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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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SPECIAL FEATURE:

PowerPoint Photo Atlas: Cutaneous Lymphoma

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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 2 of *Non-Hodgkin's Lymphoma Update* is to support these global objectives by offering the perspectives of Drs Rosen, Smith and Kahl 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. **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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Dr Rosen – **Speakers Bureau**: Genentech BioOncology. **Dr Smith** – **Grants/Research Support**: Sanofi-Aventis; **Speakers Bureau**: Biogen Idec, Genentech BioOncology. **Dr Kahl** – **Grants/Research Support**: Biogen Idec, Genentech BioOncology, Millennium Pharmaceuticals Inc.

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Editor's Note

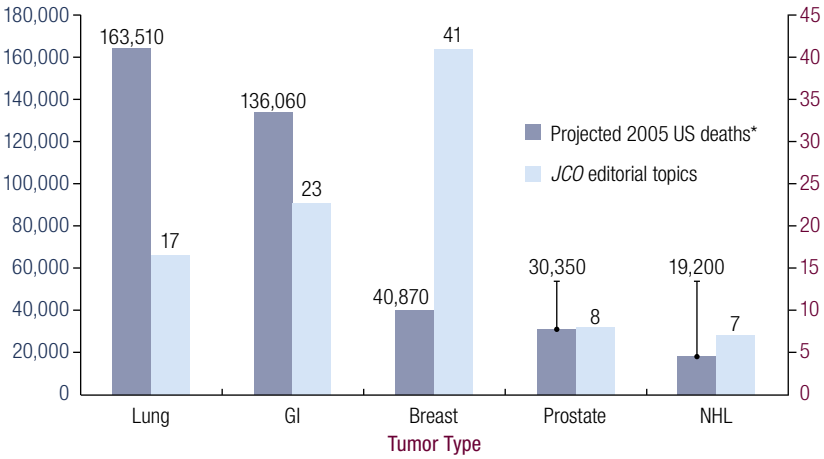
Fascinating text

For oncologists with time to read, the editorials published in the *Journal of Clinical Oncology* are some of the most interesting cancer pages available. February 2005 was a particularly noteworthy month in the *JCO* thanks to two superb commentaries about non-Hodgkin's lymphoma.[1,2]

The compelling pieces by Sandra Horning on rituximab monotherapy in B-cell lymphoma and Richard Fisher on mantle cell lymphoma are also noteworthy because NHL is a relatively rare topic for *JCO* editorials. A quick perusal of work published in the last two years is quite telling, as there is a clear emphasis on breast cancer (1.1).

We shall see if this trend continues as biologic targeted agents continue to be integrated into the management of many tumor types, including lung and colorectal cancer — two diseases that have traditionally been considered resistant to systemic therapy and frustrating for the lack of new research data to discuss, until recently.

1.1 Most Common Tumor Site Topics for *JCO* Editorials: 2003 to 2005 — Correlation with 2005 US Mortality



SOURCE: * Jemal A et al. **Cancer Statistics, 2005**. *CA Cancer J Clin* 2005;55(1):10-30. **Abstract**

Dr Horning was the first investigator interviewed for this CME audio series, and her editorial comments on three key rituximab papers published in the same issue of the *JCO*[3-5] relate to a number of current research questions with direct application to clinical practice, including management of asymptomatic patients with indolent disease. The data from these and other studies cause Dr Horning to conclude, "Rituximab monotherapy is effective and safe in patients with indolent follicular lymphoma, both at diagnosis and at progression after prior therapy." From her perspective, this has major clinical implications.

Is it still appropriate to observe asymptomatic patients with low-grade lymphoma in light of these data? Although patient preferences and physician judgment may determine the answer to this question, rituximab does present a far less toxic alternative to chemotherapy for patients who are not comfortable with being observed without treatment.

— Sandra J Horning, MD

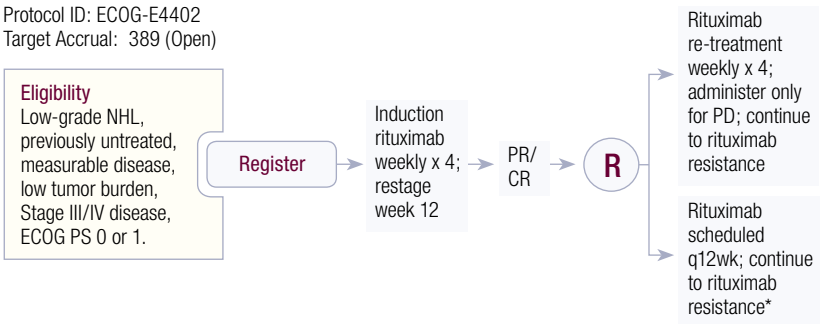
Of particular interest in this issue of the *JCO* is the oft-quoted study by John Hainsworth (the second researcher interviewed for this series) on the use of rituximab maintenance. Dr Horning astutely discusses what we know and don't know about this important treatment strategy and strongly endorses participation in ECOG-E4402 — the RESORT trial — which attempts to define clinical and biologic parameters related to the effects of rituximab and rituximab maintenance.

The principal investigator for the RESORT trial (1.2) is Brad Kahl, who on this issue describes the background, rationale and design for this important trial. I also conducted a separate interview with Dr Kahl specifically for patients, and we will be distributing this valuable conversation as part of a soon-to-be-launched patient audio series. The goal of this patient series is not only to provide patient education, but also improve accrual to important clinical trials like RESORT. This trial should be very appealing for both patients and physicians as it asks an important question related to a common dilemma in this disease. Both randomization arms include up-front rituximab monotherapy, which will greatly facilitate patient accrual. However, there are also other benefits to enrolling. Participants can help move the field forward and still receive one of two very commonly utilized schedules for this therapy, and at the same time know that their tumor tissue will be studied extensively to define the biologic effects of this landmark oncologic agent.

As practitioners, we recognize the heterogeneity of follicular lymphoma and use clinical clues, based on experience or on more formally proposed prognostic schemes such as the follicular lymphoma international prognostic index, to make management recommendations. For low tumor burden patients, observation remains the conservative standard, but rituximab can provide a less toxic therapeutic intervention for those who do not wish to wait, preferably in the context of a clinical trial such as E4402.

—Sandra J Horning, MD

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



PD = progressive disease
* Rituximab resistance is defined as no response or tumor progression at less than six months.

