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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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CME Certified

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 5 of *Non-Hodgkin's Lymphoma Update* is to support these global objectives by offering the perspectives of Drs Hagemeister, Kaminski, Coiffier and Pfreundschuh 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.

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HOW TO USE THIS MONOGRAPH

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

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UPCOMING EDUCATIONAL EVENTS

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

Oncology World Congress
November 16-19, 2005
New York, New York
Event website: **www.oncologycongress.com**

American Society of Hematology (ASH) 47th Annual Meeting and Exposition
December 10-13, 2005
Atlanta, Georgia
Event website: **www.hematology.org/meeting/**

Highlights of American Society of Hematology (ASH)
February 10-11, 2006
Miami, Florida
Event website: **www.hematology.org/meetings/highlights**

National Comprehensive Cancer Network (NCCN) 11th Annual Conference
March 8-12, 2006
Hollywood, Florida
Event website: **www.nccn.org**

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

American Society of Clinical Oncologists (ASCO) 42nd Annual Meeting
June 2–6, 2006
Atlanta, Georgia
Event website: **www.asco.org**

EDITOR'S NOTE

Neil Love, MD

Lymphoma rounds

About halfway through the enclosed interview with Dr Fredrick Hagemeister, my mind wandered to the CME disclosure forms that I review with our faculty prior to every interview. On these forms, there is a box that the interviewee needs to check if the discussion will include information that is off FDA label. Needless to say, virtually all interviewees check this box.

However, as I listened to Rick (he and his father are both "Fredricks" and for differentiation, Dad is Fred and Rick is Rick) describe a case from his practice where he used a therapy with proven safety and efficacy in mantle-cell lymphoma (R-Hyper-CVAD) in a 79-year-old man with diffuse large B-cell lymphoma who had a Burkitt's-like Ki-67 of 95 percent, I wondered if we should add a box to the form for our guests to check when they are discussing topics that the FDA hasn't even dreamed about.

This case certainly falls into that category. At diagnosis, the patient presented with a virulent lesion behind his eye that was causing a disfigurement of his face and was invading the dura of his brain. Over the course of just a few days, the lesion visibly progressed, and the patient's vision began to further deteriorate.

At the time, the MD Anderson Group was about to implement a study comparing R-Hyper-CVAD to R-CHOP in patients with diffuse large B-cell lymphoma, but the trial was still moving through the approval process. After a long discussion with this man and his family, Dr Hagemeister began R-Hyper-CVAD treatment that day (with plans to not alternate ARA C and methotrexate), and remarkably, a documented complete remission occurred in two weeks, at which point the patient's visage returned to normal and now includes a cautious smile.

The interview with Dr Hagemeister was part of our CME group's visiting professorship program, and as Rick prepared to head back to Houston from Miami, he fretted that clinicians would get the wrong idea from the case he presented. "I wasn't trying to recommend that oncologists use this approach outside a protocol setting," he said. "I normally would have treated this patient as part of a study, but the one that was best suited for him was still awaiting approval, and this patient was progressing too rapidly for us to wait." I reassured Dr H that the message was clear, and perhaps even more impor-

tantly, that oncologists would benefit from hearing about the newest research strategies from one of our country's most prestigious cancer institutions.

Like many of the other MD Anderson clinical investigators our group has had the honor of working with on oncology programs in the past, Dr Hagemeister is also tuned in to the complex psychosocial needs of cancer patients. The second case he presented was a woman with favorable prognosis Stage IV follicular lymphoma. What made the case a particular challenge was that the patient had an obvious and severe clinical depression, which prompted Dr H to immediately refer her to a psychiatrist who started fluoxetine (Prozac®).

This psychiatric complication — which occurred without a prior history of mood disorder — seemed to be an acute reaction to the diagnosis, and Dr H considered this a critical factor in his initial treatment recommendation. Like most of MD Anderson's lymphoma group, Dr H generally prefers to use R-chemo rather than R alone as first-line therapy for indolent lymphoma, but in this case, chemo was delayed to give the patient a chance to become accustomed to the infusion room and to allow the fluoxetine to take effect.

Some months later, with the depression improving and the tumor progressing, FND was added to the rituximab. The patient completed four cycles of that regimen, which resulted in a complete remission. She is now back on R alone as maintenance, and during a recent office visit, she suggested to Dr Hagemeister that perhaps she didn't require the antidepressant anymore.

