to Bcl-2 PCR-undetectable, indicating that they were in a molecular remission.[29] A trial involving frontline chemoimmunotherapy followed by either RIT consolidation or rituximab maintenance that compares RIT consolidation with 2 years of rituximab maintenance is still needed.

Table 4. Most Common Combination Frontline Regimens

Regimen	Strengths	Weaknesses
R-CHOP	Long follow-up Rapid response Curative on FL grade 3 Possible reduced transformation	Concerns about cardiotoxicity
R-CVP	Long follow-up No concerns about cardiotoxicity	Means different regimens Possibly lowest complete response rates
F-R	Low infection	Myelosuppression 2 consecutive days of treatment
B-R	Better progression-free survival No alopecia	Shorter follow-up Concerns about long-term marrow injury 2 consecutive days of treatment

R-CHOP=rituximab plus cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone or prednisolone; R-CVP=rituximab plus cyclophosphamide, vincristine, and prednisone or prednisolone; F-R=fludarabine and rituximab; B-R=bendamustine and rituximab. Data from Friedberg J et al. *J Clin Oncol*. 2009;27:1202-1208[55] and Czuczman M et al. *J Clin Oncol*. 2005;23:694-704.[56]

In a very impressive trial by Kaminski and colleagues, iodine-131 (131I)-tositumomab therapy alone was used as frontline treatment for advanced-stage follicular lymphoma.[30] The phase II, single-center trial enrolled 76 patients. Dr. Kaminski will discuss the results later in this monograph.

Relapsed Disease

For patients with relapsed disease, algorithms must be developed to determine treatment plans. Patients who are considered relapsed because their lymph nodes are increasing on CAT scans do not necessarily need treatment. If a young patient relapses quickly after a frontline treatment, then stem cell transplant should be discussed. Stem cell transplant has many different regimens and approaches, which will not be covered here. However, autotransplant should be considered for young patients who have a very short first remission of their disease. Current clinical trials are examining reduced intensity allotransplants in patients with extensive bone marrow involvement who have relapsed quickly after their frontline therapy.[31,32]

For older patients who relapse, the options are similar to those for frontline treatments. My recommendation, especially for elderly patients with comorbid conditions, is RIT at first relapse. Some patients have extremely durable responses. Using RIT earlier in the course of the disease gives more durable responses and CRs than using it later.[33,34] Many studies have examined treatment of relapsed disease with R-CHOP, if it was not used as an initial treatment, followed by 2 years of maintenance rituximab[35-37] The arm receiving rituximab maintenance instead of observation had improved OS (74% vs 64%; *P*=.07).[37] Notably, the patients in that study had not previously been treated with anthracycline or rituximab.

Today, almost every patient receives rituximab, either alone or with chemotherapy, when they relapse. Results from some older trials cannot be applied to the treatments of today for patients who relapse. For patients who are refractory to rituximab (relapsing while on rituximab treatment, or relapsing within 6 months of rituximab treatment), the 2 approved agents are RIT and bendamustine. If the patient has already been treated with bendamustine upfront, then the patient should receive RIT or be enrolled on a clinical trial. Clinical trials should always be offered to patients if they are available.

Novel Agents

Novel agents include the newer monoclonal antibodies, several of which are humanized anti-CD20 monoclonal antibodies.[38,39] Clinical trials are examining immunoconjugates, in which the antibody may be conjugated to a toxin. An example is the anti-CD22 monoclonal antibody attached to the toxin calicheamicin, which has been in clinical trials for patients with relapsed disease that is refractory to rituximab.[40,41] Some of these newer immunoconjugates have had some very nice responses. Likewise, RIT is an immunoconjugate of an antibody conjugated to radiation.

Both bortezomib, a proteasome inhibitor, and lenalidomide, an immunomodulatory drug, are in extensive clinical trials for relapsed and refractory low-grade follicular lymphoma.[42-47] Fowler and coworkers combined rituximab and lenalidomide as frontline treatment for low-tumor-burden follicular lymphoma patients, and achieved overall response rates (ORRs) of 86%, with 79% of patients achieving CRs.[48] Now, those regimens are being incorporated into some Eastern Cooperative Oncology Group (ECOG) trials. The frontline ECOG trial for patients with higher tumor burden is comparing treatment with bendamustine, rituximab, and bortezomib to treatment with rituximab and bortezomib alone to treatment with rituximab and bendamustine alone.[49] Patients who respond receive different maintenance regimens, one with rituximab and one with both rituximab and lenalidomide.

Many different combinations of the novel agents are being examined. However, these are all still in clinical trials. These novel agents include Bruton tyrosine kinase inhibitors[50] and CAL-101,[51-52] which are newer agents that inhibit pathways that are dysregulated in all types of lymphoma, including follicular lymphoma.

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Optimal Use of Radioimmunotherapy in Follicular Lymphoma

Mark S. Kaminski, MD

Radioimmunotherapy (RIT) is a treatment whereby radiation is targeted to cancer cells wherever they may be in the body. In the case of lymphoma therapy, antibodies that can recognize a specific antigen (for instance, CD20) on lymphoma cells are tagged with a radionuclide and injected intravenously. The radioactive antibody circulates in the blood, and when the antibody encounters a tumor cell or a cell with the target of the anti-CD20, not only does that attachment stimulate an immune response to the antibodies, but it also delivers radiation directly to that immediate vicinity, relatively sparing normal surrounding tissues. This approach makes a lot of sense when it comes to treating lymphoma, which is a radiosensitive neoplasm. Low-grade and indolent lymphomas are extremely sensitive to radiation. For example, a very low dose of external beam radiation in the range of only 4 Gy delivered to a localized site of disease can result in a complete response in that site about 90% of the time.[1] But lymphoma is rarely in only 1 site, and thus the trick is to distribute the radiation in a way that targets all tumor sites, which is not possible with conventional radiation therapy, such as external beam. RIT with radioactive antibodies allows the radiation to be distributed to target all tumor sites.

Radioimmunotherapy has been in development for many years. The earliest trials in lymphoma started in 1985,[2] and the initial trials of anti-CD20 antibodies began in 1990.[3] Many clinical trials have been performed since that time, and there are years of follow-up data on the durability of patient responses, late toxicities, and implications for managing postrelapse patients who have received RIT.