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

Another speaker on this program — Steven Rosen — presents a patient from his practice who chose to enter the RESORT trial. This 36-year-old man was initially followed with watchful waiting; however, when the disease progressed, active antitumor therapy was indicated. Rather than join the tens of thousands of patients each year who are treated off protocol and therefore out of sight of the hoards of translational scientists who would love to study the genomics, proteomics and other biologic aspects of this disease, this patient entered RESORT with confidence that his treatment would be monitored as part of the protocol and that the studies of his tumor tissue would benefit future patients and perhaps even himself.

If we can utilize molecular diagnostics to predict long-term survival for follicular lymphoma, the efficacy of numerous therapeutic options, such as rituximab, combination chemotherapy, radioimmunotherapy or autologous or allogeneic transplantation can be defined in biologic subsets in future clinical investigations to ultimately lead to new therapeutic algorithms for clinical practice. Patients who consent to both tissue acquisition and clinical trials and oncologists who commit to continuous therapeutic progress will be required to fully translate these important new data to optimize therapy for follicular lymphoma.

— Sandra J Horning, MD

None of the 72 *JCO* editorials since 1983 focusing on lymphomas have addressed the topic of cutaneous lymphoma, which is Dr Rosen's career passion, and he eloquently reviews this subject during his interview. We have included a number of interesting clinical photos from Dr Rosen's practice in a mini-atlas contained in this booklet. PowerPoint slides of these are also available on the enclosed CD and our website, **www.NHLUpdate.com**.

While Dr Horning discussed one of the more common and well-known variants of NHL, the editorial by Dr Fisher succinctly summarizes the relatively recent gestation and birth of the concept of a less common tumor, mantle cell lymphoma — a disease that has always been out there but was not delineated in lymphoma classification systems until the early 1990s.

> *Morphology alone was not sufficient to accurately separate these cases from other "small round cell" lymphomas. However, morphology plus an immunophenotype consisting of CD20+, CD22+, IgM+, IgD+, and CD5+, as well as either detection of the characteristic chromosomal translocation t(11;14) or overexpression of the resultant gene product cyclin D1, result in an accurate diagnosis.*
>
> ***— Richard Fisher, MD***

Another recent and conceptually related *JCO* editorial by Hal Burstein and Eric Weiner[6] suggested that the 20 to 25 percent of breast cancer patients with HER2-positive tumors should be considered to have a separate disease. Similarly, Mark Kris and others have begun to position EGFR mutation-positive non-small cell lung cancer as a separate disease entity with an annual incidence rate of perhaps 10,000 to 20,000 cases in the United States.

Mantle cell is less common than HER2-positive breast cancer and EGFR-mutated lung cancer, but the tumor follows the same paradigm by having distinct molecular markers and clinical characteristics that do not fit well with the current concepts for either "indolent" or "aggressive" NHL.

> *…In comparison with the indolent lymphomas, which were incurable but had a median survival of seven to 10 years, and the aggressive lymphomas, which could be cured in 40 percent to 50 percent of all cases, patients with MCL could be viewed as having the worst prognosis of all forms of lymphoma.*
>
> ***— Richard Fisher, MD***

Dr Fisher notes the benefits of executing clinical trials specifically focused on mantle cell, and comments on *JCO* papers by O'Connor[7] and Goy[8] documenting excellent response rates to the novel proteasome inhibitor, bortezomib. Also on this issue of our series, Mitchell Smith, who is currently running an ECOG study evaluating R-CHOP plus radioimmunetherapy for patients with mantle cell lymphoma, discusses these and other trends in clinical research on this distinct tumor type.

After reviewing this critical topic for the practicing oncologist, Dr Smith also sat with me to talk about these same concepts for the upcoming patient audio series. Some months ago, MD Anderson's Fred Hagemeister mentioned during an interview that patients with mantle cell lymphoma are highly connected through websites and chatrooms. Our hope is that Dr Smith's interview will serve as another useful resource for these patients.

Both ASCO and the *JCO* should be congratulated for accelerating efforts in recent years to improve the availability of high-quality cancer education. For example,

the ASCO-SUO-ASTRO-PCF* multidisciplinary meeting on prostate cancer held in February in Orlando was one of the finest education programs I have attended. Other ASCO education review meetings are proliferating rapidly as well.

During this time, the *JCO*, under the lead of Dan Haller, has also risen to new heights with many innovations that have improved an already great product. The *JCO* now provides PowerPoint slides from graphics in published papers, and series such as "The Art of Oncology" are truly welcome additions to the educational armamentarium.

Our CME group is gratified to be part of the oncology publishing arena, and we hope that our slightly less formal audio reports from the front line are helpful supplements to traditional communication methods such as journals and meetings.

— Neil Love, MD
NLove@ResearchToPractice.net

* The American Society of Clinical Oncology, the Society of Urological Oncology, the American Society for Therapeutic Radiology and Oncology and the Prostate Cancer Foundation.

References

[1] Horning SJ. **Optimizing rituximab in B-cell lymphoma.** *J Clin Oncol* 2005;23(6):1056-8. **Abstract**

[2] Fisher RI. **Mantle cell lymphoma. At last, some hope for successful innovative treatment strategies.** *J Clin Oncol* 2005;23(4):657-8. **Abstract**

[3] Witzig TE et al. **Rituximab therapy for patients with newly diagnosed, advanced-stage follicular grade I non-Hodgkin's lymphoma: A phase II trial in the North Central Cancer Treatment Group.** *J Clin Oncol* 2005;23(6):1103-8. **Abstract**

[4] 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**

[5] Gordan LN et al. **Phase II trial of individualized rituximab dosing for patients with CD20-positive lymphoproliferative disorders.** *J Clin Oncol* 2005;23(6):1096-102. **Abstract**

[6] Burstein HJ, Winer EP. **HER2 or not HER2: That is the question.** *J Clin Oncol* 2005;23(19); [Epub ahead of print]. **Abstract**

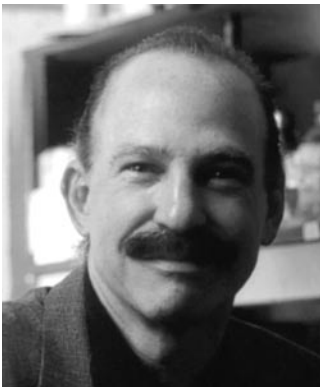
[7] O'Connor OA et al. **Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma.** *J Clin Oncol* 2005;23(4):676-84. **Abstract**

[8] 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**

Steven T Rosen, MD

EDITED COMMENTS

WHO-EORTC classification for cutaneous lymphomas



Recently, the classification of cutaneous lymphomas has been revised. This was a monumental effort undertaken by the EORTC and WHO, which previously had separate classifications (Willemze 2005).