These two fascinating cases are reminders that there is no better way to learn medicine than to follow master clinicians on rounds, listen to them talk to patients and then discuss the intricacies of these situations with them. In that regard, this issue of *NHL Update* includes our second attempt at a patient education audio program, and for this ongoing experiment, we decided to apply the model of "oncology rounds."

For this supplement, we visited with medical oncologist Dr Lowell Hart who, along with founding father Bill Harwin, leads a 40-oncologist group on the West coast of Florida. Our CME team enjoys working with these docs, who eat up clinical research information as voraciously as they do Joe's Stone Crabs.

I asked Lowell to select three patients with lymphoma from his practice who would be willing to participate in one-on-one recorded interviews with me and tell their stories to hopefully tens of thousands of other physicians, nurses, patients and loved ones. The final edited program is enclosed and includes chats with a retired septuagenarian and his wife, a 65-year-old receptionist in a dental office and a 39-year-old man who spent most of his adult life touring as a drummer with a rock band. What unites all three of these patients is their recent experience being treated with R and various forms of chemotherapy.

The consistent message from these interviews is that while R-chemotherapy for lymphoma is a challenge, it is also generally quite tolerable. A second clear theme from these three patients was that, in their view, a positive outlook on

the future is an important coping mechanism as is continuing to engage in enjoyable lifestyle activities during treatment.

Using the rounds format, we not only hear the perspectives of these patients and their oncologist (Dr Hart), but also Dr Hagemeister, who provides an update on new research concepts in lymphoma in a deliberate, well-thought-out and very understandable manner.

Our goal with this new patient education initiative is to allow patients to learn "at the bedside" in the same manner that physicians have been doing for centuries. Any feedback in this continuing experiment in oncology education would be most appreciated. ■

— Neil Love, MD
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SELECT PUBLICATIONS

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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**

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

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

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

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**

Liu Q et al. **Stage IV indolent lymphoma: 25 years of treatment progress.** *Proc ASH* 2002;**Abstract 1446**.

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**

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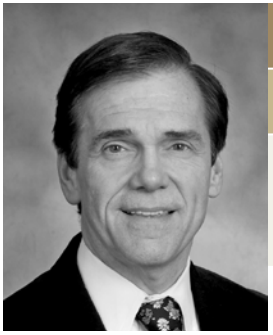
Sehn LH et al. **Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia.** *J Clin Oncol* 2005;23(22):5027-33. **Abstract**



INTERVIEW

Fredrick B Hagemeister, MD

Dr Hagemeister is a Professor of Medicine in the Department of Lymphoma/Myeloma at The University of Texas MD Anderson Cancer Center in Houston, Texas.

CD 1 — Tracks 2-15

Track 2 Case discussion: A 79-year-old man with massive orbitosinus diffuse large B-cell lymphoma

Track 3 Clinical use of R-Hyper-CVAD for a patient with high-risk diffuse large B-cell lymphoma

Track 4 German study evaluating R-CHOP-14 versus R-CHOP-21 in elderly patients

Track 5 Complete remission of high-risk diffuse large B-cell lymphoma to R-Hyper-CVAD

Track 6 Use of PET scan results to tailor treatment decision-making

Track 7 Case discussion: Patient with follicle center-cell lymphoma and clinical depression

Track 8 ECOG-E4402: Rituximab Extended Schedule Or Re-Treatment (RESORT) trial

Track 9 Responsiveness to chemotherapy after development of resistance to rituximab

Track 10 Nonprotocol use of maintenance rituximab

Track 11 PRIMA study: Maintenance versus no maintenance rituximab after response with chemotherapy-R in advanced follicular lymphoma

Track 12 Improvement in complete response rates with the combination of GM-CSF plus rituximab

Track 13 Complete remission to R-FND after progression on rituximab

Track 14 Potential curability of patients with indolent lymphoma

Track 15 Clinical experience with R-FND therapy

Select Excerpts from the Interview*

CD 1, Track 8

DR LOVE: I'm curious about your thoughts on the RESORT trial comparing R followed by R maintenance versus R alone and R re-treatment on progression. I find it interesting that maintenance therapy is given indefinitely, as opposed to being given for two years.