The US Food and Drug Administration (FDA) has approved 2 radioimmunotherapeutics, 131I-tositumomab and yttrium-90 (90Y) ibritumomab tiuxetan, for patients with relapsed or refractory indolent lymphoma or transformed lymphoma, and also in patients who are rituximab refractory.[4,5] Additionally, 90Y-ibritumomab tiuxetan is approved as a consolidative treatment after chemotherapy for frontline treatment of indolent lymphoma.

Radioimmunotherapy is a single-cycle treatment in which all the treatment is essentially administered in 1 week. In contrast, conventional chemotherapy involves administration of many cycles. 131I-tositumomab is administered in a 2-step process. First, patients receive an injection of the anti-CD20 antibody tositumomab and 131I-tositumomab as a test dose, which is also known as a dosimetric or imaging dose. This injection is used to determine how quickly the tracer or test dose disappears from the body after 1 week. The therapeutic dose, which has a much higher level of radioactive content in the radiolabeled antibody, is administered about 1 week after the test dose.

The other approved CD20 antibody, ibritumomab tiuxetan, which is radiolabeled with 90Y, is dosed based only on the weight of the patient. The test dose is not required. The therapy is administered in about 1 week.

The main toxicity with both agents is reversible myelosuppression,[6] which occurs 4–6 weeks after the therapeutic dose has been delivered. Although each of these treatments has different restrictions regarding radiation safety, both can be given as outpatient procedures.

Tositumomab, the original anti-CD20 antibody, was developed at Harvard in the late 1970s.[7] It is a mouse monoclonal protein that is now known as a type 2 anti-CD20 antibody. Tositumomab has a different mechanism of action from ibritumomab tiuxetan, which is essentially rituximab, but with a radioisotope attached to it. Tositumomab and 131I-tositumomab mechanisms are directed more at nonapoptotic pathways and at a pathway that is regulated by the MAP kinase and extracellular signal-regulated kinases (ERK), while being independent of *BCL-2*.[8] Ibritumomab tiuxetan cell kill, in contrast, is *BCL-2*–dependent. Its rituximab backbone kills cells primarily through complement activation rather than by direct cell death, as is the case with tositumomab.[9]

Relapsed Setting

Most studies of these RIT agents have been performed in the relapsed setting of follicular lymphoma, with the initial trials done in the style of phase I or phase II trials of the early 1990s.[3,10-13] These trials were followed by multicenter, phase II studies that confirmed the results.[14,15] Then, a trial

was conducted in follicular lymphoma patients who were chemotherapy-refractory.[16] A trial examined how much activity the radioisotope actually adds to the treatment through a randomized study that compared the unlabeled antibody by itself to the radiolabeled antibody.[17] Further trials of 90Y-ibritumomab tiuxetan were performed in patients who were refractory to rituximab.[18] All of these trials, at least in terms of 131I-tositumomab, formed the basis of the approval by the FDA in 2003. The pattern of clinical trials was similar for 90Y-ibritumomab tiuxetan, which was approved in 2002.

Notably, prolonged remissions were obtained with CD20-directed RIT in all the clinical trials of it, unlike other treatments for patients with relapsed or refractory disease.[19,20] When an aggregate of studies involving both 131I-tositumomab and 90Y-ibritumomab tiuxetan is considered, approximately 20–30% of patients have extremely durable remissions that last more than 5 years. My patients are still coming back, including one who is 16 years out with no relapse. This is a unique situation in the relapse setting, since it is unexpected to never treat a patient again with anything else. Typically, the relapse setting involves waiting for events that signal a need for another treatment.

The key now is to identify which patients can benefit from treatment and which can achieve prolonged remissions. These are active areas of investigation. We do know that the chance of achieving long-term remission depends on whether a patient achieves a CR. In general, patients with relapsed disease with both agents have about a 70% response rate and about a 30–40% CR rate.[21] The patients who are most likely to achieve good responses, especially CRs, are those who are treated further upfront in the course of the natural history of their disease rather than with RIT as a last-line treatment. Most importantly, RIT should be considered in the earlier stages of treatment, and it should be discussed with patients as an option at that time.

Frontline Setting

The successes obtained in the relapse setting led to trials in the frontline setting. Therapy with 131I-tositumomab as a frontline treatment was tested at the University of Michigan in a single-center study involving 76 patients with advanced follicular lymphoma.[22] Even though 85% of the enrolled patients had intermediate- to high-risk FLIPI scores, 95% had a response to the 1-week treatment, and 75% had a complete remission. The duration of response, especially in those with a CR, is particularly noteworthy. The patients had a CR rate of 75%, with a median PFS of about 11 years.[23] Among the total population of patients, including those with CRs and partial responses (PRs), 38%

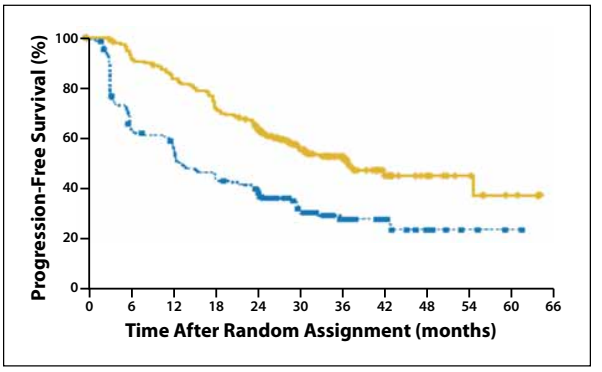

Figure 1. Median progression-free survival of all patients in a phase III trial of consolidation therapy with 90Y-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. Adapted from Morschhauser F et al. *J Clin Oncol.* 2008;26:5156-5164.[26]

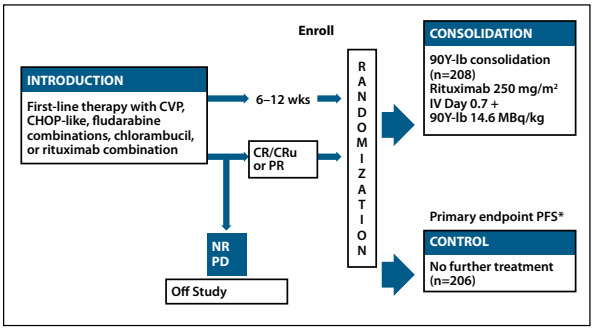

Figure 2. Design of the FIT (Frontline Indolent Trial). 90Y-Ib=90Y-ibritumomab tiuxetan. *Calculation of PFS starts at enrollment, not from induction. Adapted from Morschhauser F et al. *J Clin Oncol.* 2008;26:5156-5164.[26]

of the patients have not had any progression after 10 years. This treatment, as a single entity, appears to be able to put patients into very long remissions.

