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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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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 4 of *Non-Hodgkin's Lymphoma Update* is to support these global objectives by offering the perspectives of Drs Cheson, Czuczman and Armitage on the integration of emerging clinical research data into the management of non-Hodgkin's lymphoma.

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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**.

Table of Contents

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UPCOMING EDUCATIONAL EVENTS

Hematology and Medical Oncology Board Review
September 21-28, 2005
Alexandria, Virginia
Event website: **www.hemoncboardreview.com/**

American Society for Therapeutic Radiology and Oncology (ASTRO) 47th Annual Meeting
October 16-20, 2005
Denver, Colorado
Event website: **www.astro.org/annual_meeting**

ECCO 13 — The European Cancer Conference
October 30-November 3, 2005
Paris, France
Event website: **www.fecs.be/emc.asp?pageId=10&Type=P**

Chemotherapy Foundation Symposium: Innovative Cancer Therapy for Tomorrow
November 2-5, 2005
New York, New York
Event website: **www.mssm.edu/tcf**

American Society of Hematology (ASH) 47th Annual Meeting and Exposition
December 2-6, 2005
New Orleans, Louisiana
Event website: **www.hematology.org/meeting/**

American Association for Cancer Research 97th Annual Meeting
April 1-5, 2006
Washington, DC
Event website: **www.aacr.org**

Editor's Note

Is overall survival the only important endpoint in Phase III randomized clinical trials?

In the early 1980s, a number of adjuvant clinical trials in early breast cancer demonstrated a disease-free survival advantage for tamoxifen. However, at that time, the concept of targeted adjuvant therapy was still embryonic, and most oncologists did not prescribe TAM in this setting believing that "cytostatic" therapy might temporarily delay tumor growth but would not impact overall survival (OS).

It was not until the 1985 NIH Consensus Conference on Early Breast Cancer that Oxford statistician Richard Peto's first international meta-analysis proved that the lack of OS benefit in individual trials of tamoxifen was the result of too few events (deaths), rather than a lack of efficacy. Peto's clear-cut demonstration of an OS impact instantly changed the standard of care and led a generation of women worldwide to take TAM in the early setting. However, even prior to Peto's presentation, a number of clinical investigators began to question whether a disease-free survival (DFS) benefit alone was sufficient enough to justify the use of a treatment with relatively few side effects or toxicities. The OS requirement of the "pre-Peto" era stemmed in large part from the significant toxicity profile of cytotoxics observed in prior adjuvant studies. It is interesting to speculate whether the rationale of using TAM for a DFS advantage would have ever gained acceptance if Peto and his colleagues never addressed the issue of breast cancer.

Twenty years after Peto's bombshell, we can reflect on several other oncologic situations in which disease-free survival benefits have been accepted to justify new standards of care. At the 2001 San Antonio Breast Cancer Symposium, the first results of the massive ATAC trial demonstrated a disease-free survival benefit for the use of the aromatase inhibitor anastrozole over tamoxifen in postmenopausal patients. More than four years later, this study and several other similar trials have still not revealed an OS benefit for AIs over tamoxifen; yet, these agents are now the most commonly utilized endocrine intervention in early breast cancer. Another example of DFS justifying a therapy occurred after the 2003 ASCO meeting, in which Aimery de Gramont and colleagues demonstrated that FOLFOX conferred a three-year DFS advantage over 5-FU/leucovorin as adjuvant therapy for Stage III colorectal cancer. Part of the acceptance of these data as the basis to change practice was the expectation that this DFS benefit would eventually translate into a five-year OS benefit. However, a follow-up MOSAIC data set presented at the recent 2005 ASCO meeting continues to reveal no OS advantage. FOLFOX, however, remains the accepted standard of care, in

spite of the considerable increase in toxicity associated with this treatment. In NHL, the much-discussed and controversial topic of rituximab maintenance seems to fit this model well. As in virtually every other issue of this audio series, the three interviewees featured on the enclosed program identify the role of rituximab maintenance therapy as among the most common questions asked of them by medical oncologists.

There is considerable heterogeneity in the approach taken by lymphoma specialists to this question, but most believe — mainly based on John Hainsworth's study of R maintenance in patients treated initially with R monotherapy for relapsed indolent lymphoma — that continuation of R will initially delay tumor progression. There is also general agreement that other than financial cost and inconvenience, there are few known risks of R maintenance. The controversy stems from two questions:

1. Would the same long-term tumor control be observed without R maintenance, and R was not utilized until progression?

As discussed on a previous issue of this series by principal investigator Brad Kahl, ECOG's RESORT trial is attempting to address this critical question (1.1). Of particular interest, in RESORT, R maintenance is administered indefinitely, whereas Hainsworth utilized only two years of therapy — a common nonprotocol approach currently used. A key endpoint in RESORT is the time to first chemotherapy, which obviously has important quality-of-life implications. If R maintenance does not improve OS but leads to a significant delay in the first use of chemotherapy, this may be viewed as a positive benefit-risk ratio.

