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Non-Hodgkin's Lymphoma™ UPDATE

Conversations with Oncology Research Leaders
Bridging the Gap between Research and Patient Care

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Non-Hodgkin's Lymphoma Update
A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

Non-Hodgkin's lymphoma is increasing in incidence in the United States and is the most commonly occurring hematologic malignancy. This treatment arena continues to evolve, and published results from ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — practicing hematologists and oncologists must be well informed of these advances. To bridge the gap between research and patient care, *Non-Hodgkin's Lymphoma Update* utilizes one-on-one discussions with leading hematology and oncology investigators. By providing access to the latest research developments and expert perspectives, this CME activity assists hematologists and oncologists in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in non-Hodgkin's lymphoma (NHL) treatment and incorporate these data into management strategies for patients with NHL.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Utilize individual patients' risk factors and disease classification to tailor therapy for individual subgroups of patients with NHL.
- Discuss the risks and benefits of monoclonal antibody therapy and radioimmunotherapy alone and in combination with chemotherapy for patients with NHL, and counsel appropriately selected patients about the risks and benefits of these agents.
- Describe and implement an algorithm for sequencing of therapies in the management of indolent and aggressive NHL.

PURPOSE OF THIS ISSUE OF *NON-HODGKIN'S LYMPHOMA UPDATE*

The purpose of Issue 3 of *Non-Hodgkin's Lymphoma Update* is to support these global objectives by offering the perspectives of Drs Leonard, Coleman and Zelenetz on the integration of emerging clinical research data into the management of non-Hodgkin's lymphoma.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 3 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

HOW TO USE THIS MONOGRAPH

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **www.NHLUpdate.com** includes an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **blue underlined text**.

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Research To Practice is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved by a peer review content validation process. The content of each activity is reviewed by both a member of the scientific staff and an external independent reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

In addition, the following faculty (and their spouses/partners) have reported real or apparent conflicts of interest that have been resolved through a peer review process:

Dr Leonard — **Grants/Research Support:** Amgen Inc, Biogen Idec; **Consultant:** Biogen Idec, Genentech BioOncology, GlaxoSmithKline, Sanofi-Aventis; **Honorarium and Speakers Bureau:** Biogen Idec, Genentech BioOncology. **Dr Coleman —** **Consultant:** Celgene Corporation, OSI Pharmaceuticals; **Stock Shareholder:** Immunomedics Inc; **Speakers Bureau:** Biogen Idec, Millennium Pharmaceuticals Inc, OSI Pharmaceuticals. **Dr Zelenetz —** **Grants/Research Support and Speakers Bureau:** Biogen Idec, Genentech BioOncology, GlaxoSmithKline; **Consultant:** Celgene Corporation, Cell Therapeutics Inc, GlaxoSmithKline; **Honorarium:** Amgen Inc, Biogen Idec, GlaxoSmithKline.

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UPCOMING EDUCATIONAL EVENTS

Mayo Clinic Presents: 15th Annual Hematology/ Oncology Reviews — State of the Art Answers to Most Common Cancer Questions
July 26-31, 2005
Amelia Island, Florida
Event website: **www.mayo.edu/cme/hematology-oncology.html**

XXXth World Congress of International Society of Hematology (ISH)
September 28-October 2, 2005
Istanbul, Turkey
Event website: **www.ish2005istanbul.org**

2005 American Society for Therapeutic Radiology and Oncology Annual Meeting
October 16-20, 2005
Denver, Colorado
Event website: **www.astro.org/annual_meeting/**

The American Society of Hematology 47th Annual Meeting and Exposition
December 3-6, 2005
New Orleans, Louisiana
Event website: **www.hematology.org/meeting/**

Editor's Note

Audio for patients

In the fall of 2000, I found myself at the Miami airport waiting to board a flight to DC for the NIH Consensus Conference on Early Breast Cancer. This was my pre-cell phone era, and my beeper went off alerting me to a call I had been anxiously anticipating for weeks. Greg McIntosh, from the market research firm ReedHaldyMcIntosh, wished to speak with me.

I scrambled for a pay phone to find out about the initial report from the first formal external, independent study of our breast cancer audio series. Greg told me that the initial five interviews with medical oncologists went flawlessly, and based on this, he was confident that his team would be able to recruit and study the remaining 145 randomly selected United States-based physicians in the next few weeks. For some inexplicable reason, this situation was reminiscent of my clinical research years as a member of the University of Miami faculty, when patients would return after their first course of an experimental therapy and I would anxiously pull out x-rays (remember those?) to assess for response.

"Greg, how many of these first five docs listen to our program?" I held my breath waiting for the answer. Greg paused for a moment, checking his notes, and said, "Let's see…1, 2, 3, 4…four of the five." My prolonged exhalation lasted the entire five-hour air and land journey to the Holiday Inn in Bethesda. After years of wondering whether our work was having an impact, the answer was about to emerge.

Third-party continuing medical education programs supported by grants from pharmaceutical companies and distributed without charge to physicians are rarely evaluated independently. Minimal scientifically validated information exists to indicate how often physicians utilize these resources. Programs are generally considered successful if used by five to 10 percent of recipients, and as we all know, a plethora of such educational publications regularly inundate oncologists' mailboxes.