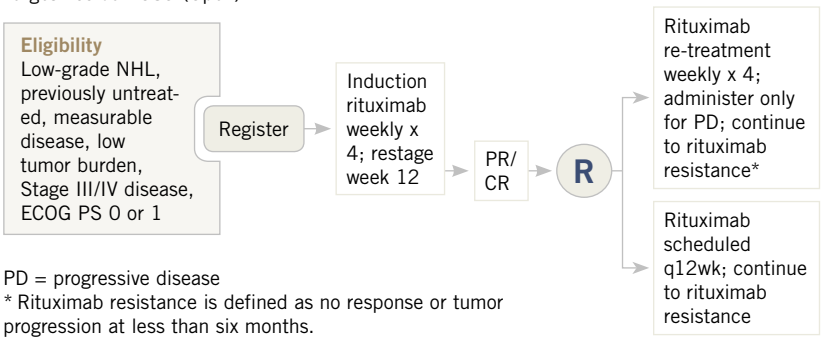
DR HAGEMEISTER: I love the maintenance program in this study — it's based on real data from the Gordon trial. I like the idea, ultimately, of giving the rituximab as maintenance, until the patient develops disease progression.

* *Conducted on August 10, 2005*

1.1

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

Protocol ID: ECOG-E4402
Target Accrual: 389 (Open)



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

Study Contacts:
Brad Kahl, MD, Tel: 608-265-9358
Michael Williams, MD, Tel: 434-924-9637
Eastern Cooperative Oncology Group

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

This is a very interesting study (1.1); however, I would love to see an additional question addressed, and that is, Will patients who subsequently are treated with chemotherapy — or whatever additional therapy they receive when they develop progressive disease — will patients on both arms have the same responsiveness to chemotherapy? There is a suggestion that patients who are "refractory" to rituximab tend to be resistant to chemotherapy agents.

However, there are no clinical data to support that. In fact, patients seem to have more favorable disease at the time of recurrence and survive for longer periods of time, it appears, when they receive rituximab as therapy. Although there's no real hard, strong data right now in a randomized study to demonstrate that, there is a strong suggestion that patients are living longer because they receive rituximab.

The Hainsworth study of R maintenance is in patients with relapsed lymphomas, not front-line therapy. With these patients, time to treatment failure is better when you give maintenance rituximab, but time to receiving other drugs or a new treatment is no different whether you adopt a maintenance therapy or a re-treatment therapy.

What will ultimately answer this question is the PRIMA study, which evaluates R-chemotherapy followed by rituximab maintenance every three months for two years versus none (1.2). In that trial, it may be that rituximab maintenance actually ends up prolonging the patient's time to treatment failure — but maybe not survival.

1.2

Phase III Study Comparing Maintenance Therapy with Rituximab After Induction of Response with Chemotherapy Plus Rituximab versus No Maintenance Therapy

Protocol ID: NCT00140582
Target Accrual: 640 (Open)

* Chemotherapy consists of either CVP x eight cycles or CHOP x six cycles or FCM x six cycles or MCP x six cycles.

Study Contacts:
Gilles A Salles, MD, Tel: 33-478-59-80-79
Germain Delphine, BS, Tel: 33-472-66-93-33

SOURCE: www.Clinicaltrials.gov, September 2005.

CD 1, Track 12

DR LOVE: Would you provide an update of your study of rituximab plus GM-CSF?

DR HAGEMEISTER: We've been conducting a study that shows that administering GM-CSF along with rituximab leads to much higher complete response rates than we see with single-agent rituximab. It was not a randomized study, and it wasn't in patients who were rituximab resistant. In fact, patients had to have sensitive disease. They had to have a response to their last rituximab treatment that lasted at least six months in order to be entered on the study.

Recently, Peter McLaughlin presented our data at the lymphoma meeting in Lugano, Switzerland. The complete response rates are in the range of 40 percent. They're very dramatic. We've treated approximately 75 patients, and the side effects have not been any more than what you would expect with rituximab as a single agent.

Patients didn't receive maintenance therapy on the trial. The most interesting aspect of that whole study is that we actually demonstrated that ADCC (antibody-dependent cellular cytotoxicity) is upregulated by the administration of GM-CSF.

We're currently considering this as a new study — a Phase II/III study with rituximab/GM-CSF in patients with indolent follicular lymphoma who have zero to one adverse feature in the Follicular Lymphoma International Prognostic Index (FLIPI) score.

CD 1, Track 14

DR LOVE: Fernando Cabanillas has discussed the concept of cure, or extended survival, in patients treated for indolent lymphoma, and the series of trials that have been done at MD Anderson (1.3). What are your thoughts on that?