The cutaneous T-cell and natural killer (NK) cell lymphomas include a host of entities. For the average clinician who may see one case in a lifetime, these may be confusing.

However, almost 90 percent fall into a few categories: (1) mycosis fungoides and its variants; (2) Sézary syndrome, the leukemic form of mycosis fungoides and (3) CD30-positive lymphoproliferative disorders of the skin, including CD30-positive anaplastic lymphomas and its benign counterpart, lymphomatoid papulosis.

The B-cell family of cutaneous lymphomas has three major entities. Primary follicle center lymphomas can be confusing to clinicians, because sometimes the report will say diffuse large cell lymphoma, but diffuse large cell lymphoma of the skin of the follicle center type is treated differently. It can either be observed or treated with local radiation, depending on the clinical circumstances.

The MALT type of lymphoma of the skin is indolent with a 100 percent five-year survival rate. It is often treated for cosmetic purposes. The last type, a very unusual entity that is usually seen in elderly women, is a large cell lymphoma that typically tends to be more aggressive and only about half of the patients are alive at five years.

Pathogenesis of cutaneous lymphomas

It has been speculated that viruses cause several cutaneous lymphomas. The human T-cell lymphoma virus type 1 (HTLV-1) has been associated with a form of non-Hodgkin's lymphoma that often presents in the skin. In fact, the first patient diagnosed with HTLV-1 lymphoma was one I took care of as a fellow.

Dr Rosen is the Director of the Robert H Lurie Comprehensive Cancer Center of Northwestern University in Chicago, Illinois.

Photo atlas of cutaneous lymphoma courtesy of Christiane Querfeld, MD, Northwestern University, Robert H Lurie Comprehensive Cancer Center.

In the initial report it was called the CR virus, named after the patient who had this unusual presentation of lymphoma. It subsequently was discovered that the CR virus was HTLV-1 and that the patient's clinical presentation resembled the HTLV-1 type of infections seen in the Kyushu Province of Japan where it's endemic.

Although this patient had not been to Japan, he had a clinical presentation similar to that seen in patients in the Kyushu Province: Skin lesions, hepatosplenomegaly, a lytic bone lesion with hypercalcemia, brain metastases, opportunistic infections and an expansion of the CD4-positive cells.

Some investigators have provided data suggesting HTLV-1 is present in mycosis fungoides, but others have not verified that. No definitive virus has been associated with the other T-cell processes, but the Epstein-Barr virus has been associated with the NK cell-like T-cell processes involving the skin. One outbreak of B-cell lymphoma in Scotland has been associated with the organism found in Lyme's disease.

Evaluation of patients with cutaneous lymphomas

The main issues are the clinical presentation (eg, the appearance of the skin) and the biopsy information. The histology and the immunophenotyping and molecular analyses will help direct therapy — especially for patients with B-cell lymphomas in whom you can often have the wrong impression unless you have those data.

Primary cutaneous follicle center lymphomas: Effects of rituximab

This is a fairly common entity. It presents as slightly raised papules or tumors. The biopsy shows a lymphoid infiltrate consistent with lymphoma, and immunophenotyping shows it as a B-cell process that expresses CD20.

Inexperienced clinicians often mistake it for a large cell lymphoma in the skin that should be treated with combination chemotherapy with or without radiation therapy. In reality, you can observe these patients even if they have multiple indolent lesions, unless there's a cosmetic concern. You can also treat it with local radiation therapy. It's rare to use chemotherapy as the initial treatment. The five-year survival approaches 100 percent.

Rituximab is also effective (Heinzerling 2000, Kennedy 2004). The first patient I treated with rituximab — about five or six years ago — had this entity and presented with two lesions on the face. It was a cosmetic issue and that was the rationale for using rituximab.

The patient also had lesions scattered about his trunk and extremities, and he has been in remission since receiving treatment with rituximab. I've treated about a half dozen patients with rituximab, and they have had universal benefit.

Clinical trial of lenalidomide in patients with cutaneous lymphomas

We anticipate beginning accrual to our lenalidomide (Revlimid®) trial within the next four to six weeks. Lenalidomide has been shown to be an effective agent for the treatment of multiple myeloma (Richardson 2002) and, more recently, myelodysplastic syndromes (List 2005). It's a thalidomide analog and an immune modulator. The mechanism of action is unknown, but speculation exists about its effects on cytokines and angiogenesis.

The drug is well tolerated and is administered orally, which is nice for patients with cutaneous lymphomas who have significant skin disease for whom it can be difficult to use intravenous agents. The main side effects associated with lenalidomide are cytopenias. The patients' blood counts will be monitored throughout the trial.

Clinical trial of alemtuzumab and rituximab in patients with chronic lymphocytic leukemia

We're about to initiate a trial of alemtuzumab, targeting the CD52 antigen, and rituximab as the sole up-front therapy in patients with previously untreated chronic lymphocytic leukemia. Patients will receive alemtuzumab subcutaneously three times a week for 16 weeks and rituximab intravenously every two weeks for a total of eight doses. We're anticipating durable responses without some of the toxicity associated with traditional chemotherapy.

In patients who previously failed traditional chemotherapy and were treated with alemtuzumab and rituximab, we saw responses and acceptable toxicity. The preliminary data indicate no additive toxicity (Nabhan 2004, Faderl 2003). A report from Dr Österborg in Sweden demonstrated that up front, alemtuzumab had results comparable to those of fludarabine and was well tolerated with durable remissions (Österborg 1996).

Currently, none of the therapies we utilize in patients with chronic lymphocytic leukemia are curative. Significant long-term toxicity is associated with fludarabine, when administered alone or with cyclophosphamide, although it is effective. Rituximab combined with chemotherapy appears to be a significant advance. We're exploring its activity in combination with alemtuzumab as first-line therapy to determine if the combination should be compared in a Phase III trial to other chemotherapy regimens that are considered more standard.