Although it was clear that some oncologists listened to our programs, I was concerned that the "ratings" would be minuscule and that perhaps our company would go out of business. Needless to say, the decision to conduct this study was one of the greatest risks of my totally non-MBA-like business career.

In one sense, the survey would differentiate our work from many other CME groups because it was an independent review. The core of our group includes

clinician writers who are used to the scientific method because of prior experience with clinical research. Greg's company was similar to the external data monitoring committees we had long dealt with in clinical trials. Of course, the other side of this slippery slope is that if our work was not being utilized, we would all need to seek other jobs.

The impetus for the decision to do the study came from Brian Moss, a former AstraZeneca marketing person on the Nolvadex® (tamoxifen) team, who left the company to seek an MBA from Columbia. Brian consulted with our group part-time during his two years in New York and strongly recommended that we do the study, partly because he believed in the work, and partly because it was the only way to ensure fiscal security for the future. Brian would later move his family to Miami and join our group as Executive Vice President of Business Development.

The next day, at the nonmomentous and possibly last NIH breast cancer consensus conference, I was still somewhat on cloud nine. During one of the breaks, I ran into Hy Muss and Kathy Pritchard and told them about the first five "patients" in the study of our audio series. Hy quipped, "If I were looking for a 10 to 20 percent response rate in a Phase II trial, and four of the first five patients responded, I'd be pretty optimistic." Kathy — ever the skeptic and usually the first person to the microphone to shoot holes in the data after a research presentation — talked about confidence intervals and events; however, on a deep and personal level, I knew things had changed.

By the following month, Greg and his team had discovered that almost two thirds of the oncologists in the United States were listening to our tapes. (Although the series began in 1988, CDs were not added until 2001.) We now produce nationally distributed audio series on cancer of the lung, prostate, breast, colon-rectum and, of course, NHL. Our US-based audience includes medical oncologists, radiation oncologists, surgeons, urologists and nurses. Enclosed with this medical oncologist issue of *NHL Update* is our first series for cancer patients and perhaps the biggest leap of faith we have taken since the 2000 market research study.

We had been thinking about producing a series for patients for a long time and have consulted endlessly with physicians, nurses and patients to determine if the concept has merit and how to optimally distribute this type of product. After much time, reflection and forethought, our hope is that we have developed a resource that will provide general background information that can supplement and reinforce the specific individualized recommendations made by a treating oncologist.

For this first issue, we utilized the successful approach of our audio series for healthcare professionals — one-on-one interviews with clinical research leaders. The initial interviews were fascinating, and I quickly learned that some researchers naturally rattle off well-thought-out explanations of diagnostic and therapeutic procedures in layperson's terms while others persistently use language that most "normal people" would find impossible to comprehend.

The first speaker is John Leonard, who describes in detail a de-identified case from his practice, and throughout the interview, he recreates his discussions with this 55-year-old mother of one of the nurses in his hospital.

The theme of this first issue is the role of clinical research in patient care, including ongoing studies that patients may join and recently reported trials with data that are relevant in treatment decisions. John's patient had high-risk diffuse large B-cell lymphoma, and in a remarkably understandable manner, he explains how this patient's somewhat adverse IPI score was derived and what this meant in terms of prognosis.

He reviews R-CHOP, the standard therapy in this situation, and patiently discusses the expected side effects and toxicities associated with each agent in the regimen. He then comments on clinical research and how prior trials have moved the field forward and, in this case, defined the risks and benefits of R-CHOP in this situation.

Dr Leonard then explains the difference between chemotherapy and immune therapy, such as rituximab, and expounds on the new agents and approaches that are under active investigation, including a trial at his institution evaluating R-CHOP plus bortezomib. John then discusses this patient's decision to enter that trial, the tumor regression that ensued and a two-day hospitalization for neutropenic fever, which occurred in spite of the use of pre-emptive growth factors.

The next speaker on the program is Mitchell Smith, who tackles mantle-cell lymphoma and presents a patient treated on a Phase II ECOG study of R-CHOP followed by radioimmunotherapy. Mitch is another physician with the rare and unique ability to make complex concepts comprehensible, and he has a kind but honest approach to discussing the threats posed by this disease.

Brad Kahl, the final researcher interviewed for the patient series, reviews the challenging topic of follicular lymphoma. Brad is the principal investigator of ECOG's Phase III RESORT trial, which evaluates indefinite rituximab maintenance after up-front single-agent treatment compared to up-front rituximab followed by re-administration on relapse. Brad not only beautifully explains the background to this important trial and the difficult-to-comprehend concept of randomization, but also why the associated correlative science work on tissue specimens in the study is so important in helping us to better understand the effect of the monoclonal antibody rituximab on lymphoma cells.

The goal of this patient education program is to provide expert perspectives that will supplement and reinforce what patients learn from their physicians and nurses. Our next issue will take a different approach, as we will interview a number of patients with NHL and present relevant comments from research leaders.

This is somewhat of a bold new world for our CME group, but we have confidence that by using a scientific approach to evaluate this work, we will find something helpful for patients. We invite patients and healthcare professionals to

listen to the enclosed CDs or to visit our website (**www.NHLUpdate.com/Patients**) and download the audio program without cost. The full transcript of the patient program is also available on our website and on the first audio CD.