DR HAGEMEISTER: We've demonstrated in sequential trials that survival appears to have improved continuously over the last 30 years, first with CHOP alone or CHOP-Bleo initially, then with CHOP/interferon and, ultimately, with alternating triple therapy plus interferon. Then, when we introduced FND, things also significantly improved, and finally, with the addition of rituximab in the last five years — more than 90 percent of those patients are still alive at five years with R-FND-type therapies (Liu 2003).

1.3

MD Anderson Experience in the Treatment of Stage IV Indolent Lymphoma

			Survival		
Regimen	Treatment period	No. of patients	5-year (%)	10-year (%)	15-year (%)
CHOP-Bleo	1977-1982	96	64	37	29
CHOP-Bleo → IFN	1982-1988	131	75	52	42
ATT → IFN	1988-1992	136	82	60	—
ATT → IFN vs FND → IFN	1992-1997	142	82	—	—
FND-R versus FND → R (+ IFN)	1997-2002	200	90	—	—

IFN = interferon; ATT = alternating triple therapy with CHOD-B/ESHAP/NOPP
FND = fludarabine, mitoxantrone and dexamethasone

SOURCE: Liu Q et al. *Proc ASH* 2003;**Abstract 1446**.

DR LOVE: Fernando talked about a plateau in the curves at eight years. What are your thoughts on that?

DR HAGEMEISTER: We've evaluated patients who have Stage IV follicular lymphoma who were all submitted for the FLIPI analysis. Every patient had Stage IV disease and had been treated on a trial.

We looked at time to progression and after about nine or 10 years, approximately 40 percent of the patients who have a low beta globulin serum tumor marker have not developed progressive disease, and there is very definitely a plateau out to 15 years. ■

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**

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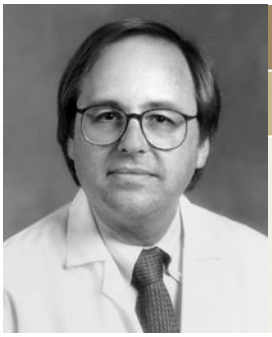

INTERVIEW

Mark S Kaminski, MD

Dr Kaminski is a Professor of Internal Medicine and Co-Director of the Leukemia/Lymphoma and BMT Program at the University of Michigan Comprehensive Cancer Center in Ann Arbor, Michigan.

CD 1 — Tracks 17-22; CD 2 — Tracks 1-4

Track 17 Radioimmunotherapy as first-line treatment of follicular lymphoma

Track 18 Bcl-2 translocation as a predictor of PCR negativity and response to radioimmunotherapy

Track 19 Interpreting radioimmunotherapy data in comparison to other clinical trials of first-line therapy

Track 20 Acute and long-term toxicities associated with radioimmunotherapy

Track 21 SWOG trial of CHOP followed by Bexxar® consolidation in responding patients

Track 22 SWOG trial S0016 comparing R-CHOP versus CHOP followed by Bexxar in patients with newly diagnosed follicular NHL

CD 2

Track 1 Potential strategies for evaluating the optimal use of radioimmunotherapy

Track 2 Treatment algorithm for newly diagnosed indolent lymphoma

Track 3 Incorporation of radioimmunotherapy in the treatment of indolent lymphoma

Track 4 Evaluating immunologic and novel targeted therapies in NHL

Select Excerpts from the Interview*

CD 1, Track 17

DR LOVE: One of the most discussed publications in lymphoma this year was your paper in *The New England Journal of Medicine* evaluating radioimmunotherapy as first-line treatment for follicular lymphoma (Kaminski 2005). Can you comment on the background to that trial?

DR KAMINSKI: We performed a lot of the developmental work on radioimmunotherapy with CD20 radio-labeled antibodies. We had shown how to administer it, what its toxicities were and where its greatest value appeared to be, which was in the follicular lymphomas. We had also done a lot of work in patients with refractory disease, and it was working in them.

* *Conducted on April 8, 2005*

The natural idea here is that if it works in the back-line setting, it should work even better in the front-line setting, where there's less potential resistance — the patients are more immunocompetent. So especially in an incurable disease such as follicular lymphoma, it made all the sense in the world to use something that appeared in some of our trials to be superior to chemotherapy as front-line therapy.

The trial evaluated Bexxar in patients with Stage III and IV follicular lymphoma — advanced-stage disease — with no prior treatment. Our first patient was accrued in June of 1996, so we have quite a long follow-up on these patients. The first-patient phenomenon worked in this trial: That patient is still in complete remission.

DR LOVE: Can you summarize the data that you recently reported in *The New England Journal of Medicine*?