2. Will overall survival be improved with R maintenance?

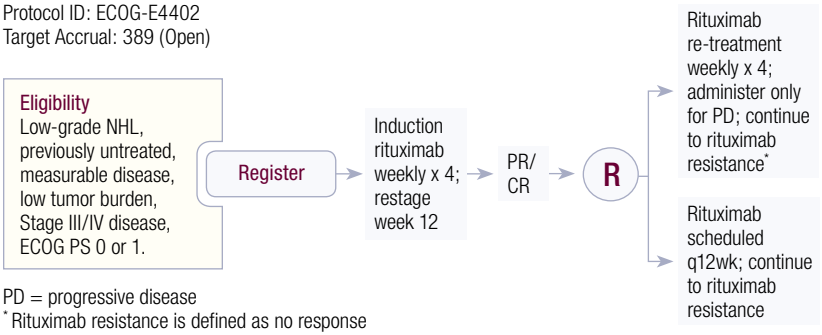
This research issue is clearly the major impetus to conduct any study of an early versus delayed systemic intervention in oncology. For aggressive tumors such as diffuse large B-cell lymphoma, overall survival is a rational endpoint that can be assessed fairly quickly. In this issue of *NHL Update*, James Armitage comments on a population-based study from British Columbia that demonstrated fewer deaths from diffuse large B-cell lymphoma within the 18 months after the Canadian government approved rituximab.

However, the prolonged natural history of indolent lymphomas means that any trial with a primary endpoint of overall survival may be impractical and likely to deliver results at such a delayed time point that newer and more effective forms of treatment will already be available. It is also possible that in some way, R maintenance may result in inferior long-term tumor control and OS, but few if any clinical investigators have raised that as a serious concern. The primacy of OS as a trial endpoint triggering changes in practice patterns is logical when the intervention results in significant short- and long-term toxicity, but what about therapies like rituximab that result in minimal adverse effects?

For the foreseeable future, it seems that oncologists must develop a clinical strategy that takes into account these uncertainties. This is no small task, particularly in light of the recent emergence of a number of new effective biologic treat-

ment strategies that have substantially increased the overall financial burden for cancer placed on society. Even more importantly, oncologists must decide whether to proactively discuss issues such as R maintenance with patients, even if only to say, "This is an option that some oncologists use in this situation, but I am not recommending this to you because..."

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, July 2005; Gregory S. Presentation. Research To Practice, May 17, 2004.

In some ways, the R maintenance question reminds me of the current debates about tamoxifen versus an AI as up-front adjuvant therapy. Everyone agrees that AIs result in fewer relapses in the short term, but some have argued that better long-term results may occur if tamoxifen is administered initially for two to three years followed by the AI. The only major, large, prospective randomized trial (BIG FEMTA) addressing this question will not have results for years.

Putting aside the issue of the differential side effects of these therapies, oncologists have understandably balked at recommending that patients accept initial treatment with a greater risk of relapse (tamoxifen), hoping and expecting that in the long term, fewer relapses will occur. Similarly, by foregoing R maintenance, patients with NHL are being asked, in essence, to go with a treatment strategy that in the short term will result in a greater likelihood of tumor progression, with the expectation/hope that in the long term, the outcome will probably be the same. We and others have conducted a number of patient surveys in breast, prostate and colorectal cancer to determine how patients balance risk-benefit considerations to make treatment decisions. It would be fascinating to ask patients with NHL how they see this trade-off when it is explained in this manner.

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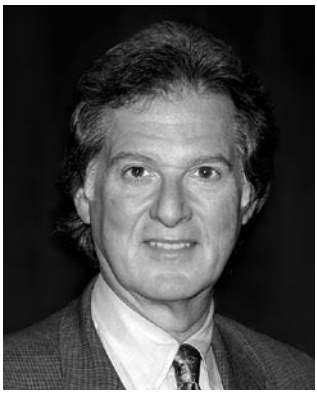
Treatment advancements in NHL



The most revolutionary occurrence in the treatment of patients with NHL has been the availability of active monoclonal antibodies, particularly rituximab. This has provided a wonderful building block on which to develop newer and more effective regimens, both in combination with chemotherapy and other biological agents. One of the most important advances in the last year or two has been the recognition that rituximab adds to the activity and efficacy of chemotherapy.