This experiment in patient education requires careful evaluation. We are interested in knowing whether the discussions on this audio program are understandable and useful and what other topics might be of interest to patients. We are also anxious to find out how the web works as a method of distribution. We are particularly curious whether patients who are internet naïve will ask their children or grandchildren to utilize their music downloading experience to assist in obtaining our program. Feedback from all is most welcome, and we invite you to tell us what works and what needs to be fixed.

—Neil Love, MD
NLove@ResearchToPractice.net

Select publications

Ghielmini M et al. **Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule.** *Blood* 2004;103(12):4416-23. **Abstract**

Habermann TM et al. **Rituximab-CHOP versus CHOP with or without maintenance rituximab in patients 60 years of age or older with diffuse large B-cell lymphoma (DLBCL): An update.** *Proc ASH* 2004;**Abstract 127**.

Hainsworth JD et al. **Maximizing therapeutic benefit of rituximab: Maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma — A randomized phase II trial of the Minnie Pearl Cancer Research Network.** *J Clin Oncol* 2005;23(6):1088-95. **Abstract**

Hainsworth JD et al. **Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: A phase II trial of the Minnie Pearl Cancer Research Network.** *J Clin Oncol* 2003;21(9):1746-51. **Abstract**

Halaas JL et al. **The Follicular Lymphoma International Prognostic Index (FLIPI) is superior to WHO/REAL histological grade for identifying high-risk patients: A retrospective review of the MSKCC experience in 260 patients with follicular lymphoma.** *Proc ASH* 2004;**Abstract 3268**.

Hiddemann W et al. **Effect of the addition of rituximab to front line therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) on the remission rate and time to treatment failure compared to CHOP alone in mantle cell lymphoma: Results of a prospective randomized trial of the German Low Grade Lymphoma Study Group.** *Proc ASCO* 2004;**Abstract 6501**.

Hochster HS et al. **Results of E1496: A phase III trial of CVP with or without maintenance rituximab in advanced indolent lymphoma (NHL).** *Proc ASCO* 2004;**Abstract 6502**.

Marcus R et al. **CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma.** *Blood* 2005;105(4):1417-23. **Abstract**

Romaguera JE et al. **Rituximab plus hypercvad (R-HCVAD) alternating with rituximab plus high-dose methotrexate-cytarabine (R-M/A) in untreated mantle cell lymphoma (MCL): Prolonged follow-up confirms high rates of failure-free survival (FFS) and overall survival (OS).** *Proc ASH* 2004;**Abstract 128**.

van Oers MH et al. **Chimeric anti-CD20 monoclonal antibody (rituximab; Mabthera®) in remission induction and maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: A phase III randomized Intergroup clinical trial.** *Proc ASH* 2004;**Abstract 586**.

Nonprotocol approach to patients with follicular lymphoma

I see this as a chronic disease. The goal is to keep it quiescent for as long as possible while maintaining quality of life and hopefully improving survival. When I see a new patient, I conduct an assessment with the usual staging methods.

Unless the patient is sick, I do nothing for three or four months to develop a sense of the pace of the disease. This allows me to determine if "watch and wait" is a possibility. If the disease progresses, I may say, "Let's just cut to the chase and start treatment."

I find that some patients and physicians are minimalists, wanting to hold off on treatment and use less intensive treatments. Rituximab alone, for example, is a godsend to those patients because they want to avoid chemotherapy. Other patients are much more proactive and want to use intensive treatments because they want to go into remission and, at least psychologically, have the disease under control.

In my practice, if a patient needs treatment, I use either single-agent rituximab or, if I am using chemotherapy, in most situations it's chemotherapy plus rituximab. I use single-agent rituximab for relatively few patients because most of my patients prefer to be observed initially, and they receive chemotherapy plus rituximab when they clearly require treatment. However, in some situations I'll use rituximab alone, and in other patients I may use chlorambucil.

Rituximab maintenance in patients with indolent lymphomas

ECOG-E4402 (the RESORT trial) treats patients who by definition are less sick and have less tumor burden with up-front rituximab alone. The trial will evaluate whether patients treated with induction rituximab do better with maintenance rituximab than with re-treatment with rituximab at the time of disease progression (1.1).

Dr Leonard is the Clinical Director at the Center for Lymphoma and Myeloma and Associate Professor of Medicine at Weill Medical College of Cornell University, New York Presbyterian Hospital, New York, New York.

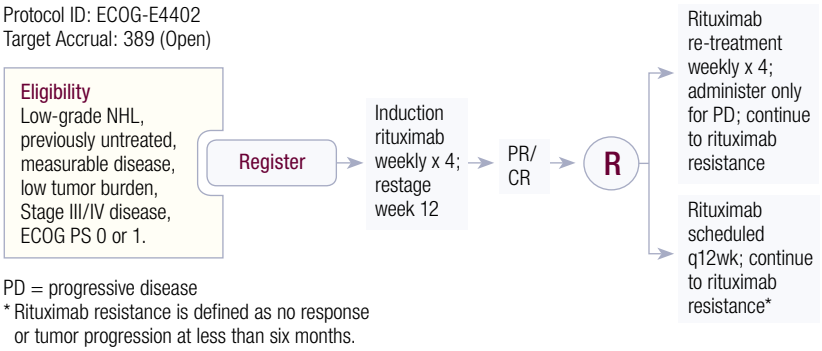
The RESORT trial uses maintenance rituximab until disease progression, instead of for two years. It's hard to say which strategy is best because without the data, we don't know the answer in this setting. We need studies to determine: (1) if there are long-term toxicities associated with indefinite maintenance, which we haven't yet seen with two years of maintenance, and (2) if benefits exist for patients with long-term therapy.