Because the treatment is radiation, concerns have been raised about the potential development of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). Retrospective analyses of the data from all the clinical trials performed in the relapsed setting did not find an increased risk for developing MDS or AML compared with the population of patients who received other treatments for their disease.[24,25] Notably, all the patients received chemotherapy, and chemotherapy is known to be able to cause MDS or AML. The data are not clear about the extent to which RIT may contribute to the risk of MDS, but the analyses have not raised any major flags. They are always compromised because the patients under analysis have all received chemotherapy.

Our frontline trial of the 76 patients now has a minimum follow-up of 12 years of all survivors, and 82% of the patients are still alive (these updated data have not yet been published). Only 1 case of MDS was detected,

which occurred in a patient who relapsed, received RIT once more, had multiple rounds of chemotherapy, and then developed MDS 3 years later. Again, the question arises regarding whether the chemotherapy or RIT caused the MDS to occur in this patient. These data have led to a move toward using RIT combined with chemotherapy in the frontline setting, so that RIT is used as a cleanup after frontline treatment with chemotherapy or rituximab-based chemotherapy. As mentioned by Dr. Gregory, the FIT trial demonstrated a PFS benefit for patients who had received various forms of chemotherapy followed either by 90Y-ibritumomab tiuxetan or by observation (Figures 1 and 2).[26] One point to consider is that very few of the patients received rituximab as part of their initial treatment, prior to receiving RIT. Therefore, the study is not examining current treatments. Furthermore, when RIT is given, in an effort to enhance the delivery of the radiolabeled antibody to tumor sites, the unlabeled antibody is given first to "prime the pump." Many B cells in the circulation are normal, and many of these have residence in the spleen, which is a very vascular organ. If radiolabeled antibody were simply given outright, much of it would be absorbed by the normal components, which would have the first opportunity to engage the antibody. The importance of giving a predose was found in many of the clinical trials of both 131I-tositumomab and 90Y-ibritumomab tiuxetan. However, the FIT trial involved patients who had never received any antibody treatment, and then received 90Y-ibritumomab tiuxetan at 250 mg/m^2 twice, because of the predose. This has a therapeutic effect all by itself. Hence, the FIT trial looked very positive for RIT, but the important caveat is that a considerable amount of the effect may have been dictated simply by the antibody treatment.

Sequence for Radioimmunotherapy and Chemotherapy

Another question is the sequence in which RIT and chemotherapy should be administered. Currently, chemotherapy is followed by RIT. One of the principles of RIT is that the isotope that is attached to the antibody emits beta particles. The beta particles travel a distance of many cell diameters away from their decaying nucleus, damaging DNA in adjacent cells but not necessarily damaging much of the DNA in the cell being targeted. Cells are radiating other cells within a tumor. This is the crossfire effect, with the beta particles essentially crisscrossing across a tumor. If you imagine a very small target, such as very few cells in a minimal residual disease state, the crossfire effect is theoretically decreased, so less radiation may be effectively delivered to the cancer cells.

An additional effect of predosing first with unlabeled antibody is a masking effect that can further interfere with the binding of the subsequently administered radioactive antibody. The sites of interest become occupied by the unlabeled antibody, and, thus, are unavailable for the radiolabeled antibody to occupy. In contrast, if the order of the antibodies is reversed, the crossfire effects and unlabeled antibody predosing are much more efficient and optimal for a patient with a measurable amount of disease. Chemotherapy could be envisioned occurring after RIT, as a cleanup, since it does not depend on any bulk or crossfire effects.

Two clinical trials reported at the recent American Society of Hematology (ASH) Annual Meeting give pause to the idea that RIT is a reasonable option in the frontline setting, or if it should be used as a consolidation. First is the Southwest Oncology Group (SWOG) trial, which was an intergroup study that randomized patients with advanced follicular lymphoma between R-CHOP given in the style developed by Myron Czuczman, MD, versus CHOP followed by 131I-tositumomab.[27] The PFS curves and outcomes in this trial were rather disappointing in regard to any benefit from RIT. No statistical difference was found in any parameter between the 2 arms. Furthermore, another study was reported using 131I-tositumomab in a transplant setting for patients with large B-cell lymphoma who had chemotherapy-sensitive disease.[28] These patients were randomized to receive either a preparative regimen with 131I-tositumomab followed by carmustine, etoposide, cytarabine, melphalan (BEAM) chemotherapy or with rituximab followed by BEAM chemotherapy. Again, this study found no benefit in the RIT arm.

Conclusion

Most of the patients in both of these studies had gone into a minimal residual disease state when they were being treated with RIT. At this point, we must reevaluate the sequence of RIT and other agents in the frontline setting.

Acknowledgment

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Current Uses of Radioimmunotherapy as Part of Hematopoietic Cell Transplantation Regimens for Follicular Lymphoma

John M. Pagel, MD, PhD

Despite the fact that non-Hodgkin lymphomas (NHL) are considered among the most sensitive neoplasms to chemotherapy and radiation therapy, these approaches are obviously far from adequate for preventing relapse in most cases. Generally, we concede that patients with relapsed lymphomas are incurable with conventional therapy. Perhaps a fraction of these patients, however, can have a significant change in the natural history of their lymphoma with hematopoietic cell transplantation (HCT), which makes HCT a critically important therapeutic modality for selected patients. Unfortunately, HCT for treatment of patients with NHL frequently fails because of disease recurrence. One approach to reduce relapse has focused on attempts to intensify the preparative regimen prior to HCT. This approach, in general, has been limited by associated toxicities due to the nonspecific nature of most conditioning agents. To overcome this limitation, radiolabeled antibodies have been investigated to deliver targeted therapy to sites of lymphoma involvement to decrease the risk of relapse after HCT, without increased toxicity. The combination of radioimmunotherapy (RIT) and HCT for patients with NHL has been examined in a variety of settings.[1] One approach has focused on the use of non-ablative doses of radiolabeled antibodies combined with high-dose chemotherapy, particularly a BEAM conditioning regimen prior to HCT (Figures 1 and 2).[2-7] Other approaches have used high doses of a radiolabeled antibody consisting of myeloablative doses of either 131I-tositumomab or 90Y-ibritumomab tiuxetan combined with high-dose chemotherapy and HCT.[8,9]