RESORT trial (ECOG-E4402): Maintenance rituximab compared to rituximab re-treatment upon disease progression in patients with low tumor burden indolent lymphomas

A number of investigators who have evaluated rituximab as up-front therapy demonstrated significant activity, durable responses and good tolerability (Colombat 2001, Hainsworth 2002, Ghielmini 2004). One of the critical issues is whether to administer maintenance rituximab or to re-treat at the time of progression. The RESORT trial (ECOG-E4402) will, in part, answer that question.

It will also evaluate some quality-of-life and cost issues, which are critical in the use of agents of this nature. I've enrolled only one patient in the study, but I've treated a large number of patients with follicular lymphoma with rituximab as the sole agent. I've treated the majority of them with maintenance rituximab, after Dr Hainsworth's study (Hainsworth 2002) demonstrated durability of remission using this approach and after dialogue with patients who preferred a maintenance approach to being re-treated at the time of progression.

When counseling patients about the risks and benefits of maintenance rituximab, I try to provide them with data. Maintenance therapy clearly results in a longer time until the patient requires additional rituximab or other therapy. I also tell them there's no proof that using maintenance rituximab is advantageous and that we haven't seen any obvious long-term toxicities associated with maintenance rituximab to preclude my comfort level with using a maintenance approach. ECOG-E4402 will take a number of years to provide a definitive answer about which approach is most prudent.

Select publications

Colombat P et al. **Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: Clinical and molecular evaluation.** *Blood* 2001;97(1):101-6. **Abstract**

Faderl S et al. **Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies.** *Blood* 2003;101(9):3413-5. **Abstract**

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. **Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma.** *J Clin Oncol* 2002;20(20):4261-7. **Abstract**

Heinzerling LM et al. **Reduction of tumor burden and stabilization of disease by systemic therapy with anti-CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphoma.** *Cancer* 2000;89(8):1835-44. **Abstract**

Kennedy GA et al. **Treatment of primary cutaneous follicular centre lymphoma with rituximab: A report of two cases.** *Australas J Dermatol* 2004;45(1):34-7. **Abstract**

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

Nabhan C et al. **A pilot trial of rituximab and alemtuzumab combination therapy in patients with relapsed and/or refractory chronic lymphocytic leukemia (CLL).** *Leuk Lymphoma* 2004;45(11):2269-73. **Abstract**

Österborg A et al. **Humanized CD52 monoclonal antibody Campath-1H as first-line treatment in chronic lymphocytic leukaemia.** *Br J Haematol* 1996;93(1):151-3. **Abstract**

Richardson PG et al. **Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma.** *Blood* 2002;100(9):3063-7. **Abstract**

Willemze R et al. **WHO-EORTC classification for cutaneous lymphomas.** *Blood* 2005;[Epub ahead of print]. **Abstract**

Photo Atlas of Cutaneous Lymphoma

(See audio CD for PowerPoint slides or visit www.NHLUpdate.com.)

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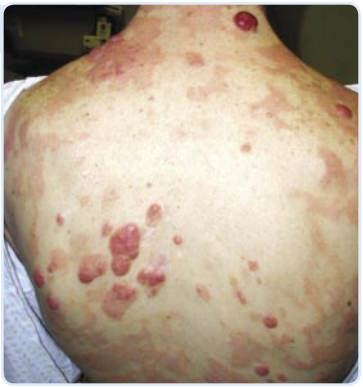

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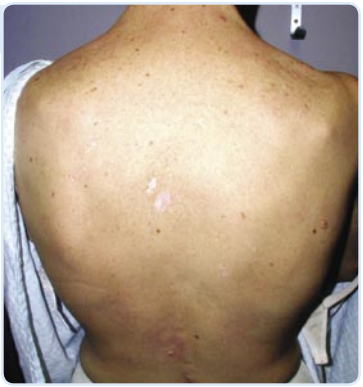

Patient 1: A 48-year-old woman with mycosis fungoides (MF), clinical stage IIB; pre (a) and post (b) donor-unrelated reduced-intensity allogeneic transplant.

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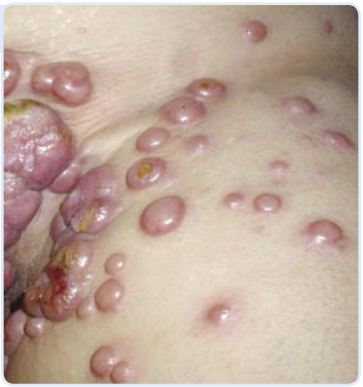

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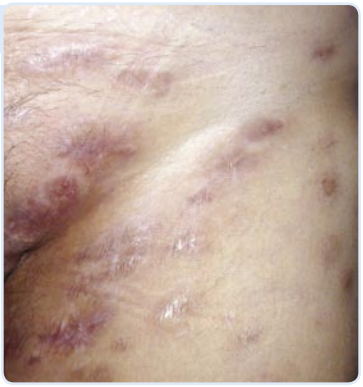

Patient 2: A 49-year-old woman with primary cutaneous anaplastic large cell lymphoma; pre (a) and post (b) treatment with liposomal doxorubicin.

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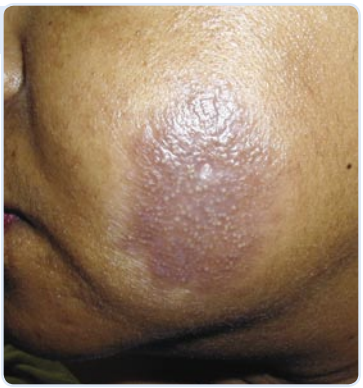

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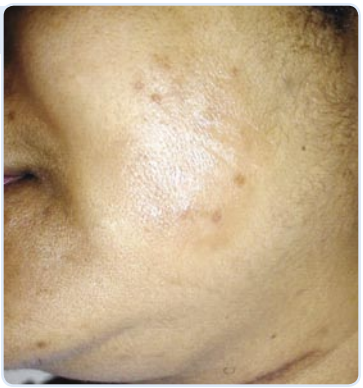

Patient 3: A 50-year-old woman with MF with follicular mucinosis; pre (a) and post (b) treatment with intralesional triamcinolone injections.

Photo Atlas of Cutaneous Lymphoma

(See audio CD for PowerPoint slides or visit **www.NHLUpdate.com**.)