In a patient receiving rituximab monotherapy or rituximab plus chemotherapy for indolent lymphoma, I base my decision about the use of maintenance rituximab on what I expect the patient's disease to do following initial treatment. If I'm expecting the patient to have a long remission with the induction regimen — based on their past history, the extent of the disease and how they did with their last regimen — I would probably not be as aggressive about using maintenance rituximab. On the other hand, in someone with a relatively short remission, I would be more prone to use maintenance rituximab to try to extend it, because I'd be worried that the induction regimen may not do the job.

Limited data exist in this regard and most of the time in my practice, this is determined by the patients. Some patients like to be on therapy. Being proactive makes them feel good. Others say, "I'd rather not see you if I can go another year without treatment. I don't like the reminder of having to come back to be treated." There's room for different practice styles and patients' perspectives.

Studies in patients receiving rituximab alone (Hainsworth 2005) or chemotherapy alone (Hochster 2004) followed by maintenance rituximab clearly suggest that maintenance rituximab extends progression-free survival. The question is, do patients who receive chemotherapy and rituximab together as induction benefit from maintenance rituximab? That relatively common scenario is also currently being studied.

1.1 RESORT Trial: Phase III Randomized Study of Rituximab in Patients with Low Tumor Burden Indolent Non-Hodgkin's Lymphoma



SOURCES: NCI Physician Data Query, June 2005; Gregory S. Presentation. Research To Practice, May 17, 2004.

CALGB trials of rituximab in combination with other biologic agents

The CALGB is evaluating a variety of biologic agents in combination with rituximab. For patients who need intensive treatment because they're sick, the chemotherapy plus rituximab regimens can be very useful. However, many patients who need treatment aren't that sick, and rituximab is useful. Can we add other biologic agents to enhance its activity?

To avoid chemotherapy altogether, we're pursuing the use of immunomodulatory drugs to enhance rituximab's activity without the toxicity associated with chemotherapy. Preclinical data suggest that lenalidomide, a derivative of thalidomide, may enhance a variety of immune functions that could augment the activity of rituximab. The CALGB is planning a randomized Phase II trial in patients with relapsed follicular lymphomas comparing the combination of rituximab and lenalidomide to rituximab alone.

The CALGB is also planning a single-arm, up-front trial of rituximab plus galiximab, an anti-CD80 monoclonal antibody. Dr Myron Czuczman has data from a Phase I trial with single-agent galiximab published in the *Journal of Clinical Oncology* (Czuczman 2003). In addition, I'm presenting our initial data of rituximab plus galiximab at the Ninth International Conference on Malignant Lymphoma in Lugano, Switzerland (Leonard 2005). I believe the approach of antibody cocktails for patients who don't need chemotherapy is both promising and appealing to patients.

Lenalidomide (Revlimid®)

Many are familiar with lenalidomide from Dr Alan List's work in patients with myelodysplasia (List 2005). This agent is also being studied in patients with multiple myeloma, where it has activity. Lenalidomide was developed as a second-generation thalidomide to minimize toxicity and enhance efficacy. It has immunomodulatory effects, and in preclinical models it enhances the activity of rituximab. It's probably related to natural killer cells and enhancement of antibody-dependent, cell-mediated cytotoxicity. The main side effects associated with lenalidomide are cytopenias, which have been seen in the studies in patients with myeloma or myelodysplasia. In patients with lymphomas, the clinical trials are just starting.

Galiximab (IDEC-114)

Galiximab is an antibody against CD80, originally developed as a therapy for psoriasis. CD80 is a costimulatory molecule expressed on a variety of cells, including B-cell lymphomas. It may be another target that could be used in conjunction with CD20, rituximab's target. Preclinical studies have suggested that galiximab can bind to lymphoma tumor cells. In addition, preclinical mouse models suggest galiximab can also enhance the activity of rituximab.

The Phase I study, which will be published soon, found that four weekly doses of galiximab had some clinical activity across a wide variety of dose levels in

patients with follicular lymphomas (Czuczman 2003). Clinical responses were seen, which took some time to develop. In some cases it took six months to a year, suggesting there might be some secondary immune effect. The agent was well tolerated with minimal side effects (mainly infusion reactions) that appear to be limited compared to rituximab. Our next step with galiximab was to combine it with rituximab. We will report that the combination is well tolerated and has clinical activity in patients with follicular lymphomas (Leonard 2005).

Recent clinical trials in mantle-cell lymphoma

Mantle-cell lymphoma is a disease of older patients. One of the challenges is that many patients are not great candidates for more intensive regimens. Much of the work that has been done is trying to dose-intensify treatment. Traditionally, CHOP, CVP or some purine-analog regimen has been used for patients with mantle-cell lymphomas. Autologous transplants have been done in first remission in a variety of studies, with some suggestions of improved outcomes. However, randomized trial data have not been available until recently.