DR KAMINSKI: We showed in 76 patients that we could achieve a 95 percent response rate with only one course of treatment, which only takes a week to give, and a 75 percent complete remission rate (2.1). We now have long-term follow-up — the median follow-up is over five years — and the progression-free survival at five years is 60 percent for all the patients entered on the trial.

Of those who had a complete response, more than 70 percent — 75 percent — were still in remission at five years. At this point, an abundant number of patients are beyond five years. We only had four relapses, and of those four, three relapsed only in a solitary site, and we treated that with conventional radiation therapy and put them back into remission. That's one aspect.

The other aspect of this trial was that we were interested to see if we could induce a molecular remission. If the treatment had any chance of being a potential cure, to be molecularly negative would certainly be going a long way in that direction, so we actually measured the Bcl-2 translocation using PCR techniques, serially, in the

2.1

Clinical Trial of Tositumomab/Iodine I-131 Tositumomab (Bexxar) as Initial Treatment for Follicular Lymphoma: Hematologic Toxicity Data (N = 76)

Efficacy parameter	Outcome
Response rate	95%
CR rate	75%
Five-year PFS rate (estimated)	59% (95% CI: 49-71)
Five-year PFS rate for patients with CR	77% (95% CI: 67-89)
Median PFS	6.1 years (95% CI: 3.0-upper level not reached)*
Five-year OS rate	89% (95% CI: 83-97)

* Median follow-up of 5.1 years

CR = complete response
PFS = progression-free survival
OS = overall survival

SOURCE: Kaminski MS et al. *N Engl J Med* 2005;352(5):441-9. **Abstract**

bone marrow of these patients. We found that of the patients who had the Bcl-2 translocation, more than 90 percent showed molecularly negative results at some point in the follow-up.

CD 1, Track 20

DR LOVE: What did you see in terms of short- and long-term toxicities?

DR KAMINSKI: Myelodysplastic syndrome and acute myelogenous leukemia are the long-term toxicities we're most concerned about, and we didn't see any — zero — with a median follow-up of five years.

As for the short term, the major toxicity is hematological (2.2). It occurs at about six to seven weeks in terms of the nadir of blood counts, but none of these patients had to have any transfusions. No one had febrile neutropenia requiring hospitalization or antibiotics, and none of them received growth factors; it was very well tolerated.

2.2

Clinical Trial of Bexxar as Initial Treatment for Follicular Lymphoma: Hematologic Toxicity Data (N = 76)

Variable	Absolute neutrophil count	Hemoglobin	Platelet count
Median nadir value	1,300 per mm^3	12.2 g/dl	83,000 per mm^3
Median time to nadir (days)	47	44	29
Toxicity			
Grade III or IV	34%	0%	17%
Grade IV	5%	0%	0%
Median duration of toxicity (days)*			
Grade III or IV	22	NA	22
Grade IV	22	NA	NA
Median time to return to baseline grade (days)	60	56	43

NA = not applicable

* Duration of toxicity was defined as the number of days from the last count before Grade III or IV toxicity to the first day of the documented return to Grade II toxicity.

SOURCE: Kaminski MS et al. *N Engl J Med* 2005;352(5):441-9. **Abstract**

CD 2, Track 3

DR LOVE: In the clinical management of indolent lymphomas, where does radioimmunotherapy generally fit into your algorithm?

DR KAMINSKI: I try to utilize it as early as possible in the course of the disease. If a patient has had a long remission with chemotherapy and then they require more therapy, we have the options to give just rituximab or go on to give additional chemotherapy or to give radioimmunotherapy. I would clearly use radioimmunotherapy in patients who have short responses to chemotherapy and who have relatively poor responses to rituximab.

In general, because of the simplicity of the treatment and the brevity of it, I really have a hard time not thinking of radioimmunotherapy for a patient who has relapsed with a follicular lymphoma if the disease is progressing and is potentially beginning to become or is symptomatic. That's where the highest complete response rates are, and that's where the duration of response is greatest. If you obtain a complete response, you have an excellent chance of remaining that way for five years, and very few chemotherapeutic approaches out there demonstrate that. ■

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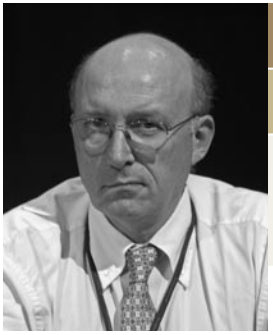

INTERVIEW

Bertrand Coiffier, MD, PhD

Dr Coiffier is a Professor of Hematology and Head of the Department of Hematology at Hospices Civils de Lyon and Université Claude Bernard in Lyon, France.