The Groupe d'Etude des Lymphomes de l'Adulte compared CHOP with or without rituximab in patients with diffuse large B-cell lymphomas and demonstrated a survival advantage (Coiffier 2002). Several other groups have confirmed these results, and R-CHOP has replaced standard CHOP as a more effective therapeutic option for patients with diffuse large B-cell lymphomas. In patients with indolent lymphomas, rituximab also adds to the efficacy of chemotherapy. Compared with chemotherapy alone, rituximab plus chemotherapy enhances the response rate and time to progression. Although a survival benefit has not been demonstrated, it may become apparent with longer follow-up (Forstpointner 2004; Hiddemann 2004; Marcus 2005).

Rituximab Extended Schedule Or Re-Treatment (RESORT) trial

In the RESORT trial, patients with indolent lymphomas receive the standard four weekly infusions of rituximab. Then they are randomly assigned to: (1) observation until disease progression, at which time they receive rituximab re-treatment or (2) rituximab every three months until their disease progresses (1.1). It's somewhat similar to a study conducted by Hainsworth et al, in which they administered rituximab for four infusions followed by either maintenance for two years (eg, four infusions every six months) or no further treatment until relapse (Hainsworth 2005). In that study, which involved patients with relapsed or refractory disease, there was a marked difference in time to progression with maintenance rituximab. However, the time at which patients needed some therapy other than rituximab was virtually identical: 31 months in the maintenance arm and 27 months in the re-treatment arm (Hainsworth 2005; [2.1]).

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To date, no regimen prolonging time to progression has impacted on overall survival. However, those results have been primarily with the older forms of treatment, and hopefully, with antibody therapy, we'll find we not only prolong time to progression but also survival. Obviously, concerns exist about keeping patients on a monoclonal antibody indefinitely. One concern is the expense. The other concerns include: Are there risks of chronic B-cell depletion? Will patients be at risk several years down the line for bacterial or other forms of infections? Will they develop some form of resistance to monoclonal antibody therapy?

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

	R maintenance (n = 44)	R re-treatment (n = 46)	*p*-value
Median PFS	31.3 months	7.4 months	0.007
Median duration rituximab benefit	31.3 months	27.4 months	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**

Clinical use of maintenance rituximab

Some recent abstracts suggest that maintenance rituximab may be a beneficial approach (Hiddemann 2005; Habermann 2004; Van Oers 2004), but we haven't seen a full manuscript we can critically evaluate to demonstrate that this is the way to go. So we use maintenance rituximab, currently, in the context of a clinical trial. We do present maintenance rituximab to patients as an option, and I won't say we never use it. When we discuss maintenance rituximab with patients, I usually present a balanced view of the pros and cons. Most of the time, they decide to receive it at the time of recurrence rather than continuously. The advantage we pose to them is that maintenance rituximab will prolong the time to disease progression, but we don't know whether it will prolong survival.

Potential survival advantage associated with rituximab

Two recent studies go against our former concept that we can't prolong the survival of patients with follicular lymphoma. They demonstrate that recent regimens containing monoclonal antibodies, particularly rituximab, appear to enhance survival when compared with comparable historical controls from clinical trials. One trial is in press in *JCO*. The other study was conducted by the Southwest Oncology Group (Fisher 2004). Dr Fisher conducted a retrospec-

tive analysis of a large number of patients treated with CHOP, a more aggressive chemotherapy regimen (ProMACE-MOPP) and CHOP followed by monoclonal antibody therapy. Although the duration of follow-up was much shorter with the antibody-containing regimen, both the time to progression and the survival curves were significantly in favor of the antibody-based therapy (Fisher 2004; [2.2]). Whether these differences will remain with prolonged follow-up is yet to be seen.

2.2 Impact of New Treatment Options on the Natural History of Patients with Advanced Follicular Lymphomas Treated on SWOG Trials

	CHOP + MoAb[1] (1998-2000) n = 179	ProMACE-MOPP[2] (1988-1994) n = 425	CHOP[3] (1974-1978) n = 356
Four-year PFS	61%*	48%	46%
Four-year OS	91%†	79%	69%

[1] SWOG-S9800/SWOG-S9911; [2] SWOG-8809; [3] SWOG-7426/SWOG-7713

MoAb = monoclonal antibody therapy (rituximab or Bexxar®); PFS = progression-free survival; OS = overall survival; * $p = 0.005$; † $p < 0.0001$

SOURCE: Fisher RI et al. **New treatment options have changed the natural history of follicular lymphoma.** *Proc ASH* 2004;**Abstract 583**.

Select publications

Coiffier B et al. **CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma**. *N Engl J Med* 2002;346(4):235-42. **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**

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**.