At ASCO 2004, Dr Hiddemann presented a complicated study comparing CHOP to R-CHOP and evaluating the role of autologous transplant. It appears that R-CHOP is better than CHOP to a modest degree, with improvements in response rates and time to progression (Hiddemann 2004). I think if you're going to use a CHOP-based regimen, it's important and useful to incorporate rituximab as part of the regimen. But I think the long-term outcomes with R-CHOP are quite limited, and we need to do more.

At ASH 2004, Dr Martin Dreyling presented data from a trial evaluating patients receiving R-CHOP or CHOP as induction therapy who were randomly assigned to a less intensive maintenance (eg, interferon) or autologous stem cell transplant (ASCT) at first remission. The preliminary results from this study suggest that patients stay in remission longer when treated with ASCT. However, thus far we have not seen an overall survival benefit (Dreyling 2004).

Another approach, popularized by the MD Anderson group, uses the rituximab plus the hyper-CVAD combination. At ASH 2004, Dr Jorge Romaguera presented some of their data in close to 100 patients treated with a regimen of rituximab plus hyper-CVAD. Those data show multiyear progression-free and overall survivals for patients treated with rituximab plus hyper-CVAD (Romaguera 2004).

Clinical approach to patients with mantle-cell lymphoma

A regimen of rituximab plus CHOP may be appropriate in more elderly patients with an impaired performance status. In some cases, you can even use rituximab plus CVP. Most of the time in younger patients or patients with a better performance status, we're looking at a more intensive approach. In my mind, the approaches with the best activity, albeit in selected patients, are either rituximab plus CHOP followed by an autologous transplant or rituximab plus hyper-CVAD. Since we don't have randomized trials comparing them, the treatment is determined by what's more tolerable to the patient.

Select publications

Czuczman MS et al. **Interim results from a phase I/II study of anti-CD80 antibody (IDEC-114) therapy for follicular NHL.** *Proc ASCO* 2003;**Abstract 2310**.

Dreyling M et al. **Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: Results of a prospective randomized trial of the European MCL Network.** *Blood* 2005;105(7):2677-84. **Abstract**

Forstpointner R et al. **The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group.** *Blood* 2004;104(10):3064-71. **Abstract**

Ghielmini M et al. **Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: A study of the Swiss Group for Clinical Cancer Research (SAKK).** *J Clin Oncol* 2005;23(4):705-11. **Abstract**

Goy A et al. **Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma.** *J Clin Oncol* 2005;23(4):667-75. **Abstract**

Hainsworth JD et al. **Maximizing therapeutic benefit of rituximab: Maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma — A randomized phase II trial of the Minnie Pearl Cancer Research Network.** *J Clin Oncol* 2005;23(6):1088-95. **Abstract**

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Hochster HS et al. **Results of E1496: A phase III trial of CVP with or without maintenance rituximab in advanced indolent lymphoma (NHL).** *Proc ASCO* 2004;**Abstract 6502**.

Lenz G et al. **Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: Results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG).** *J Clin Oncol* 2005;23(9):1984-92. **Abstract**

Leonard J. **Results from a phase I/II study of galiximab (anti-cd80) in combination with rituximab (anti-cd20) for relapsed or refractory, follicular NHL.** Presentation. Ninth International Conference on Malignant Lymphoma 2005. No abstract available

List A et al. **Efficacy of lenalidomide in myelodysplastic syndromes.** *N Engl J Med* 2005;352(6):549-57. **Abstract**

Marcus R et al. **CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma.** *Blood* 2005;105(4):1417-23. **Abstract**

O'Connor OA et al. **Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma.** *J Clin Oncol* 2005;23(4):676-84. **Abstract**

Romaguera JE et al. **Rituximab plus hypercvad (R-HCVAD) alternating with rituximab plus high-dose methotrexate-cytarabine (R-M/A) in untreated mantle cell lymphoma (MCL): Prolonged follow-up confirms high rates of failure-free survival (FFS) and overall survival (OS).** *Proc ASH* 2004;**Abstract 128**.

van Oers MH et al. **Chimeric anti-CD20 monoclonal antibody (rituximab; Mabthera®) in remission induction and maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: A phase III randomized Intergroup clinical trial.** *Proc ASH* 2004;**Abstract 586**.

PET scans as prognostic tools in large cell lymphoma or Hodgkin's disease

In patients with large cell lymphoma, we did PET scans around day 18, 19 or 20, prior to the second dose of chemotherapy. In patients with Hodgkin's disease, we did PET scans just prior to the second cycle of therapy (eg, after two treatments of doxorubicin/bleomycin/vinblastine/dacarbazine [ABVD]) on day 25, 26 or 27 (Kostakoglu 2002). We found that if the PET scan went from positive before therapy to totally negative after one cycle, none of those patients relapsed after nearly two years of follow-up.

In contrast, the overwhelming majority of patients who had a positive PET scan after the first cycle of chemotherapy have relapsed. A few patients who were positive after the first cycle went into complete remission and stayed in complete remission. The majority of these patients had initial standardized uptake value (SUV) scores that were very high and became low, although not back to baseline, after the first cycle of therapy. However, an overwhelming number of patients with high initial, persistent SUV scores relapsed.