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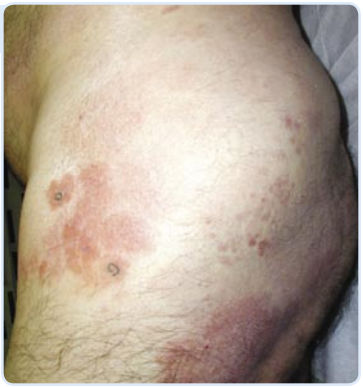

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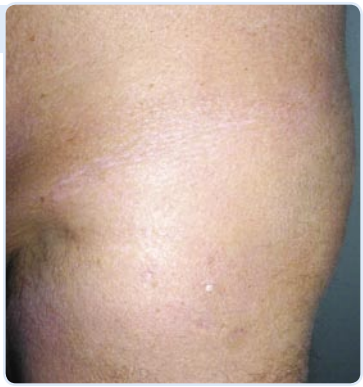

Patient 4: A 52-year-old man with MF, Stage IB; pre (a) and post (b) treatment with low-dose bexarotene and psoralen plus ultraviolet light A (PUVA).

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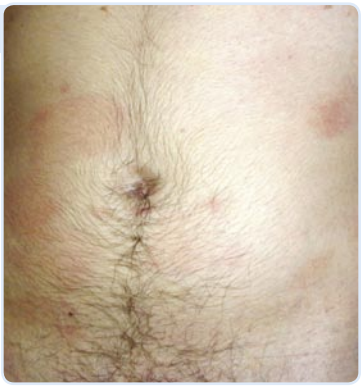

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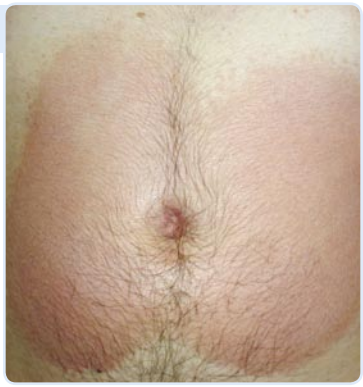
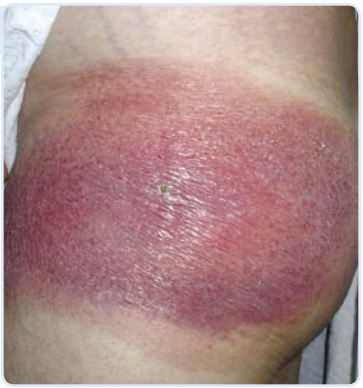
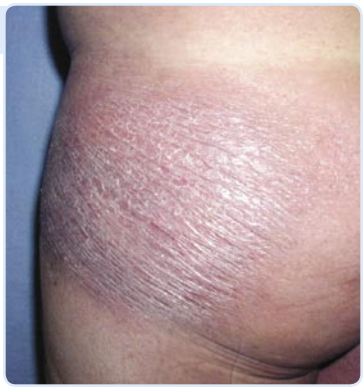


Patient 5: A 29-year-old man with MF, Stage IA; pre (a) and during (b) treatment with topical bexarotene, irritative contact dermatitis caused by bexarotene (b).

A

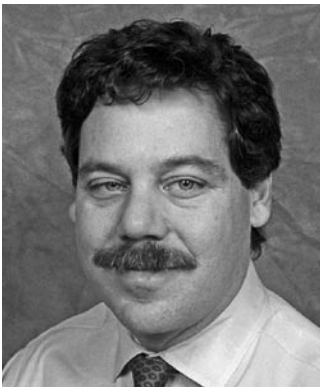


B



Patient 6: A 54-year-old man with MF, Stage IA; pre (a) and during (b) treatment with low-dose bexarotene and PUVA.

Mantle cell lymphoma



This disease was described for the first time in the early 1990s. We achieve high response rates to chemotherapy, but the disease always returns, and investigators have been searching for better treatments.

High-dose chemotherapy with stem cell transplant initially generated enthusiasm but that faded away because patients weren't being cured; however, a low level of enthusiasm still exists and investigators continue to evaluate that approach.

MD Anderson published considerable data on the hyperfractionated cyclophosphamide, vincristine, Adriamycin and dexamethasone (CVAD) regimen followed by transplant. Single-institution trials always generate concern but over the years they demonstrated good results, and after rituximab was added to hyper-CVAD, the transplant really didn't add much more. Currently, the best data is with the rituximab-hyper-CVAD (R-hyper-CVAD).

CHOP alone resulted in an average remission of approximately one year. Then Dana Farber ran a Phase II trial with R-CHOP and virtually every patient responded and the median duration of remission was approximately 16 months. So we can achieve high response rates, but can we maintain the remission? Transplant didn't seem to do it, so we asked: If we can achieve high response rates with R-CHOP, will administering radioimmunotherapy take care of those remaining cells rather than waiting for relapse?

ECOG trial E1499: R-CHOP followed by rituximab + I-111-labeled ibritumomab tiuxetan (Zevalin®)

It took almost five years from the conception of this trial to actually opening it (2.1) due to significant concerns about the distribution of Zevalin while having rituximab on board. Thus, the FDA held up the trial for a while. The concern was that we might see excess toxicity, but we haven't. Patients have recovered their counts so far, and we haven't seen any unexpected toxicity. We can at least say that Zevalin can be administered within eight weeks of receiving rituximab

Dr Smith is the Director of the Lymphoma Service at Fox Chase Cancer Center in Philadelphia, Pennsylvania.

with CHOP. We are measuring rituximab levels and don't have that data yet, but we expect it to still be on board.

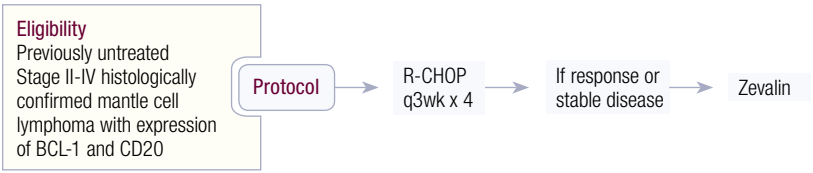
We still administer the "cold" rituximab with Zevalin, which raises another issue. If you look at the data, some cold rituximab is definitely needed when you administer Zevalin as a single agent. The radioactive antibody is actually a very small amount of protein, and if there's a lot of circulating B-cells in the blood and spleen, they soak up the radioactive antibody.

If you scan a patient after giving radioactive antibody, with no cold antibody, it's in the blood and the spleen and is rapidly cleared. It never actually gets to the lymph nodes where you want it. Administering the cold rituximab allows you to saturate those sites and allows the antibody to penetrate further into the lymph nodes.