Hiddemann W et al. **Rituximab maintenance following a rituximab containing chemotherapy significantly prolongs the duration of response in patients with relapsed follicular and mantle cell lymphomas: Results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG)**. *Proc ASCO* 2005;**Abstract 6527**.

Hiddemann W et al. **The addition of rituximab to combination chemotherapy with CHOP has a long lasting impact on subsequent treatment in remission in follicular lymphoma but not in mantle cell lymphoma: Results of two prospective randomized studies of the German Low Grade Lymphoma Study Group (GLSG)**. *Proc ASH* 2004;**Abstract 161**.

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**

Van Oers MHJ et al. **Chimeric anti-CD20 monoclonal antibody (rituximab; Mabtheraâ) 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**.

Myron S Czuczman, MD

EDITED COMMENTS

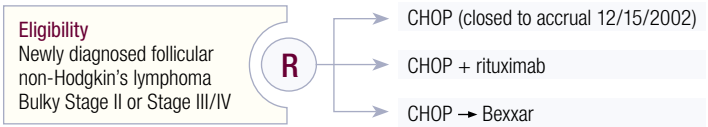
SWOG trial S0016 in patients with newly diagnosed follicular NHL

SWOG-S0016 was originally a three-arm study comparing CHOP alone, CHOP plus rituximab (R-CHOP) and CHOP times six followed by a dose of Bexxar. Early on, the trial was not accruing well, largely because patients said, "I don't want to be on CHOP alone."

Right now, it's a two-arm study comparing R-CHOP to CHOP followed by Bexxar (3.1). Hopefully, this trial will accrue enough patients. It's a large cooperative group study, and it'll be interesting to see which of these approaches may be better to determine their long-term toxicities.

3.1 Combination Chemotherapy with Monoclonal Antibody Therapy in Treating Patients with Newly Diagnosed Non-Hodgkin's Lymphoma

Protocol IDs: SWOG-S0016, CALGB-50102
Target Accrual: 775 (Open)



SOURCE: NCI Physician Data Query, June 2005.

Background for SWOG-S0016

CHOP plus rituximab

We just updated the nine-year experience of a multicenter trial evaluating the combination of rituximab and CHOP, and the data are intriguing (Czuczman 2004; [3.2]). Patients with either untreated or previously treated (up to four different treatment regimens) follicular or low-grade lymphoma were eligible. Patients could not have bulky disease (eg, >10-centimeter masses). They received six cycles of CHOP along with six infusions of rituximab (Czuczman 1999).

Dr Czuczman is the Head of Lymphoma/Myeloma Service at Roswell Park Cancer Institute and Associate Professor of Medicine in the School of Medicine and Biomedical Sciences at the State University of New York at Buffalo, New York.

Thirty-eight of the 40 patients who enrolled were treated. The two who were not treated went off study before therapy was initiated (Czuczman 2004).

We had a 100 percent overall response rate. In the update of the nine-year follow-up, we applied the International Workshop Response Criteria (IWRC) for NHL published by Cheson et al (Cheson 1999). When we applied those criteria and compared to our more rigid initial criteria, we noted an 87 percent complete response/unconfirmed complete response (CR/CRu) rate and a 13 percent partial response (PR) rate. We have reached a median time to progression of close to seven years (Czuczman 2004; [3.2]). Therefore, at seven years, half of the patients have relapsed, and the other half are still going strong.

All 16 patients who are continuously in complete remission had an initial CR. All five patients with a PR according to the IWRC had relapsed by 2.5 years (Czuczman 2004). I think that may be a very important point. From the data I've seen with Zevalin® and Bexxar, this database and others published with chemotherapy, the patients who achieve a CR have the most durable and meaningful remissions, sometimes lasting five-plus years.

I have patients whom I treated on the R-CHOP study now going out 10 years. Being a clinician, I would not have predicted they would stay in remission that long. We also saw molecular remissions in our trial (Czuczman 2004). In a number of publications and in this database, it appears that patients who achieve a molecular CR do better than those who achieve only a clinical CR.

3.2 Efficacy of R-CHOP in 38 Patients with Low-Grade or Follicular NHL: Nine-Year Follow-Up

Overall response rate*	100%
Complete response/unconfirmed complete response rate	87%
Partial response rate	13%
Median duration of response (range)	83.5+ months (3.1 – 105.1+)
Median time to progression (range)	82.3+ months (4.5 – 105.6+)

* Based on IWRC

SOURCE: Czuczman MS et al. **Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up**. *J Clin Oncol* 2004;22(23):4711-6. **Abstract**

CHOP followed by Bexxar

The basis for CHOP followed by Bexxar was a trial conducted by Dr Press in Seattle. Over 100 patients were treated with six cycles of CHOP followed by Bexxar. They had an excellent overall CR rate and durable remissions (Press 2003). The follow-up in that trial is not as long as the follow-up in the trial of R-CHOP we've published. When you look at the same time frames, however, they appear to be comparable.