We believe the PET scan result after one cycle of therapy is highly predictive of how patients will do in terms of positive and negative predictive value. We found that a PET scan after one cycle of therapy was more predictive than a PET scan at the completion of therapy (Kostakoglu 2002). Others have done PET scans after anywhere from two to four cycles of therapy. Their data are very similar to ours in that if a patient's PET scan turns negative, the likelihood of relapsing is low. Likewise, if the PET scan remains positive, the likelihood of being cured is not good.

PET scans in patients with transformed lymphomas

The overwhelming majority of patients with low-grade lymphoma tend to have very low SUV scores (ie, two, three, four). If it is suspected that a patient's disease is transforming and a PET scan is done, one lymph node or organ often has a very high SUV score, which indicates where to obtain a biopsy. We think

Dr Coleman is a Clinical Professor of Medicine at Weill Medical College of Cornell University and Director of the Center for Lymphoma and Myeloma, New York Presbyterian Hospital, New York, New York.

PET scans are useful in differentiating the transformation from low-grade to high-grade lymphoma. We don't have enough cases to determine the significance of a negative PET scan after therapy in patients with transformed lymphoma in terms of their overall long-term survival. In fact, transformed lymphoma is far more difficult to treat than de novo aggressive lymphoma.

Nonprotocol therapy for patients with indolent lymphomas

The decision to use rituximab by itself or in combination with chemotherapy often depends on the patient's presentation. It's my impression, and data support it, that patients with bulky disease don't do as well with rituximab alone as they do with combination chemotherapy with rituximab.

Again, a great deal depends on your intent. For a young patient in whom you don't intend to transplant and would like to achieve a sustained long-term remission, I would suggest using chemotherapy with rituximab.

In terms of which chemotherapy to combine with rituximab, I think you have to be very selective. Chemotherapy selection depends on the patient and what you seek to achieve. I tend toward using fludarabine, mitoxantrone, dexamethasone and rituximab (FNDR). Not much difference exists between FN and CHOP. Some would contend you don't need to use CHOP and that you can simply use CVP or single-agent therapy with rituximab.

It's been my tendency to use combination chemotherapy. If I intend to take the patient to a transplant, I may prefer CVP or CHOP, as they are less stem cell toxic. On the other hand, if a patient wants to be engaged in full-time activity, I find that the FND is more convenient, and I don't have to put in an infusaport. The patients don't lose their hair, develop neuropathy or experience much nausea with this combination.

However, FND has drawbacks. Fludarabine has been implicated in impacting stem cells. So if future transplantation is being considered, it may not be best to use a combination regimen employing a nucleoside analog. The other disadvantage with FND or any combination with fludarabine is that it is a very potent immunosuppressant. It knocks out T cells to a large degree. This suppression of T cells translates into the potential for opportunistic infections.

Maintenance therapy with rituximab

Maintenance rituximab remains a highly controversial subject. The most telling study to date is the one by Dr Hainsworth, although it was certainly underpowered. This study evaluated maintenance rituximab versus re-treatment upon relapse. He found that the total amount of time a patient would derive benefit from rituximab was the same whether they received maintenance rituximab or were re-treated upon relapse. Nevertheless, patients who received maintenance rituximab tended to stay in remission longer (Hainsworth 2005; [2.1]).

Besides being more expensive, when maintenance rituximab is used, almost all of the patients become hypogammaglobulinemic. A small subset of those patients develops chronic sinusitis, which does not respond to antibiotics or any

other type of symptomatic treatment. These patients ultimately require treatment with gamma globulins in much higher doses than we commonly use. I don't view rituximab as an innocuous therapy.

I bring up the issue of maintenance rituximab with my patients, and sometimes I believe maintenance rituximab is necessary. In situations in which I'm worried that relapse will carry additional problems, I maintain the patients on rituximab. For example, Waldenstrom's macroglobulinemia can often be associated with neuropathy. We don't want patients to relapse and have the neuropathy return. Therefore, in patients with Waldenstrom's macroglobulinemia, I use maintenance rituximab. It's important to obviate any kind of complication that may be a result of the malignancy.

2.1 Phase II Randomized Trial Comparing Maintenance Rituximab to Rituximab Re-treatment at Progression in Patients with Indolent NHL

	Rituximab maintenance (n = 44)	Rituximab re-treatment (n = 46)	*p*-value
Median PFS	31.3 mo	7.4 mo	0.007
Median duration rituximab benefit	31.3 mo	27.4 mo	0.94
Three-year survival	72%	68%	NS
Number in continuous remission	20	11	0.05
Number in complete remission	10	1	0.03

PFS = progression-free survival; NS = not significant

SOURCE: Hainsworth JD et al. **Maximizing therapeutic benefit of rituximab: Maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma — A randomized phase II trial of the Minnie Pearl Cancer Research Network.** *J Clin Oncol* 2005;23(6):1088-95. **Abstract**

Select publications

Habermann TM et al. **Rituximab-CHOP versus CHOP with or without maintenance rituximab in patients 60 years of age or older with diffuse large B-cell lymphoma (DLBCL): An update.** *Proc ASH* 2004;**Abstract 127**.