Non-Myeloablative Radioimmunotherapy and Autologous HCT

Non-myeloablative approaches for autologous HCT that combine either 131I-tositumomab or 90Y-ibritumomab tiuxetan with a conditioning regimen such as BEAM were

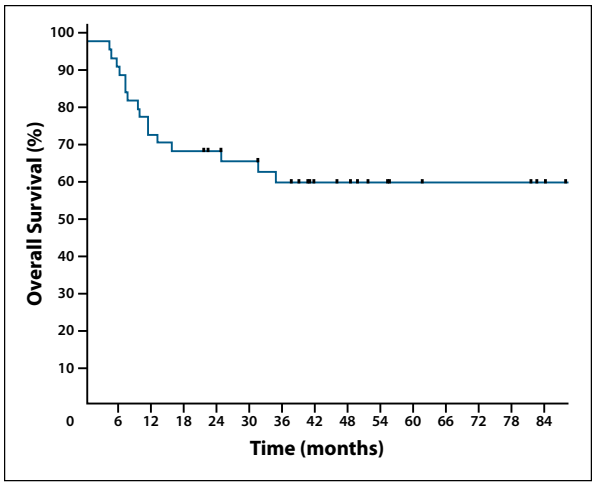

Figure 1. Overall survival among patients receiving yttrium-90 ibritumomab tiuxetan combined with high-dose BEAM and autologous transplantation. Adapted from Winter JN et al. *J Clin Oncol.* 2009;27:1653-1659.[4]

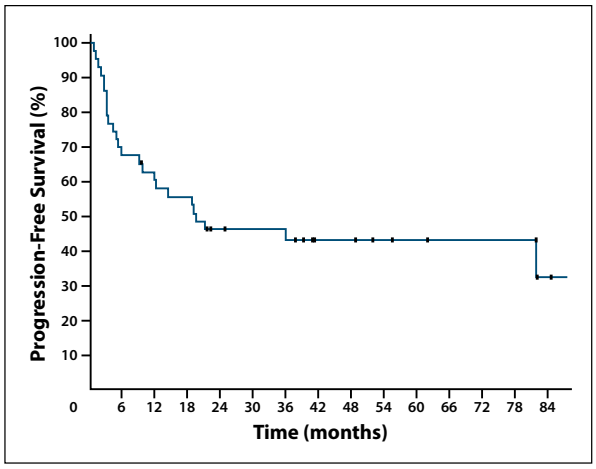

Figure 2. Progression-free survival among patients receiving yttrium-90 ibritumomab tiuxetan combined with high-dose BEAM and autologous transplantation. Adapted from Winter JN et al. *J Clin Oncol.* 2009;27:1653-1659.[4]

initially investigated by early phase II studies. Krishnan and colleagues led a phase II trial in 41 patients with NHL who were ineligible for total-body irradiation, using 90Y-ibritumomab tiuxetan at a standard dose of 0.4 mCi/kg in combination with BEAM chemotherapy.[3] After these advanced patients received autologous stem-cell rescue, their overall survival (OS) rates after 4 years were 80% or higher, and their PFS rates were about 60% at 4 years. In a similar manner, the combination of 131I-tositumomab and BEAM chemotherapy was studied by Vose and colleagues in a population of 23 patients with advanced NHL.[2] This approach was tolerable, with an OS of 55% after a median follow-up of 38 months.

The obvious question is whether adding the radiolabeled antibody provides a significant benefit in these studies over the use of standard high-dose chemotherapy alone. This question was examined in a cohort study in which 90Y-ibritumomab tiuxetan was added to BEAM conditioning prior to an autologous HCT for high-risk diffuse large-cell lymphoma patients.[10] The OS was improved by approximately 25% at 2 years compared with patients who received only standard BEAM conditioning, albeit not in a randomized setting. Importantly, this improvement also occurred even if the patients had had rituximab in their previous treatments. Nonetheless, very few randomized studies in the transplant setting have compared the use of radiolabeled antibodies either with or without a high-dose chemotherapy regimen. A recently reported randomized study examined 90Y-ibritumomab tiuxetan combined with BEAM chemotherapy versus BEAM alone to autologous stem cell rescue.[11] After 2 years of follow-up, the PFS was about 25% better for the patients who received both 90Y-ibritumomab tiuxetan and BEAM chemotherapy instead of only BEAM chemotherapy (49% vs 33% for high-risk patients). The results of this study are interesting in light of the randomized study that was described by Dr. Kaminski, in which 131I-tositumomab was examined in the autologous HCT setting. In this randomized study led by Vose and colleagues, patients received 131I-tositumomab with BEAM chemotherapy or rituximab and BEAM chemotherapy prior to HCT.[12] This study conversely found no difference in PFS, which was found to be nearly 50% for each arm. The OS rate was about 61.0% for patients receiving 131I-tositumomab and 65.6% for patients receiving rituximab (P=.38). Moreover, outcomes from the 2 arms did not differ in their cumulative incidence of relapse. Relapse therefore remains a significant problem as noted in all these studies that utilized non-ablative or standard doses of either 131I-tositumomab or 90Y-ibritumomab tiuxetan combined with BEAM chemotherapy.

Escalated Myeloablative Doses of Radiolabeled Antibody With Autologous HCT

The problem of relapse has led investigators to explore the use of escalated doses of a radiolabeled antibody combined with autologous stem cell rescue in an attempt to improve outcomes. It has widely been accepted that the dose of therapy can make a difference in a patient undergoing HCT. If in this case, the dose of radiation can be safely escalated to sufficiently high levels, the rates of relapse may be reduced. This escalated dose typically has employed the use of total body irradiation (TBI). Of course, the problem is that we are limited in how much TBI we can deliver, and a dose that has been escalated to very high levels has been shown to incur increased rates of

transplant-related mortality that are obviously not warranted. TBI as part of a transplant regimen therefore could possibly be replaced with high doses of radiolabeled antibodies, such as 131I-tositumomab or 90Y-ibritumomab tiuxetan, to target therapy to sites of disease and reduce normal organ toxicities.