Since then, Mark Kaminski has published a trial of Bexxar alone as up-front therapy. Patients who were enrolled in that trial needed to have less than 25 percent marrow involvement, and the majority did not have bulky disease. In general, they were probably a good prognostic group of patients, and they did very well (Kaminski 2005). I think that trial involved a select group of patients who might have done well with rituximab alone. Data from the French suggest that around 25 percent of "good-risk" patients, at five years, are still in CR.

Phase II trial of rituximab plus fludarabine in patients with low-grade or follicular NHL

We've published, in *JCO*, the four-year follow-up of a trial with rituximab plus fludarabine (R-fludarabine). Six cycles of standard fludarabine and seven infusions of rituximab were administered. We had a 90 percent overall response rate and an 80 percent CR rate. At almost four years, we had not reached the median time to progression (3.3). We still had a little over 60 percent of the patients in remission. Toxicity was very acceptable, and nonhematologic toxicity was minimal (Czuczman 2005). Patients could work full time and were active. The treatment did not cramp their lifestyles.

In the first 10 patients, we saw too much hematologic toxicity, and we adjusted the protocol. We discontinued Bactrim® (trimethoprim/sulfamethoxazole) prophylaxis, because we weren't using steroids with fludarabine, as in the FND regimen, which leads to a higher risk of developing *pneumocystis carinii* pneumonia. If the patients experienced prolonged cytopenias, we reduced the dose of fludarabine from five to three days. We also limited the amount of G-CSF, because we would sometimes have worse neutropenia if filgrastim were administered soon after fludarabine was completed (Czuczman 2005).

Two patients had to be taken off of the study due to disease progression, and those two patients had transformed lymphomas. So I think R-CHOP is probably better for patients with a more aggressive presentation. In addition, the patients required acyclovir prophylaxis, because about 15 percent developed either primary or secondary herpes infections. With the use of acyclovir, we saw no other herpes infections, and no other opportunistic infections occurred (Czuczman 2005).

Comparing R-CHOP and R-CVP as initial therapy in patients with follicular lymphoma

I don't use R-CVP. I trained at Memorial Sloan-Kettering, and R-CHOP, at that time, was not a bad thing. Anthracyclines were not evil, but many don't like to use them. If you look at historical data to compare CVP to CHOP, you can have a quicker response with the addition of doxorubicin, but you don't necessarily change overall survival.

When I look at the data recently published by Marcus from the randomized trial comparing CVP to R-CVP, what strikes me the most — although R-CVP beats the CVP — is that the median time to treatment failure was 27 months for R-CVP (Marcus 2005; [3.4]). I'm seeing patients whom I have treated with R-CHOP going

out seven, eight-plus years; therefore, less than 2.5 years is not very satisfying. In my own interpretation of the data, R-CHOP is providing better results.

Preclinical work and in vitro studies demonstrate that doxorubicin and rituximab have synergy. In my mind, I'm not just treating the patient with CHOP. I'm adding rituximab, which is synergistic with doxorubicin. Hence, I'm providing a better chance of having a quality remission and taking advantage of the synergy. By using CHOP or R-CHOP early on, I have not seen, in my own series of patients, a very high rate of transformation in patients with low-grade lymphomas. This has to be studied prospectively, but I think it makes a very good question.

3.3 Efficacy of R-Fludarabine in 40 Patients with Low-Grade or Follicular NHL: Median Follow-Up of 44 Months

Overall response rate*	90%
Complete response/unconfirmed complete response rate	80%
Partial response rate	10%
Median duration of response (range)	Not reached
Median time to progression (range)	Not reached

* Based on modified IWRC

SOURCE: Czuczman MS et al. **Rituximab in combination with fludarabine chemotherapy in low-grade or follicular lymphoma**. *J Clin Oncol* 2005;23(4):694-704. **Abstract**

3.4 Phase III Trial of CVP versus R-CVP in Previously Untreated Patients with Stage III/IV CD20-Positive Follicular NHL (N = 322)

	R-CVP	CVP	*p*-value
Overall response rate	81%	57%	<0.0001
Complete response rate	41%	10%	<0.0001
Median time to treatment failure	27 months	7 months	<0.0001
Time to progression	32 months	15 months	<0.0001

CVP = cyclophosphamide 750 mg/m^2 (day 1), vincristine 1.4 mg/m^2, maximum 2 mg/m^2 (day 1), prednisone 40 mg/m^2 (days 1-5) every 21 days x 8
R-CVP = same regimen + rituximab 375 mg/m^2 on day 1 of each cycle

SOURCE: 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**

Maintenance rituximab versus re-treatment with rituximab

In some patients who have minimal treatment options, I do consider utilizing maintenance rituximab. When I look at the Hainsworth data, it is clear that patients had the same duration of benefit with rituximab whether it was admin-

istered as four doses every six months for two years or at the time of progression (Hainsworth 2005). If you continue administering rituximab without a good reason, there may be a theoretical increased risk of developing biological resistance in the primary tumor cells, which we're studying in the laboratory.