However, if you already have circulating levels of rituximab, do you need this or not? We don't really know. That's the way the drug was approved, so we administered it in the approved fashion. How much cold rituximab is necessary? Whether patients received rituximab 50 mg/m^2 or 250 mg/m^2 didn't seem to matter. We're not seeing undue toxicity with the 250 mg/m^2 added to the circulating levels, and we don't believe it's a problem to give extra rituximab.

2.1 Phase II Study of R-CHOP Followed by Zevalin

Protocol ID: ECOG-1499
Target Accrual: 57 (Open)



Study Contacts:
Eastern Cooperative Oncology Group
Mitchell Smith, MD, PhD, Protocol Chair
Tel: 215-728-2674; 888-369-2571

Leo Gordon, MD, Protocol Co-Chair
Tel: 312-695-4546

R-CHOP = rituximab + cyclophosphamide, doxorubicin, vincristine and prednisone

SOURCE: NCI Physician Data Query, April 2005.

Nonprotocol therapy for patients with mantle cell lymphoma

Based on the MD Anderson data, I usually discuss R-hyper-CVAD with younger patients. It's an intensive regimen, and for many patients it's questionable whether they will get through the treatment. Next I discuss R-CHOP, with the understanding that it will not cure them. Finally, we have a number of backup, second-line and biologically targeted therapies. Certainly, if patients don't have a complete remission from R-CHOP, then autologous transplant — if the patient

can tolerate it — may prolong the duration of remission, although it's not likely to be curative.

Counseling patients about the risks and benefits of R-hyper-CVAD

Patients receiving R-hyper-CVAD are in the hospital for a fair amount of time receiving hyperfractionated cyclophosphamide followed by alternating methotrexate and cytarabine. They have a significant risk of infection during that time and they experience fatigue, so the therapy has a big impact on their ability to work and on their quality of life. In addition, the regimen carries a several percent risk of mortality and a significant risk of morbidity.

The incidence of neutropenia is high with this regimen, and neutropenic fever occurs in over 50 percent of the cases, even with growth factors. In patients who become neutropenic, I tend to use prophylactic antibiotics in an attempt to keep them out of the hospital, but a significant number of patients are still hospitalized with fever. I try to keep them on the treatment schedule at full dose, because if we reduce the dose, we compromise the result.

When treating a patient with R-hyper-CVAD for mantle cell lymphoma, I usually tell them it's not considered curable today. A young, healthy patient who can get through this regimen has probably a 70 percent to 75 percent chance of being alive at two to three years, but their chance of being alive at five years is probably more like 20 percent to 25 percent. Of course, the hope is that we will develop new treatments during that period of time to deal with the expected relapse. We have some patients who are four or five years post-treatment, so a fraction of patients may be cured, but we can't promise that at this point.

Role of radioimmunotherapy in patients with indolent lymphoma

When considering the treatment algorithms for low-grade lymphoma, obviously a wide range of options exists. Sometimes we agonize over the order in which to use them; however, over time we'll probably use all of the treatments, and the order is probably not critical. Currently, I believe radioimmunotherapy should be considered after first relapse; whether it's used as second-, third- or fourth-line therapy will depend on the patient. These are good treatments, and patients like them because it's a targeted therapy and they complete treatment in a week.

Interesting data using Bexxar® (tositumomab + I-131 tositumomab) up front was recently published in the *New England Journal of Medicine* (Kaminski 2005). Obviously, this is not an approved use for the drug, and I don't believe this should be done off study. In the accompanying editorial, Dr Connors warns that selection bias might have affected the results.

The median age of patients was the late forties, and some had slowly progressive disease so they may have had good risk features. This is not your typical elderly patient coming into the office with low-grade lymphoma. Some patients were older and it may apply to them as well, but we have to be careful about jumping to that conclusion.

The response rates to radioimmunotherapy have generally been in the 70 percent to 80 percent range in any line of therapy. In Kaminski's data, the response rates were at least that good. The key was the duration of remission, which was quite long — a number of patients are out three, four, five years or longer without evidence of disease. Certainly, the potential for one week of therapy to induce a long remission and possibly cure a small group of these patients is exciting, but it's too early to know.

Integrating rituximab with radioimmunotherapy

A number of ways to integrate radioimmunotherapy with rituximab are being studied with rituximab as a pretreatment or as a maintenance therapy. One of the concerns with the radioimmunotherapy data is that although the response rates are high, the response duration is disappointing. In most of the studies, the duration was 12 to 18 months.

One idea is to add rituximab maintenance to take advantage of the high response rate and try to prolong duration. Dr Hainsworth's group has examined rituximab followed by rituximab/chemotherapy, followed by radioimmunotherapy in low-grade lymphoma (Shipley 2004).

The degree of bone marrow involvement can be a problem when considering radioimmunotherapy — if more than 25 percent is involved, the patient is ineligible. We could possibly expand the pool of eligible patients by cytoreduction and clearing the marrow. One way to do that would be with rituximab, if their disease is not refractory. One could consider using chemotherapy, but using rituximab to reduce the bone marrow tumor burden would allow patients to then receive radioimmunotherapy.

Select publications

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**

Hagemeister FB. **Mantle cell lymphoma: Non-myeloablative versus dose-intensive therapy.** *Leuk Lymphoma* 2003;44(Suppl 3):69-75. **Abstract**

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**.

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

Shipley DL et al. **Phase II trial of rituximab and short duration chemotherapy followed by 90Y-ibritumomab tiuxetan as first-line treatment for patients with follicular lymphoma: A Minnie Pearl Cancer Research Network phase II trial.** *Proc ASCO* 2004;**Abstract 6519**.

Williams ME. **ECOG 4402: Randomized phase III-trial comparing two different rituximab dosing regimens for patients with low tumor burden indolent non-Hodgkin's lymphoma.** *Curr Hematol Rep* 2004;3(6):395-6. No abstract available

Brad S Kahl, MD

EDITED COMMENTS

Management of indolent lymphoma

When selecting initial therapy for patients with indolent lymphoma, I consider many factors, including the patient's age, comorbidities, how aggressively the disease is behaving, the extent of the lymphadenopathy, the LDH level, whether the patient is symptomatic and needs quick relief and how many downstream options I want to leave open for later.

In a patient who is symptomatic or has several adverse prognostic factors, I am more aggressive and likely to include an anthracycline up front, so I use something like R-CHOP. In an older patient, who has heart disease or in a patient who doesn't need a quick response, I might select R-CVP.