This approach using myeloablative doses of radiolabeled antibodies and autologous HCT was pioneered by Press and colleagues at the Fred Hutchinson Cancer Research Center in Seattle. This strategy has been performed successfully for almost 2 decades utilizing organ-specific dosimetry. In this approach, patients first receive a small outpatient trace dose of radiolabeled antibody. The initial trials in Seattle used 131I as the therapeutic radionuclide[13-16] and were followed by gamma-camera imaging studies to determine organ-specific dosimetry.[8,17] The therapeutic dose is delivered about 7–14 days after the trace dose, based on the highest dose that can be delivered to the normal limiting organ. For lymphoma, this limitation has been typically posed by the dose delivered to the cardiopulmonary system. The use of radioiodine—which is very different from yttrium-90, a pure bets-emitter—requires radiation isolation for patients because of the high-energy gamma emissions associated with the radioiodine. In this setting, patients have typically been in radiation isolation for approximately 1 week and subsequently have received hematopoietic stem cell rescue with autologous cells.

Early single-agent studies with escalated-dose 131I-tositumomab delivered very promising tumor-to-whole-body ratios of at least 10 to 1.[14,18-20] Also, the tumor-to-normal-organ ratios were found to range from 2–4 to 1 in these settings. Clearly, high doses of radiation can be targeted to the tumor site over the whole body or normal organs. The question remains whether TBI can be supplanted by myeloablative RIT as part of the stem cell conditioning regimen. A nonrandomized analysis exploring this concept compared patients treated with high-dose radiolabeled antibody combined with high-dose cyclophosphamide and etoposide to patients treated with the same chemotherapy conditioning regimen plus 12 Gy of TBI.[21] In the modest number of patients (N=44), the results suggested that myeloablative doses of targeted radiation as part of the transplant regimen may lead to significant improvement in OS compared with TBI. It is presumed that this improvement may be due to the ability to deliver escalated doses of therapy directed more to the targets with less associated toxicity and morbidity.

This myeloablative RIT approach has been examined by other groups, including the outstanding group from the City of Hope in Duarte, California. In a similar manner, their study examined 90Y-ibritumomab combined with high-dose etoposide and cyclophosphamide, followed by autologous stem cell rescue for advanced NHL patients.[9] Their results suggested an excellent OS rate of 92% and a relapse-free survival rate of 78% at 2 years. The University of Chicago has used a comparable approach, finding success with escalated doses of 15 Gy in combination with a BEAM conditioning regimen and autologous HCT.[4] Their work reported an encouraging 3-year PFS rate of 43% and OS rate of 60%, again in an advanced NHL patient population.

RIT and Reduced-Intensity Allogeneic HCT Approaches

The problem remains, however, that even with these high-dose approaches prior to autologous HCT, patients still have a significant chance of relapse. One known factor that contributes to relapse after HCT clearly has been that the autologous stem cells stored for cryopreservation may be contaminated with lymphoma cells.[22] Consequently, allogeneic HCT with a reduced-intensity approach may be a reasonable option for some lymphoma patients. Typically, however, this regimen has been reserved for younger patients who have fewer comorbidities; this approach has been successful and relatively well-tolerated in these selected patients.[23] However, this approach may not be particularly effective in patients with high-risk lymphoma features, such as rapidly growing disease, bulky lymphoma, or multiple-relapsed disease with either chemotherapy-resistant or chemotherapy-refractory NHL. These high-risk patients continue to have high rates of relapse and are often unable to generate the necessary graft-versus-lymphoma effect in an adequate time period that may provide a long-term benefit.

Similar to the approach in the autologous transplantation setting using radiolabeled antibodies, reduced-intensity allogeneic HCT approaches have been investigated for patients with relapsed NHL. For example, in a study by Gopal and colleagues, 90Y-ibritumomab tiuxetan was added prior to a non-myeloablative transplant conditioning regimen using fludarabine and 200 cGy of TBI.[24] The expectation was that this approach may provide some significant benefit to improve disease control in these very high-risk patients compared with similar patients who received the same regimen without the radiolabeled antibody. This strategy was relatively well-tolerated, as the 100-day nonrelapse mortality rate was less than 5%, and this very difficult patient population had an OS rate of 54.1% and a PFS rate of 31.1% at a median follow-up of 30 months after HCT. Notably, this study used standard doses of 90Y-ibritumomab tiuxetan, and while promising, current approaches are exploring the use of escalated doses of 90Y-ibritumomab tiuxetan in combination with a reduced-intensity allogeneic HCT approach in Seattle. This current trial will likely use up to 4 times the standard dose of 90Y-ibritumomab tiuxetan (eg, 1.5 mCi/kg) for patients with advanced, relapsed, NHL who need additional measures to control aggressive disease.

Conclusions and Future Directions for RIT and HCT

While it is recognized that the use of radiolabeled antibody therapy and HCT may not be an option for most patients, and that these approaches can have significant toxicities as well as morbidity associated with the procedure, the use of RIT and HCT for appropriate high-risk patients remains an important research endeavor. Ongoing efforts continue to explore the best target, antibody, and therapeutic radionuclide combinations for the delivery of radiation to sites of disease in combination with HCT. New investigations are now targeting new antigenic targets, such as the CD45 antigen that is widely expressed on almost all hematopoietic cells, as opposed to CD20, making CD45 an appealing target when combined with HCT.[25] Lastly, new investigations currently being explored in the preclinical setting are attempting to optimize the delivery of radiolabeled antibodies through techniques such as pretargeted RIT. It is hoped that this method may allow for further delivery of even higher doses of radiation to disease sites and will continue to be associated with low rates of significant toxicity.[26]

Acknowledgment

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RIT in Follicular Lymphoma: Q&A

Stephanie A. Gregory, MD As we have discussed, there are many clinical trials of RIT, with much activity in Dr. Pagel's area of RIT in transplant. Some trials that combined chemotherapy and RIT were developed when our current knowledge and data did not yet exist. Outside of a clinical trial, are you using RIT today in your clinical practice?