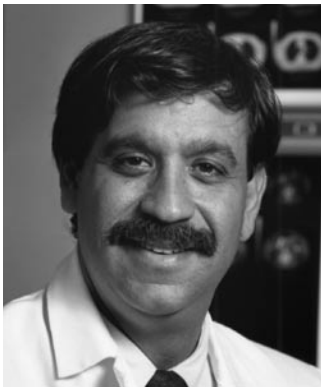
Hainsworth JD et al. **Maximizing therapeutic benefit of rituximab: Maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma — A randomized phase II trial of the Minnie Pearl Cancer Research Network.** *J Clin Oncol* 2005;23(6):1088-95. **Abstract**

Kostakoglu L et al. **PET predicts prognosis after 1 cycle of chemotherapy in aggressive lymphoma and Hodgkin's disease.** *J Nucl Med* 2002;43(8):1018-27. **Abstract**

Andrew D Zelenetz, MD, PhD

EDITED COMMENTS

Clinical algorithm for patients with follicular lymphoma



In a young patient with a low bulk of disease and a low-risk Follicular Lymphoma International Prognostic Index (FLIPI) score, I might recommend observation, although many young patients are uncomfortable with that concept.

In a patient we want to treat — maybe because of a high FLIPI score or progression of disease — the decision comes down to age, stage, extent of disease and nature of the symptoms.

For example, we would treat a patient presenting with a 12-centimeter mesenteric mass who is anorexic and losing weight with combination chemotherapy — probably CHOP — and rituximab for a more rapid response, rather than a milder treatment. If that same patient were 68 years old with cardiac issues, we might try a less toxic regimen like FND.

I would not recommend FND for a younger patient because it prevents the collection of peripheral blood progenitor cells for autologous stem cell transplant — which I believe should be included in the list of treatment options for younger patients. Although we may not cure the patient, there is no question that autologous stem cell transplant can provide long-term remissions.

Histological grade versus FLIPI to identify patients at high risk

I'm not interested in the grade of the disease when considering how to treat a patient. We published data at ASH in 2004 that suggest grade has no impact on outcome (Halass 2004; [3.1]).

The most important factor, which has an enormous impact on outcome, is the FLIPI. This is the most predictive tool we have for outcome in patients with follicular lymphoma. The median survival for patients at low risk, according to the FLIPI score, is 16 years, whereas patients at high risk have a median survival of five years.

Dr Zelenetz is Chief of Lymphoma Service at Memorial Sloan-Kettering Cancer Center in New York, New York.

3.1 FLIPI versus WHO/REAL Histological Grade for Identifying Patients at High Risk

Category	Number of patients (%)	Median survival	10-year survival
FLIPI*			
Low risk	128 (49%)	16.5 years	76%
Intermediate risk	76 (29%)	12.4 years	52%
High risk	56 (22%)	5.4 years	24%
Histological grade†			
Grade 1	72 (28%)	25.4 years	62%
Grade 2	102 (39%)	10.3 years	56%
Grade 3a	68 (26%)	18.7 years	60%
Grade 3b	18 (7%)	Not reached	65%

* p-value < 0.0001
† p-value = 0.41

SOURCE: Halaas JL et al. **The Follicular Lymphoma International Prognostic Index (FLIPI) is superior to WHO/REAL histological grade for identifying high-risk patients: A retrospective review of the MSKCC experience in 260 patients with follicular lymphoma.** *Proc ASH* 2004;**Abstract 3268**.

Clinical trials of radioimmunotherapy

The Phase II study of CHOP followed by tositumomab/iodine I-131 tositumomab (Bexxar®) in previously untreated patients with follicular lymphoma served as a pilot for the current Phase III trial (Press 2003). In the Phase II trial, the complete response rate increased from 39 to 66 percent after radioimmunotherapy was added.

The shape of the curves to date in this trial looks unlike that of other historical curves generated by SWOG — at three years of median follow-up, the curve is still up around 80 percent. While this is not a substitute for a randomized trial, and the Phase III trial is ongoing, it is an intriguing result.

In 2003, I reported on a study in untreated mantle-cell lymphoma in which patients received Bexxar as initial treatment followed by CHOP, a reverse of the Press regimen (Zelenetz 2003). We also saw impressive, high response rates of approximately 75 percent, with approximately 40 percent of patients experiencing a complete response following treatment.

Whether it's better to give radioimmunotherapy followed by chemotherapy or the reverse will have to be determined by prospective trials.

The Kaminski data are also quite interesting (Kaminski 2005). In this trial, 76 patients with previously untreated Stage III or IV follicular lymphoma at a single center received Bexxar as initial therapy. It was an unusual patient population in that the median age of the patients was 49 years.

The article did not categorize the patients by risk; however, it did suggest in a multivariate analysis that total tumor bulk of maximal node diameter greater than 5 cm was associated with less of a response and a shorter duration of remis-

sion. I find the data quite intriguing — it's a simple treatment, and the majority of patients remain disease free for a prolonged period of time. It's clearly an approach that warrants further study, but it requires a carefully controlled randomized study. At this time, I don't believe patients should receive radioimmunotherapy as their first treatment outside of a clinical trial.

Use of radioimmunotherapy in a nonprotocol setting

I use radioimmunotherapy in patients with rituximab-refractory disease and in patients who have relatively chemo-refractory disease. I try not to use radioimmunotherapy in fourth, fifth or sixth relapse; rather, I use it second, third or fourth line because that's where we've seen much higher proportions of long-term durability. With both agents, 20 to 25 percent of treated patients experience durable long-term remissions — and approximately 20 percent are still in remission at five years.