If I have a patient who appears to have early relapse following an autologous transplant (eg, the nodes are slowly progressing, but they're too small to obtain a biopsy), I have no problem using rituximab weekly times four. In a number of cases, I have seen their tumors regress. I use a common-sense approach. If the patient's disease is progressing, the patient is post an autologous transplant, the patient is elderly or the patient did not handle chemotherapy well in the past, I don't have a problem using rituximab at the time of re-treatment.

Mantle-cell lymphoma is another condition in which you have older patients who may not be able to tolerate an aggressive hyper-CVAD regimen. If patients are treated with R-CHOP and are not candidates for transplantation, then maybe using set doses of rituximab on a regular basis is reasonable.

In CALGB, one of the trials we're discussing takes patients in first CR to an autologous stem cell transplant, and we're adding some maintenance type of treatment. We're discussing bortezomib alone or in combination with rituximab, although rituximab may be used in combination with other agents.

Select publications

Cheson BD et al. **Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group**. *J Clin Oncol* 1999;17(4):1244. **Abstract**

Czuczman MS et al. **Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up**. *J Clin Oncol* 2004;22(23):4711-6. **Abstract**

Czuczman MS et al. **Rituximab in combination with fludarabine chemotherapy in low-grade or follicular lymphoma**. *J Clin Oncol* 2005;23(4):694-704. **Abstract**

Czuczman MS et al. **Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy**. *J Clin Oncol* 1999;17(1):268-76. **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**

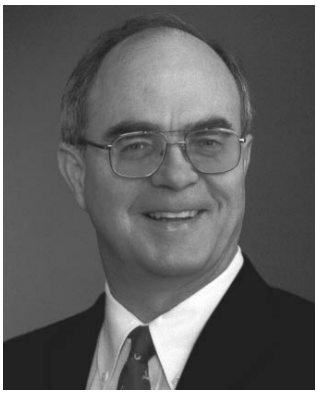
Kaminski MS et al. **131I-tositumomab therapy as initial treatment for follicular lymphoma**. *N Engl J Med* 2005;352(5):441-9. **Abstract**

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**

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**

Schmits R et al; German High-Grade Non-Hodgkin's Lymphoma Study Group. **The best treatment for diffuse large B-cell lymphoma: A German perspective.** *Oncology (Williston Park)* 2005;19(4 Suppl 1):16-25. **Abstract**

Impact of monoclonal antibodies in the treatment of NHL



Antibodies have had a much bigger impact on the treatment of patients with lymphoma than anticipated. Essentially, all the current antibodies are directed against CD20, and almost all the important groups of lymphoma express CD20.

These drugs were developed for follicular lymphoma; however, while rituximab clearly has a real effect on follicular lymphoma, as do the radioantibodies ibritumomab and tositumomab, it appears rituximab's most important impact is on diffuse large B-cell lymphoma.

Several trials, including the French trial evaluating CHOP plus rituximab, the MInT trial in Europe, the ECOG trial in the United States and the population-based analysis from British Columbia have all shown that rituximab has a tremendous impact on the survivability and curability of diffuse large B-cell lymphoma, which is the most common lymphoma and much more aggressive than follicular lymphoma (Coiffier 2002; Pfreundschuh 2005; Habermann 2004; Sehn 2005).

I believe the data from the British Columbia study (Sehn 2005; [4.1]) is even more convincing than the three randomized trials. In Canada, a central approval exists for drugs, and on a specific day, rituximab/CHOP became the recommended treatment for diffuse large B-cell lymphoma. The researchers examined data 18 months before that date (the prerituximab era) and 18 months after that date (the postrituximab era) to determine whether rituximab impacted this disease throughout the entire province.

Indeed, a sudden drop in mortality was seen after the introduction of rituximab. Even though a few patients before that date had received rituximab and approximately 15 percent after the date of approval did not receive the drug, the mortality rate went down approximately 20 percent for diffuse large B-cell lymphoma in British Columbia. I believe that is the most important impact of unlabeled antibodies.