John M. Pagel, MD, PhD As we all believe, standard approved radiolabeled antibodies have historically been underutilized in NHL. The appeal for me in my clinic is that patients can tolerate this treatment quite well. I very much like the approach that Dr. Kaminski has proposed of providing a radiolabeled antibody upfront before giving any chemotherapy. I would even go further and say that this could be a chemotherapy-sparing approach for many patients. In particular, this could be appealing for older or infirmed patients, who may not be able to tolerate chemotherapy. It is possible that a radiolabeled antibody could be given upfront as a single agent and then if the patient has a good response, this approach could be followed with just maintenance rituximab, as an example. Perhaps in this approach, chemotherapy will not be needed for many years or at all in some patients. Consequently, using these RIT agents earlier rather than later may be appealing.

Stephanie A. Gregory, MD I think that is such an important point. Many of us are looking at the frontline trial by Dr. Kaminski and colleagues. I think we have to be very careful in selecting the patient population that will receive RIT upfront. I think we do not want to use it in patients who do not necessarily need treatment.

Mark S. Kaminski, MD In follicular lymphoma, we are using RIT as the first treatment after relapse, especially in those patients who have relatively short remissions from their previous therapies. In fact, many of our patients are opting for this treatment versus an autologous stem cell transplant. An autologous stem cell transplant could potentially be done later if the RIT is not adequate.

Regarding underutilization, one of the problems with the use of RIT is that many of the published study results are not widely known. In addition, many phobias have arisen about this type of RIT. The most prominent phobia for patients is that this treatment will be the last one that can be administered; patients may fear that RIT will prevent future harvesting of bone marrow and use of other cytotoxic treatments. These fears are far from the truth.

Stephanie A. Gregory, MD We have all harvested patients who have had RIT. We have been able to carry them through transplant, and they have done very well.

It would be of interest to look at some of the algorithms that have been put forth over the years that include RIT. A consensus conference report published in 2011 by Thomas Witzig, MD, discussed treatment recommendations for RIT and follicular lymphoma.[1] In both untreated advanced follicular lymphoma and relapsed follicular lymphoma, RIT is recommended quite early in the course of frontline treatment and when used after chemotherapy. We published a very small phase II trial examining abbreviated chemotherapy with rituximab, fludarabine, and mitoxantrone for only 4 months, which was then consolidated with RIT.[2] This regimen was followed by 2 years of rituximab maintenance. We demonstrated very high ORRs, CRs, and continued improvement in conversion from PR to CR by adding 90Y-ibritumomab tiuxetan and with rituximab as maintenance therapy.

I think these are some of the kinds of trials that should be considered. The amount of chemotherapy administered can be minimized. At our institution, I am treating about 1 patient per month with RIT. It is often used in patients who have been referred by community doctors. I have spoken to community doctors about using less chemotherapy. A common scenario is one of my colleagues in the community will call me about a patient who has received 2–4 cycles of chemoimmunotherapy and is now doing well. I will often recommend consolidative RIT in this setting.

We must be careful about the type of chemotherapy we are using if we are then considering RIT. I no longer use fludarabine. We have seen some MDS after fludarabine use, as has Peter McLaughlin, MD, with his rituximab, fludarabine, mitoxantrone, and dexamethasone (RFND) treatment.[3]

Mark S. Kaminski, MD I agree with everything that you said. I also like the concept that Dr. Pagel suggested about treatment-sparing. We are trying to maintain the quality of life in these patients, who have long natural histories. Science does not stand still over the years. A treatment that might be good today might not be given 5 or 10 years from now. In fact, every time we see these improvements, I think we are moving closer and closer to curing our patients. I am beginning to believe that there are patients whose long remissions must be considered a cure. For example, 16 years in remission has to be good enough.

Stephanie A. Gregory, MD I was fortunate to participate with Dr. Kaminski in some of those early trials, as was Dr. Pagel. I also have 8 patients in my practice from the early 131I-tositumomab trials who are more than 10 years out without a relapse. I must mention that one of those patients had 10 prior chemotherapy regimens and was on

the re-treatment protocol. Her second re-treatment with 131I-tositumomab resulted in her long-term remission, which is now 11 years with no evidence of MDS.

Patient-oriented programs, such as the Lymphoma Research Foundation program, with which Dr. Pagel and I are involved, are important. Patients are the ones who will call us and ask for RIT. We must get more long-term survivors who have received RIT to become patient advocates and continue to highlight how good this treatment is.

Mark S. Kaminski, MD I agree. Most of the information now resides with the patients. Unfortunately, doctors are not offering their patients RIT as frequently as they should. It is very dramatic when a patient presents for a second opinion—not knowing that a treatment like this even exists—and then is told about it. We find ourselves in a difficult situation because the patient's trust in his or her doctor is decreased.

Some barriers to RIT do exist. Economics can be a concern. The hematologists/oncologists do not have the license to prescribe RIT. Patients must be referred to a nuclear medicine or radiation oncology department.

Stephanie A. Gregory, MD Yes. The oncologist may believe that he loses not only the patient but the finances, and that is not true. The patient can certainly go back to the hematologist/oncologist for the weekly blood counts.

We should mention the requirements for RIT and selecting patients. Patients are not ideal candidates for RIT if they have B symptoms or bulky disease, or if they need immediate therapy and immediate responses. Those patients certainly are candidates for abbreviated chemotherapy, and then perhaps consolidation with RIT. We have to remember that bone marrow tests must be done before patients receive RIT. Patients must have less than 25% marrow involvement with the lymphoma within at least 1 month of receiving treatment. Patients should have an adequate hematologic reserve, with an absolute neutrophil count of at least 1,500 cells/μL and a platelet count between 100,000–150,000 mL or higher. We also have to remember that the nadir of the counts occurs later than it does with chemotherapy. We see low counts at about 6–8 weeks after RIT, with a recovery of counts by about 13 weeks. We usually perform our first CAT scan approximately 3 months after RIT, when the maximum effect is expected.

We should also mention that some clinical trials are now looking at RIT, including an international trial with patients with de novo diffuse large B-cell lymphoma, for which the standard treatment in the United States is R-CHOP every 3 weeks. The trial of patients who have diffuse large B-cell lymphoma and are treated with R-CHOP will involve those who, at the end of 6 cycles, achieve a CR and are PET-negative. The patients will be randomized to either observation alone or 90Y-ibritumomab tiuxetan consolidation therapy. Sites are already being selected for this trial.