CD 2 — Tracks 6-17

Select Excerpts from the Interview*

CD 2, Track 9

DR LOVE: What's your usual approach to initial treatment of aggressive lymphoma in younger patients?

DR COIFFIER: Currently, for a young patient with aggressive lymphoma, we don't use R-CHOP, we use a more advanced chemotherapy called ACVBP.

The ACVBP regimen is complicated (3.1). That's one of the reasons it's not really utilized in the United States. The regimen has two parts: One part consists of dose-dense, dose-intense CHOP, using higher doses of cyclophos-

* *Conducted on May 16, 2005*

phamide and doxorubicin given every two weeks for three or four cycles according to the treatment setting. This is followed by sequential consolidation chemotherapy, which consists of several agents — first methotrexate, then ifosfamide, etoposide and cytarabine — every two weeks for four months. The total length of treatment is six months.

3.1

Randomized Study Comparing ACVBP versus CHOP Combined with Radiotherapy for Localized Aggressive Lymphoma

Protocol ID: LNH 93-1
Accrual: 647 (Closed)

Eligibility
Between 15 and 61 years of age
Newly diagnosed aggressive lymphoma (diffuse mixed, diffuse large-cell or immunoblastic)
No adverse prognostic factors
Treatment naïve

R

- ACVBP q2wk × 3 followed by sequential consolidation*
- CHOP q3wk × 3 followed by involved-field radiotherapy†

ACVBP = doxorubicin 75 mg/m^2, cyclophosphamide 1,200 mg/m^2 (d1); vindesine 2 mg/m^2, bleomycin 10 mg (d1 and d5); and prednisone 60 mg/m^2 (d1 through d5).

* Sequential consolidation = methotrexate (3 g/m^2) plus leucovorin rescue × two cycles; etoposide (300 mg/m^2) and ifosfamide (1,500 mg/m^2) × four cycles; and cytarabine (100 mg/m^2) × two cycles for four days q2wk

† Administered one month after last cycle of CHOP

SOURCE: Reyes F et al. *N Engl J Med* 2005;352(12):1197-205. **Abstract**.

DR LOVE: Would you review the study of ACVBP versus CHOP that was recently published in *The New England Journal of Medicine*?

DR COIFFIER: That study included patients with localized lymphoma, but there are other studies of ACVBP in different patient populations.

The objective of our study was to demonstrate whether dose-intense chemotherapy was better than the standard three-weekly CHOP followed by radiation therapy. Patients in one arm received three cycles of CHOP followed by involved-field radiation therapy. In the other arm, patients received ACVBP and sequential consolidation chemotherapy without radiation therapy.

ACVBP with sequential consolidation chemotherapy was better than CHOP with radiation therapy in the intent-to-treat population (3.2). If you look at the data for patients without a large tumor mass, ACVBP was also better. We have previously published similar findings in *Blood* (Tilly 2003), in which we evaluated Stage III and IV patients and compared ACVBP to eight cycles of CHOP.

The study was initiated before the availability of rituximab. At the time, ACVBP was better than eight cycles of CHOP. We now know that R-CHOP

is much better than CHOP, so the question is, Is R-ACVBP the same or better than R-CHOP? We are currently investigating this question, but we do not have the results.

3.2 **Five-Year Event-Free Survival and Overall Survival in Patients with Newly Diagnosed Aggressive Lymphoma**

	ACVBP	CHOP/radiotherapy	*p*-value
EFS (95% CI)*	82% (78%-87%)	74% (69%-78%)	<0.001
OS (95% CI)*	90% (87%-93%)	81% (77%-86%)	0.001

* Differences in EFS and OS remained significant when patients without bulky disease and those with bulky disease were analyzed separately ($p < 0.05$ for all comparisons).
EFS = event-free survival; OS = overall survival

SOURCE: Reyes F et al. *N Engl J Med* 2005;352(12):1197-205. **Abstract**

CD 2, Track 13

DR LOVE: How do you approach patients with follicular lymphoma?