I tend not to use fludarabine in the first-line setting for follicular lymphoma because of its profound immunosuppressive effects and the effect it seems to have on the stem cell population. In some patients, it also impairs marrow health, which may impact how well the patient will tolerate future treatments.

Role of watchful waiting in patients with follicular lymphoma

One of the controversies in treating indolent or follicular lymphoma is whether watchful waiting is appropriate at this time, given the newer, less toxic agents. However, based on the existing data, I believe watchful waiting remains a reasonable management strategy. Prospective studies have shown that many patients with indolent lymphoma will not require therapy for many years — in some cases, as long as five or 10 years. Those patients are sometimes included in treatment trials, and they can make data look very good. I don't believe those patients should be subjected to the toxicities of unnecessary treatments.

In patients who received four weekly doses of rituximab and had less than a partial response — let's call it a minor response — I have tried four more doses of rituximab. For the most part, I have found that to be ineffective; however, I'm not talking about a huge personal experience, so I can't draw too many conclusions.

On rare occasions, I have been able to convert a nonresponder to a responder with this strategy. I will continue to try it in selected circumstances, particularly

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in patients for whom chemotherapy is an unattractive option, such as elderly patients or those with diabetes or heart disease.

Clinical trials of maintenance rituximab

Rituximab maintenance has been proven to prolong remission, whether it's given as a single agent or after chemotherapy. Hainsworth reported on a Phase II trial with rituximab maintenance given in four weekly doses every six months for two years, and the maintenance therapy kept patients in remission longer than just a one-time dosing (Hainsworth 2003). In addition, a trial conducted in Europe randomly assigned patients to a maintenance strategy versus a one-time dosing strategy, and the patients who received the maintenance strategy experienced longer remissions (Marinus 2004).

In ECOG-E1496, a Phase III trial, patients were randomly assigned to maintenance rituximab versus observation following CVP chemotherapy. The data showed an impressive benefit for rituximab maintenance (Hochster 2004). Patients in the maintenance arm experienced remissions that lasted approximately two and a half years longer.

However, the patients in that trial received CVP chemotherapy without rituximab, and today almost every patient receives chemotherapy plus rituximab as part of their initial therapy. Whether rituximab maintenance adds a similar benefit for patients who receive rituximab with their chemotherapy is totally unknown. Investigators in Great Britain are launching a trial evaluating R-CVP followed by rituximab maintenance versus observation in the first-line setting in an attempt to address that very issue.

ECOG-E4402: RESORT trial of maintenance rituximab (see page 4, figure 1.2)

Design and endpoints

The RESORT trial is designed to determine whether, after induction rituximab, it's better to give rituximab on a predetermined schedule or on an as-needed basis. Eight weeks after patients receive a traditional dosing of rituximab — 375 mg/m^2 weekly for four weeks — they are restaged. Patients with a partial or complete response are randomly assigned to either the re-treatment arm of four weekly doses of rituximab upon disease progression, provided the time to progression is more than six months, or the scheduled maintenance arm, where they receive a single dose of rituximab every 12 weeks until progression.

The primary endpoint is time to rituximab resistance. We want to answer such questions as: Which strategy prolongs the period of time during which the patient benefits from rituximab? Will they develop resistance to rituximab faster with one strategy versus the other? Secondary endpoints include time to first chemotherapy and survival.

Survival is not the primary endpoint because in any indolent lymphoma trial, patients move on to second-, third- and fourth-line therapies. It then becomes

difficult to determine the contribution of the first-line treatment to their overall survival when it is confounded by the six other treatments they received after that.

Correlative science studies

The RESORT trial is an excellent opportunity to address questions relating to predictors of response to rituximab because these patients have had no prior lymphoma therapy and rituximab is the only treatment they receive. Rituximab is an IgG subclass 1 antibody, and known human polymorphisms exist that have a better or worse affinity to such antibodies. Approximately 15 percent to 20 percent of the population has a favorable polymorphism for rituximab.

The remaining population has a less favorable polymorphism, but the exact impact of that polymorphism on response rates and time to progression is not consistent across small studies. In the RESORT trial, we will examine the polymorphism status of the patients and try to clarify this issue.

We will also evaluate the pharmacokinetics of rituximab, measuring serum levels at several key points. The scheduled maintenance arm consists of a single dose every three months. We want to determine if that dosing can maintain serum levels above 25 micrograms per mL.

We will also measure serum levels at the time of progression to see if patients are progressing while they have measurable serum levels. Most of us would conclude that a patient is truly rituximab refractory if the disease is growing despite measurable serum levels.

Tissue arrays are another area we will be evaluating in the RESORT trial. We will take the paraffin blocks and examine immune system factors present in the lymph node at diagnosis. An article published in the *New England Journal of Medicine* in 2004 examined RNA microarray patterns in follicular lymphoma, and attempted to correlate gene expression profiles with prognosis (Dave 2004).

The paper suggested that it's not the genes that are turned on or off in the tumor cells that make a difference, rather it's the genes that are turned on and off in the cells around the tumor cells — the macrophages and the T cells. How well an individual's immune system recognizes the lymphoma might have an important impact on the patient's ultimate prognosis and outcome and, if that were true, then immunotherapies such as antibodies or vaccines would be important to examine.

Nonproctocol use of maintenance rituximab

When I treat a patient with single-agent rituximab without chemotherapy, I administer four weekly doses and then evaluate the response. If the patient responds and experiences a nice remission, I re-treat them when they recur with four weekly doses and repeat that strategy as long as the drug is working. I do not use a maintenance strategy off protocol because I don't believe we have evidence that it's superior.

Phase II trial: First-line therapy for follicular lymphoma with Zevalin followed by rituximab

At the University of Wisconsin, we are conducting a 35-patient, Phase II trial evaluating Zevalin radioimmunotherapy followed by maintenance rituximab for patients with intermediate or high-risk disease, as determined by the Follicular Lymphoma International Prognostic Index (FLIPI) score.

The FLIPI score for follicular lymphoma is a little different than the IPI for aggressive lymphomas. The FLIPI score is based on five clinical factors at diagnosis, and the acronym to remember them is **NOLASH**: (1) **NO** is for nodes; five or more nodal groups is an adverse feature. (2) **L** is for LDH; if elevated, it's an adverse feature. (3) **A** is for age; if the patient is over 60, it's an adverse feature. (4) **S** is for Stage; Stage III or IV disease is an adverse feature. (5) **H** is for hemoglobin; if less than 12, it's an adverse feature.