The radiation sensitizer motexafin gadolinium was examined in a small phase I trial led by Andrew Evens, DO, MSc, when he was at Northwestern University.[4] There is a new randomized trial in follicular lymphoma with about 15 sites that will compare either RIT alone or RIT plus 4 infusions on week 1 and then 4 infusions on week 2 added to 90Y-ibritumomab tiuxetan RIT. The trial seeks to determine if adding a radiation sensitizer results in even better responses.

Another upcoming study that is not yet open will examine rituximab-chemotherapy. The regimens will probably be R-CHOP, R-CVP, or R-bendamustine followed by either 90Y-ibritumomab tiuxetan consolidation or 2 years of rituximab maintenance. The trial will be in advanced-stage follicular lymphoma patients who need treatment.

Mark S. Kaminski, MD We have a new trial that is now open and continuing to accrue patients for 131I-tositumomab in the frontline setting. This time we are adding very low-dose oral methotrexate prior to the treatment and afterwards, when 131I-tositumomab is given. The idea is to dampen the immune response to the mouse antibody, which tositumomab is. This regimen is very similar to the one in which rheumatologists administer antitumor necrosis factor antibodies. This approach has been very useful in reducing antichimeric antibody responses. We also have a phase I study in collaboration with Cornell University using bortezomib as a radiation sensitizer in patients who have any type of lymphoma that is not curable with transplant.

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Slide Library

Follicular Lymphoma: Diagnosis

Staging workup includes:

- An excisional lymph node biopsy, including microscopic examination, flow cytometry, and histochemical staining for selected markers
- Routine blood counts and chemistries
- Testing of uric acid, lactate dehydrogenase, and β_2 microglobulin levels
- Computed axial tomography and, on occasion, positron emission tomography to evaluate the stage of the disease
- Bone marrow biopsies
- Flow cytometry to identify the characteristic markers of follicular lymphoma: CD19, CD20, and, in particular, CD10+
- Testing to identify a translocation between the 14;18 chromosome, which causes a type of overexpression of the *BCL2* gene

Follicular Lymphoma: Management

- The disease is heterogeneous and there is no standard of care; therefore, therapy should be individualized. Both patient and disease characteristics must be considered
- In the asymptomatic patient with low tumor burden, "watch and wait" is an appropriate choice
  - Patients with high tumor burden or symptoms require immediate therapy, usually with chemoimmunotherapy or, on occasion, monotherapy with rituximab
  - Single-agent radioimmunotherapy has been used with very promising results as frontline treatment; however, this should be done only as part of a clinical trial
  - Relapsed disease has many therapeutic options. Radioimmunotherapy is an effective treatment, especially if used early before the patient has been treated with many regimens

Radioimmunotherapy

- Radioimmunotherapy is a treatment whereby radiation is targeted to cancer cells wherever they may be in the body
- In the case of lymphoma therapy, antibodies that can recognize a specific antigen (for instance, CD20) on lymphoma cells are tagged with a radionuclide and injected intravenously. The radioactive antibody circulates in the blood. When the antibody encounters a tumor cell or a cell with the target of the anti-CD20, that attachment stimulates an immune response to the antibodies and delivers radiation directly to the immediate vicinity, relatively sparing normal surrounding tissues

Radioimmunotherapy: Approved Agents

- 131I-tositumomab and 90Y-ibritumomab tiuxetan are approved for patients with relapsed or refractory indolent lymphoma or transformed lymphoma, and also in patients who are rituximab refractory
- 90Y-ibritumomab tiuxetan is also approved as a consolidative treatment after chemotherapy for frontline treatment of indolent lymphoma

Radioimmunotherapy: Administration

Currently, radioimmunotherapy is administered in a 2-step process:

- First, patients receive a test dose, which is also known as a dosimetric or imaging dose
- About a week later, the therapeutic dose, which has a much higher level of radioactive content in the radiolabeled antibody, is administered

Radioimmunotherapy in the Relapsed Setting of Follicular Lymphoma

- Prolonged remissions were obtained with CD20-directed radioimmunotherapy in all the clinical trials of it, unlike other treatments for patients with relapsed or refractory disease[1,2]
- When an aggregate of studies involving both 131I-tositumomab and 90Y-ibritumomab tiuxetan is considered, about 20–30% of patients have extremely durable remissions that last more than 5 years

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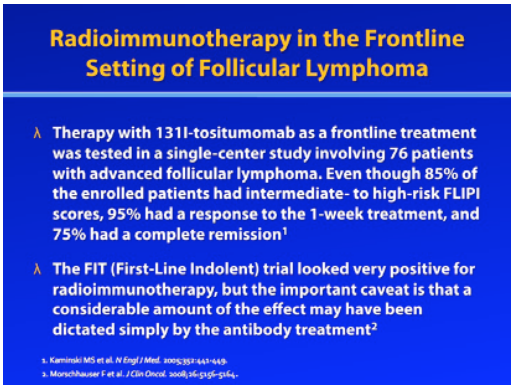