DR COIFFIER: I first evaluate the criteria for requiring treatment. I use criteria that are nearly the same everywhere for high tumor burden. If the patient does not have any of those criteria, I do nothing (watch and wait). If the patient has one criterion, he or she needs to be treated. In that case, I usually propose R-CHOP. I think there's some benefit in adding doxorubicin. If you compare the different studies, I think R-CHOP was better than R-CVP, and the duration of the response is better. So I prefer to use R-CHOP in patients up to 70 years of age. After that, R-CVP may be good treatment. If the patient shows a good response, but not a complete response — that is, persisting low involvement in any case — I do maintenance therapy with rituximab. ■

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Tilly H et al; Groupe d'Etude des Lymphomes de l'Adulte. **Randomized comparison of ACVBP and m-BACOD in the treatment of patients with low-risk aggressive lymphoma: The LNH87-1 study.** *J Clin Oncol* 2000;18(6):1309-15. **Abstract**

INTERVIEW

Michael Pfreundschuh, MD

Dr Pfreundschuh is the Director of Med Klinik I and Professor of Internal Medicine at Saarland University Medical School and is Chairman of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) in Homburg, Germany.

CD 2 — Tracks 19-25

Track 19 CHOP-21, CHOEP-21, MACOP-B and PMitCEBO with and without rituximab in young, good-prognosis patients with aggressive lymphomas

Track 20 Equivalence of R-CHOP and R-CHOEP: Rituximab as a chemotherapy "equalizer"

Track 21 Dose-dense chemotherapy in good-prognosis patients with aggressive lymphoma

Track 22 CHOP-14 with or without rituximab for six versus eight cycles

Track 23 Treatment approach to mantle-cell lymphoma

Track 24 Research strategies in follicular lymphoma

Track 25 Challenges in developing vaccines for NHL

Select Excerpts from the Interview*

CD 2, Track 19

DR LOVE: Can you review the background of the Mabthera International trial (MInT) of patients with low-risk diffuse large B-cell lymphoma (DLBCL)?

DR PFREUNDSCHUH: In 2002, it was reported that the addition of rituximab to three-weekly CHOP significantly improved outcomes in elderly patients (Coiffier 2002). Based on that finding, we wondered whether this would also be the case in young patients at low risk. Because we thought it's much more difficult to show an improvement in young patients at low risk, we calculated that we needed more than 800 patients to show a 10 percent difference in event-free survival.

To get these patients, it was clear that we would need an international effort, which requires compromise, so we were quite liberal with the selection of a CHOP-like regimen — doctors in each country could choose their own

* *Conducted on May 16, 2005*

regimen. Our philosophy was that if rituximab really does something important, then it should work overall.

The first interim analysis showed such clear-cut differences in favor of the combination CHOP-like regimen with rituximab that the Data Safety Monitoring Board urged us to stop the trial when 50 patients were still under treatment (Pfreundschuh 2004a). The first analysis of the complete trial showed a highly significant advantage with respect to all endpoints including complete remission rates, event-free survival rates, freedom from treatment failure rates and overall survival. This was the most important message (Pfreundschuh 2004b; [4.1]).

The second most important message was that, in the area of combined CHOP-like chemotherapy with rituximab, we could distinguish two subgroups. After a multivariate analysis of risk factors in patients with a good prognosis (low risk and low intermediate risk according to the age-adjusted IPI), we could distinguish a very favorable subgroup that included patients with no risk factors and no bulky disease. They had an event-free survival of 90 percent that will be very difficult to improve upon. The less favorable subgroup — patients with one risk factor and/or bulky disease — had only a 77 percent event-free survival. This definitely needs further improvement.

4.1 **MInT Trial: Outcomes in Young Patients with Low-Risk DLBCL**

	Chemotherapy (n = 410)	R-chemotherapy (n =413)	*p*-value
Two-year time to treatment failure	60%	76%	<0.00001
Complete remission	67%	81%	<0.0001
Progressive disease	15%	4%	<0.00001
Two-year survival	87%	94%	<0.001

SOURCE: Pfreundschuh M et al. *Blood* 2004;104;**Abstract 157**.

CD 2, Track 20

DR LOVE: Can you discuss the comparison of CHOEP versus CHOP and the influence of adding rituximab to these regimens?