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4.1 Population-Based Analysis of the Impact of Rituximab Combined with CHOP in Adult Patients with Diffuse Large B-Cell Lymphoma in British Columbia

Efficacy parameter	Risk ratio	95% CI	*p*-value
Outcome according to treatment era (postrituximab versus prerituximab)			
Progression-free survival	0.56	0.39-0.81	0.002
Overall survival	0.40	0.27-0.61	<0.0001
Multivariate analysis controlling for age and International Prognostic Index score			
Progression-free survival	0.59	0.41-0.85	0.005
Overall survival	0.43	0.26-0.66	<0.001
Subgroup analysis based on age (<60 years versus ≥60 years)			
Progression-free survival in older patients	0.53	0.33-0.85	0.007
Progression-free survival in younger patients	0.63	0.35-1.16	0.13*
Overall survival in older patients	0.41	0.25-0.68	0.0003
Overall survival in younger patients	0.41	0.19-0.90	0.02

* Did not meet statistical significance

SOURCE: Sehn LH et al. **Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia**. *J Clin Oncol* 2005;23(22):5027-33. **Abstract**

Use of radioimmunotherapy in patients with follicular lymphoma

The radiolabeled antibodies are the most active drugs in the treatment of follicular lymphoma. They have the highest response rate, and even after patients have failed chemotherapy, they respond to radioimmunotherapy at an unexpectedly high rate. These agents appear to be much better for treating follicular lymphoma than large B-cell lymphoma, probably because follicular lymphoma is so uniquely radiosensitive.

Still, we haven't learned the best way to use radioantibodies. In a study from the University of Michigan in which approximately 80 patients with follicular lymphoma were treated initially with iodine-labeled tositumomab, the response rate was extremely high — almost everyone responded, and the median duration of response was somewhere between six and seven years (Kaminski 2005). We need to seriously consider the potential of radioantibodies as initial therapy, at least for elderly patients. It's associated with almost no morbidity and essentially no mortality when used as front-line therapy.

Studies are examining how to utilize radioantibodies with chemotherapy. Two exciting findings have been reported recently. In one study, conducted by Zelenetz and colleagues at Memorial, patients with untreated mantle-cell

lymphoma were treated with radioimmunotherapy followed by CHOP (Zelenetz 2003). The response rate was very high, and the outcome was shockingly good.

In the SWOG study of CHOP followed by tositumomab/iodine I-131 tositumomab (Bexxar) in patients with previously untreated follicular lymphoma, when historical comparisons were made, the results were the best they'd ever seen in the treatment of follicular lymphoma (Press 2003). Another extremely interesting study is the ongoing national trial in which CHOP/rituximab is compared to CHOP followed by Bexxar in patients with newly diagnosed follicular lymphoma (SWOG-S0016).

Clinical management of indolent lymphoma

Follicular lymphoma is the second most common lymphoma, and we have so many effective treatments that it's difficult to decide how to treat patients. Single-agent cytotoxic therapy, combinations of drugs, labeled and unlabeled antibodies, auto and allogeneic transplants and interferon have all been effective. Most physicians approach this disease as incurable, which is certainly not true. If by cure we mean the disease goes away and doesn't recur before the patient dies of something else, then we have seen patients cured after allogeneic and autologous transplants, primary chemotherapy regimens and, it now appears, after radioantibodies.

I generally don't treat very elderly, asymptomatic patients immediately, and if I do need to treat them, I utilize a therapy with minimal toxicity, like an antibody. Younger patients are usually much less excited about the fact that there's a 10-year median survival; they are interested in a very long survival, preferably free of lymphoma. In such patients, my treatment goal would be to induce a complete remission, with the idea that if they relapse, we'd do either an autologous or an allogeneic transplant.

Use of maintenance rituximab

I use rituximab up front without chemotherapy in elderly patients, patients who are ill and in those of any age who are anxious to avoid any significant morbidity. Some patients say they'd rather die than lose their hair and, in such a case, rituximab is the best choice. When we treat a patient with rituximab only as initial treatment, then rituximab maintenance quite clearly prolongs the median duration of remission, and I do recommend its use.

From the available data, I believe we now know rituximab maintenance isn't necessary in large B-cell lymphoma. Also, in follicular lymphoma, for a patient who receives a regimen like CHOP/rituximab or FND/rituximab as initial therapy, I don't believe it's clear that there's an advantage to rituximab maintenance. In a study presented at ASH in 2004, patients with relapsed follicular lymphoma who had received such regimens and then received maintenance rituximab remained in remission longer (Van Oers 2004). However, I don't know of any convincing data indicating that that's true with the initial therapy.