I'm a big believer in radioimmunotherapy, and I assisted in the development of Bexxar. We have done a number of studies of Bexxar and ibritumomab tiuxetan (Zevalin®) and have been conducting such trials for almost 10 years now. These are highly active drugs — the most active drugs we have for the treatment of indolent lymphoma — but unfortunately, they are not used in the community for a variety of reasons.

In private practice, the oncologist may not know the nuclear medicine physician, and the nuclear medicine physician may not be interested in therapeutic approaches. In some areas of the country, nuclear medicine physicians are so uninterested that radioimmunotherapy is handled by radiation oncologists.

Select publications

Ghielmini M et al. **Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule.** *Blood* 2004;103(12):4416-23. **Abstract**

Hainsworth JD et al. **Maximizing therapeutic benefit of rituximab: Maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma — A randomized phase II trial of the Minnie Pearl Cancer Research Network.** *J Clin Oncol* 2005;23(6):1088-95. **Abstract**

Halaas JL et al. **The Follicular Lymphoma International Prognostic Index (FLIPI) is superior to WHO/REAL histological grade for identifying high-risk patients: A retrospective review of the MSKCC experience in 260 patients with follicular lymphoma.** *Proc ASH* 2004;**Abstract 3268**.

Kaminski MS et al. **131I-tositumomab therapy as initial treatment for follicular lymphoma.** *N Engl J Med* 2005;352(5):441-9. **Abstract**

Press OW et al. **A phase 2 trial of CHOP chemotherapy followed by tositumomab/iodine I 131 tositumomab for previously untreated follicular non-Hodgkin lymphoma: Southwest Oncology Group Protocol S9911.** *Blood* 2003;102(5):1606-12. **Abstract**

Zelenetz AD et al. **Initial Treatment of Mantle Cell Lymphoma with Sequential Radioimmunotherapy with Tositumoamb/Iodine I131 I-Tositumoamb followed by CHOP Chemotherapy Results in a High Complete Remission Rate.** *Proc ASH* 2003;**Abstract 1477**.

Post-test:

Non-Hodgkin's Lymphoma Update — Issue 3, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. ECOG-E4402 (the RESORT trial) will randomly assign patients with low-risk, indolent lymphoma treated with up-front rituximab monotherapy to:
   a. Maintenance rituximab
   b. Maintenance CHOP
   c. Treatment with rituximab upon disease progression
   d. Both a and b
   e. Both a and c

2. SWOG-S0016 randomly assigns patients with follicular lymphoma to:
   a. CHOP
   b. CHOP plus rituximab
   c. CHOP followed by Bexxar
   d. Both b and c
   e. a, b, and c

3. In a study of patients with mantle-cell lymphomas, R-CHOP was better than CHOP in terms of response rates and time to progression.
   a. True
   b. False

4. In patients with large cell lymphoma or Hodgkin's disease, PET scan results after one cycle of therapy may be more predictive than PET scan results at the completion of therapy.
   a. True
   b. False

5. According to the results of ECOG-E4494, patients with diffuse large B-cell lymphomas treated with either induction or maintenance rituximab in combination with CHOP have an improvement in the time to treatment failure.
   a. True
   b. False

6. Lenalidomide and galiximab are two investigational agents that may enhance or augment the efficacy of rituximab.
   a. True
   b. False

7. Data presented at ASH in 2004 showed that the FLIPI is _____ to histological grade for identifying patients at high risk with follicular lymphoma.
   a. Superior
   b. Equivalent
   c. Inferior

8. Trial data published by Ghielmini in 2004, comparing four weeks of standard rituximab treatment with or without four weeks of extended dosing, showed the median, event-free survival nearly doubled in the extended treatment arm.
   a. True
   b. False

9. An EORTC trial is evaluating the role of maintenance rituximab in patients who received rituximab with induction chemotherapy.
   a. True
   b. False

10. In patients with mantle-cell lymphoma, Hiddemann demonstrated that R-CHOP was better than CHOP in terms of response rates and time to progression.
    a. True
    b. False

11. Clinical trials have demonstrated that the amount of time patients with indolent NHL derive benefit from rituximab is longer if they receive it as maintenance therapy instead of as re-treatment upon progression.
    a. True
    b. False

Post-test Answer Key: 1e, 2e, 3a, 4a, 5a, 6a, 7a, 8a, 9a, 10a, 11b

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To what extent does this issue of *NHLU* address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in non-Hodgkin's lymphoma (NHL) treatment and incorporate these data into management strategies for patients with NHL. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Utilize individual patients' risk factors and disease classification to tailor therapy for individual subgroups of patients with NHL. . . . . 5 4 3 2 1 N/A
- Discuss the risks and benefits of monoclonal antibody therapy and radioimmunotherapy alone and in combination with chemotherapy for patients with NHL, and counsel appropriately selected patients about the risks and benefits of these agents. . . . . 5 4 3 2 1 N/A
- Describe and implement an algorithm for sequencing of therapies in the management of indolent and aggressive NHL. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
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Morton Coleman, MD	5 4 3 2 1	5 4 3 2 1
Andrew D Zelenetz, MD, PhD	5 4 3 2 1	5 4 3 2 1

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Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
Overall quality of material. . . . . 5 4 3 2 1 N/A
Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
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Non-Hodgkin's Lymphoma™

UPDATE

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