Patients with zero to one features are considered low risk, two features are considered intermediate risk and three to five features are considered high risk. This trial is restricted to patients with intermediate- or high-risk disease because some risks may be associated with this therapy. We did not want to expose patients at low risk to that potential; however, I believe the five- and 10-year survival rates for patients at intermediate or high risk justify this approach in these patients.

Patients enrolled in the trial will receive a single dose of Zevalin and then be restaged at three and six months. Patients who are responding will receive four weekly doses of rituximab at the six-month mark and then a single dose every three months until disease progression. In this trial and in the RESORT trial, the maintenance strategy is indefinite. The stopping points for the other maintenance trials — nine months and two years — are completely arbitrary, and I felt it was time to push the envelope. I don't know if our strategy will prove to be better, and I believe it would be wrong to use it off protocol.

We will evaluate the two-year, event-free survival in addition to the median event-free survival. It could take four or five years to determine the median event-free survival, which is a long time to wait. Therefore, it's prespecified that if the median two-year, event-free survival is 80 percent or better, that would be good enough to consider a larger trial.

Pilot trial of modified hyper-CVAD with rituximab in patients with mantle cell lymphoma

We reported a pilot study at ASH in 2004 in which 20 patients with untreated mantle cell lymphoma received a modified hyper-CVAD regimen followed by rituximab maintenance (Kahl 2004). Patients have a very difficult experience tolerating the toxicities of the traditional hyper-CVAD regimen, so we removed the cytarabine and methotrexate.

We added rituximab to the induction regimen and then followed it with four weekly doses of rituximab every six months for two years, which I refer to as

consolidation rather than maintenance, because it's given for a fixed period of time. We found the modified regimen to be very tolerable, and our two-year, event-free survival rate is currently over 70 percent, which is quite good for mantle cell lymphoma (3.1).

3.1 Phase II Study of Modified Hyper-CVAD with Rituximab Maintenance for Previously Untreated Mantle Cell Lymphoma*

Overall response rate	85%
Two-year progression-free survival	73% (95% CI = 50% - 89%)
Two-year overall survival	82% (95% CI = 60% - 95%)
Response duration	2+ to 39+ months

* Median follow-up of 22.5 months (range 4 to 45 months)

"Modified hyper-CVAD with rituximab maintenance demonstrates ORR comparable to conventional hyper-CVAD (85% vs 93%) and is less toxic, especially in patients over 60. Compared with published reports for R-CHOP, we observed higher CR rates (70% vs 34-48%) and considerably longer median PFS (not yet reached vs 16-20 months). Longer follow up will better define the effectiveness of this regimen, but the encouraging results of this pilot study provide the basis for additional study in a larger setting."

SOURCE: Kahl BS et al. **Phase II study of modified hyper-CVAD with rituximab maintenance for previously untreated mantle cell lymphoma: A Wisconsin Oncology Network Study.** *Proc ASH* 2004;**Abstract 1388**.

Select publications

Dave SS et al. **Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells.** *N Engl J Med* 2004;351(21):2159-68. **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**

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**.

Kahl BS et al. **Phase II study of modified hyper-CVAD with rituximab maintenance for previously untreated mantle cell lymphoma: A Wisconsin Oncology Network Study.** *Proc ASH* 2004;**Abstract 1388**.

Marinus HJ 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 intergorup clinical trial.** *Proc ASH* 2004;**Abstract 586**.

Solal-Celigny P et al. **Single 4-dose rituximab treatment for low-tumor burden follicular lymphoma (FL): Survival analyses with a follow-up (F/Up) of at least 5 years.** *Proc ASH* 2004;**Abstract 585**.

Witzig TE et al. **Rituximab therapy for patients with newly diagnosed, advanced-stage, follicular grade I non-Hodgkin's lymphoma: A phase II trial in the North Central Cancer Treatment Group.** *J Clin Oncol* 2005;23(6):1103-8. **Abstract**

Post-test:

Non-Hodgkin's Lymphoma Update — Issue 2, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The EORTC and WHO collaborated to revise and standardize their classification of the cutaneous lymphomas.
   a. True
   b. False

2. It is speculated that viruses cause several cutaneous lymphomas.
   a. True
   b. False

3. Which of the following is a thalidomide analog being evaluated in patients with cutaneous lymphomas?
   a. Rituximab
   b. Lenalidomide
   c. Alemtuzumab
   d. Fludarabine
   e. None of the above

4. ECOG-E4402 will randomly assign patients with low-risk indolent lymphomas 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

5. ECOG trial E1499 in patients with mantle cell lymphoma will evaluate R-CHOP followed by _____ in patients achieving a response or stable disease.
   a. Bexxar
   b. Zevalin
   c. Maintenance rituximab

6. Dr Hainsworth and colleagues reported on a Phase II trial evaluating rituximab followed by rituximab/chemotherapy followed by radioimmunotherapy as first-line therapy in patients with follicular lymphoma.
   a. True
   b. False

7. In the RESORT trial, all patients receive rituximab weekly times four and then patients with a partial or complete response are randomly assigned to receive four weekly doses of rituximab upon disease progression versus:
   a. Four weekly doses of rituximab every 12 weeks until progression
   b. A single dose of rituximab every 12 weeks until progression
   c. No further therapy

8. FLIPI is used to score risk in patients with follicular lymphoma, whereas the International Prognostic Index (IPI) score is used to score risk in patients with aggressive lymphomas.
   a. True
   b. False

9. Data reported by Solal-Celigny et al at the 2004 ASH meeting showed some patients with follicular lymphoma who receive four weekly doses of rituximab and nothing more remain in remission for two to five years.
   a. True
   b. False

10. Which of the following clinical factors comprise the FLIPI?
    a. Number of nodes
    b. LDH
    c. Age
    d. Disease stage
    e. Hemoglobin level
    f. All of the above

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

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5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor	N/A = not applicable to this issue of *NHLU*

GLOBAL LEARNING OBJECTIVES

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

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Faculty	Knowledge of subject matter	Effectiveness as an educator
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Mitchell R Smith, MD, PhD	5 4 3 2 1	5 4 3 2 1
Brad S Kahl, MD	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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As part of our ongoing, continuous, quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

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Non-Hodgkin's Lymphoma™

UPDATE

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