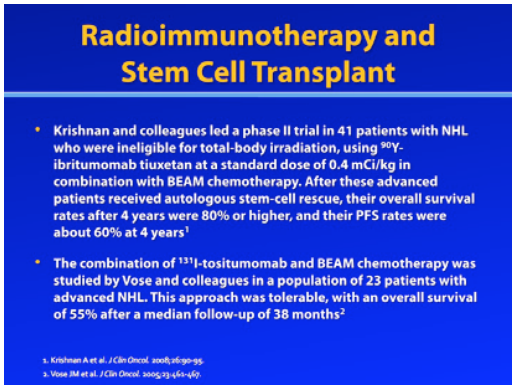

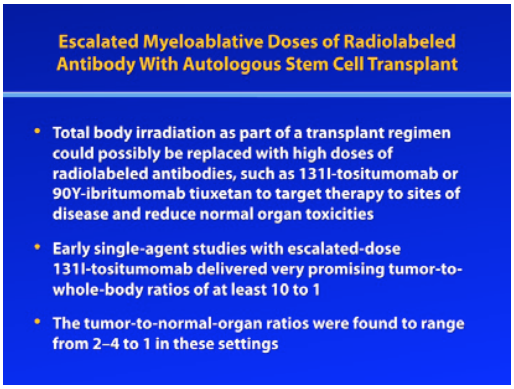

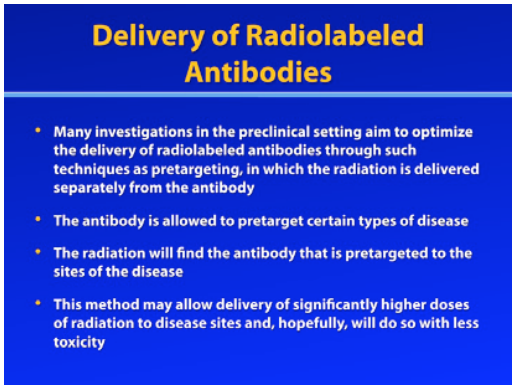

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Recent Advances in Radioimmunotherapy in the Treatment of Follicular Lymphoma

CME Post-Test: *Circle the correct answer for each question below.*

1. What is the median survival for indolent follicular lymphoma?

   a. Approximately 8 years
   b. Approximately 10 years
   c. Approximately 12 years
   d. Approximately 14 years

2. How many newly diagnosed follicular lymphoma patients present with bone marrow involvement?

   a. Approximately 20%
   b. Approximately 40%
   c. Approximately 60%
   d. Approximately 80%

3. For follicular lymphoma patients who are refractory to rituximab (relapsing while on rituximab treatment, or relapsing within 6 months of rituximab treatment), the 2 approved agents are:

   a. Radioimmunotherapy and bendamustine
   b. Radioimmunotherapy and bortezomib
   c. Radioimmunotherapy and fludarabine
   d. Radioimmunotherapy and lenalidomide

4. In the FIT (First-Line Indolent) trial of advanced-stage patients with follicular lymphoma, how many patients had received rituximab with their chemotherapy before entering the study?

   a. 15%
   b. 25%
   c. 30%
   d. 35%

5. Which radioimmunotherapy is approved as a consolidative treatment after chemotherapy for frontline treatment of indolent lymphoma?

   a. 131I-tositumomab
   b. 90Y-ibritumomab tiuxetan
   c. Both agents are approved for this indication
   d. Neither agent is approved for this indication

6. In a study by Kaminski of 131I-tositumomab as frontline treatment in 76 patients with advanced follicular lymphoma, how many patients developed myelodysplastic syndrome?

   a. 1 patient
   b. 3 patients
   c. 5 patients
   d. 7 patients

7. When an aggregate of studies involving both 131I-tositumomab and 90Y-ibritumomab tiuxetan is considered, how many patients have extremely durable remissions that last more than 5 years?

   a. Approximately 5–10%
   b. Approximately 10–20%
   c. Approximately 20–30%
   d. Approximately 35–40%

8. In a cohort study in which 90Y-ibritumomab tiuxetan was added to BEAM conditioning prior to an autologous hematopoietic cell transplantation for high-risk diffuse large-cell lymphoma patients, the addition of 90Y-ibritumomab tiuxetan improved overall survival by:

   a. Approximately 5% at 2 years
   b. Approximately 15% at 2 years
   c. Approximately 25% at 2 years
   d. Approximately 30% at 2 years

9. In a phase II trial by Krishnan examining 90Y-ibritumomab tiuxetan in combination with BEAM chemotherapy before autologous stem-cell rescue in patients with NHL, what was the progression-free survival rate?

   a. 30% at 4 years
   b. 40% at 4 years
   c. 50% at 4 years
   d. 60% at 4 years

10. In a study by Vose examining 131I-tositumomab with BEAM chemotherapy or rituximab and BEAM chemotherapy prior to autologous hematopoietic cell transplantation, what was the overall survival rate in the 131I-tositumomab arm?

    a. 61.0%
    b. 68.7%
    c. 71.3%
    d. 77.4%

Project ID: 8880

Evaluation Form: Recent Advances in Radioimmunotherapy in the Treatment of Follicular Lymphoma

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. ***You must complete this evaluation form to receive acknowledgment for completing this activity.***

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives After participating in this activity, I am now better able to:

1. Describe recent clinical data presented at the American Society of Hematology 2011 Annual Meeting in the assessment and management of follicular lymphoma, and define strategies for integrating this information into clinical practice 1 2 3 4 5
2. Assess the role of maintenance and consolidation therapy in the management of patients with follicular lymphoma based on emerging clinical trial data 1 2 3 4 5
3. Use evidence-based decision-making to select optimal treatment for patients with follicular lymphoma, including watch and wait, active treatment, maintenance, and consolidation 1 2 3 4 5
4. Identify ongoing clinical trials that are expected to impact clinical practice 1 2 3 4 5
5. Define strategies for the integration of new agents into current clinical practice 1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:
- ❒ I gained new strategies/skills/information that I can apply to my area of practice.
- ❒ I plan to implement new strategies/skills/information into my practice.
- ❒ I need more information before I can implement new strategies/skills/information into my practice behavior.
- ❒ This activity will not change my practice, as my current practice is consistent with the information presented.
- ❒ This activity will not change my practice, as I do not agree with the information presented.

What strategies/changes do you plan to implement into your practice? _____

_____

How confident are you that you will be able to make this change?
- ❒ Very confident ❒ Unsure
- ❒ Somewhat confident ❒ Not very confident

What barriers do you see to making a change in your practice? _____

_____

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

The content presented:

Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Promoted improvements or quality in health care	1 2 3 4 5
Was scientifically rigorous and evidence-based	1 2 3 4 5
Avoided commercial bias or influence	1 2 3 4 5
Provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc)	1 2 3 4 5
My opportunity for learning assessment was appropriate to the activity	1 2 3 4 5

Handout materials were useful: ❒ Yes ❒ No ❒ No handouts for this activity

Would you be willing to participate in a post-activity follow-up survey? ❒ Yes ❒ No

Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

_____

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 8880**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Request for Credit (*required fields)

Name*_____ Degree*_____

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For Physicians Only: I certify my actual time spent to complete this educational activity to be:
- ❒ I participated in the entire activity and claim 1.25 credits.
- ❒ I participated in only part of the activity and claim _____ credits.