Three different schedules of maintenance rituximab have been studied — re-induction (four treatments) every six months, the Swiss regimen of one dose every other month and the ECOG trial in which rituximab is given every three months. In the clinical setting, when using rituximab for maintenance, I give it every other month for a year.

Hyper-CVAD plus rituximab in the treatment of mantle-cell lymphoma

Mantle-cell lymphoma is a disease we've known about for only a little over a decade. For the first six or seven years, it was considered the worst disease to have. It responded least well to our treatments then; however, the hyper-CVAD regimen combined with rituximab developed at MD Anderson has truly changed that. For the first time, patients regularly achieve complete remission. We then transplant them in first remission, and they've done extremely well.

I tell my patients that rituximab with hyper-CVAD and a transplant in remission is the most active treatment we've ever used. The great majority of patients — more than 75 percent of the ones we've treated — have experienced a complete remission. We don't know whether they will eventually relapse, but they have not relapsed yet, and we're out several years. It's a difficult regimen, and not every patient can tolerate it. I'm very hesitant to recommend it to patients in their late sixties and certainly patients in their seventies. I've had some difficult experiences, although no mortalities, in older patients.

Select publications

Coiffier B et al. **CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma**. *N Engl J Med* 2002;346(4):235-42. **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**.

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

Pfreundschuh MG et al. **Treatment results of CHOP-21, CHOEP-21, MACOP-B and PMitCEBO with and without rituximab in young good-prognosis patients with aggressive lymphomas: Rituximab as an "equalizer" in the MInT (MABTHERA International Trial Group) study**. *Proc ASCO* 2005;**Abstract 6529**.

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**

Sehn LH et al. **Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia**. *J Clin Oncol* 2005;23(22):5027-33. **Abstract**

Van Oers MHJ et al. **Chimeric anti-CD20 monoclonal antibody (rituximab; Mabtheraâ) 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**.

Zelenetz AD et al. **Initial treatment of mantle cell lymphoma with sequential radioimmunotherapy with tositumomab/iodine I131 I-tositumomab followed by CHOP chemotherapy results in a high complete remission rate**. *Proc ASH* 2003;**Abstract 1477**.

Post-test:

Non-Hodgkin's Lymphoma Update — Issue 4, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. Compared to CHOP alone, R-CHOP provides a survival advantage for patients with diffuse large B-cell lymphomas.
   a. True
   b. False

2. Compared to CVP alone, R-CVP has demonstrated a survival advantage for patients with indolent lymphomas.
   a. True
   b. False

3. In a retrospective analysis of several SWOG trials, it appears that CHOP in combination with monoclonal antibody therapy may impact the natural history of patients with follicular lymphomas in terms of _____.
   a. Four-year progression-free survival
   b. Four-year overall survival
   c. Both a and b

4. In both indolent and aggressive lymphomas, bendamustine in combination with rituximab resulted in a response rate of _____.
   a. 90 percent
   b. 70 percent
   c. 50 percent
   d. 30 percent

5. In a Phase II trial of patients with low-grade or follicular NHL, R-CHOP had a _____ overall response rate.
   a. 40 percent
   b. 60 percent
   c. 80 percent
   d. 100 percent

6. In a Phase II trial of patients with low-grade or follicular NHL, R-CHOP had a median time to progression close to _____.
   a. 3 years
   b. 7 years
   c. 15 years
   d. 25 years

7. In a Phase II trial of patients with low-grade or follicular NHL, R-fludarabine had a _____ overall response rate.
   a. 50 percent
   b. 70 percent
   c. 90 percent
   d. 100 percent

8. In a Phase III randomized trial, patients with follicular NHL who were treated with R-CVP had a median time to progression of 27 months.
   a. True
   b. False

9. Three randomized clinical trials, plus a population-based analysis in British Columbia, have all shown that rituximab dramatically improves outcome of diffuse large B-cell lymphoma.
   a. True
   b. False

10. Maintenance rituximab following initial therapy with single-agent rituximab has been shown to prolong the median duration of remission.
    a. True
    b. False

11. Fewer than 25 percent of patients with mantle-cell lymphoma who are treated with hyper-CVAD-rituximab and transplant during remission experience a complete remission.
    a. True
    b. False

Post-test answer key: 1a, 2b, 3c, 4a, 5d, 6b, 7c, 8a, 9a, 10a, 11b

Evaluation Form:

Non-Hodgkin's Lymphoma Update — Issue 4, 2005

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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 into management strategies when appropriate. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials in NHL. . . . . 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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Myron S Czuczman, MD	5 4 3 2 1	5 4 3 2 1
James O Armitage, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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Related to my practice needs. . . . . 5 4 3 2 1 N/A
Will influence how I practice. . . . . 5 4 3 2 1 N/A
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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