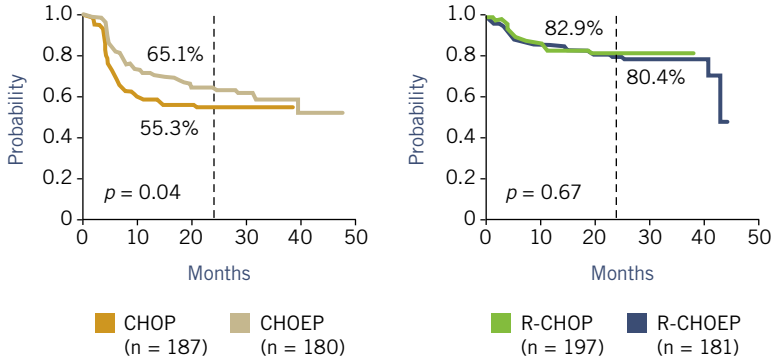
DR PFREUNDSCHUH: The trial demonstrated a significant advantage of CHOEP over CHOP (4.2). However, after the addition of rituximab, this advantage was neutralized. R-CHOP is as good as R-CHOEP, with respect to any subgroup, with respect to any endpoint. So the advantage is neutralized by the rituximab — and you could call rituximab, which has been shown to be a chemotherapy sensitizer — a chemotherapy equalizer.

I think everyone's happy with that, because we are now using a one-day regimen as the standard in this population for six cycles. We don't need eight

cycles because the results are so good that we could not expect them to be improved upon. We don't need CHOEP. The one-day CHOP regimen is as good as the three-day regimen, R-CHOEP, and it's less toxic and much easier to handle.

4.2

Time to Treatment Failure in Randomized Trial of Young Patients with Aggressive Lymphomas



p = 0.04 at 2 years

SOURCE: Reproduced with permission. Pfreundschuh MG et al. Presentation. ASCO 2005;**Abstract 6529**.

CD 2, Track 21

DR LOVE: Can you talk about your research on dose-dense chemotherapy?

DR PFREUNDSCHUH: We had two trials, one in young patients with a good prognosis and the other in elderly patients (61 to 75 years of age), in which we compared CHOP with CHOEP, each given in the three-weekly and two-weekly intervals (Pfreundschuh 2004c; Pfreundschuh 2004d).

In the young patients, the CHOEP-14 improved overall survival, complete remission rates and event-free survival compared to the gold standard, CHOP-21, but R-CHOP is clearly better than CHOEP-14, so that's not a relevant discussion anymore.

In the elderly patients, CHOEP-14 — doubling the intensity, adding etoposide and reducing the interval to two weeks — was too toxic (4.3). We had therapy-associated deaths (eight percent) and treatment delays. The two-weekly regimen, CHOP-14, was significantly better compared to the three-weekly regimen, and mostly so in patients at high risk. ■

4.3

Grade III/IV Adverse Events (%) During Randomized Trial of Elderly Patients with Aggressive Lymphomas

	CHOP-21 n = 178	CHOP-14 n = 172	CHOEP-21 n = 170	CHOEP-14 n = 169	*p*-value
Leukocytopenia	72.1	70.1	94.4	92.4	<0.001
Thrombocytopenia	4.7	15.1	28.4	50.8	<0.001
Anemia	12.5	19.5	28.7	45.1	<0.001
Infection	8.0	10.6	13.2	24.1	<0.001
Mucositis	0	7.1	4.9	14.3	<0.001

SOURCE: Pfreundschuh M et al. *Blood* 2004;104(3):634-41. **Abstract**

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Pfreundschuh MG et al. **Randomized Intergroup trial of first line treatment for patients ≤ 60 years with diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) with a CHOP-like regimen with or without the anti-CD antibody rituximab — Early stopping after the first interim analysis.** Presentation. ASCO 2004a;**Abstract 6500**.

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Pfreundschuh M et al; German High-Grade Non-Hodgkin's Lymphoma Study Group. **Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: Results of the NHL-B1 trial of the DSHNHL.** *Blood* 2004c;104(3):626-33. **Abstract**

Pfreundschuh M et al. **Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: Results of the NHL-B2 trial of the DSHNHL.** *Blood* 2004d;104(3):634-41. **Abstract**

Reyes F et al; Groupe d'Etude des Lymphomes de l'Adulte (GELA). **ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma.** *N Engl J Med* 2005;352(12):1197-205. **Abstract**

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QUESTIONS (PLEASE CIRCLE ANSWER):

1. ECOG-E4402, the RESORT trial, randomly assigns 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. Either a or c
2. The PRIMA trial, NCT00140582, compares rituximab maintenance to no further therapy in patients who have received chemotherapy and rituximab as front-line therapy for follicular lymphoma.
   a. True
   b. False
3. Hainsworth and colleagues demonstrated that maintenance rituximab resulted in an improvement in progression-free survival.
   a. True
   b. False
4. 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
5. In the trial of Bexxar as first-line therapy in patients with Stage III and IV follicular lymphoma, after just one course of treatment, the response rate was 95 percent and the complete remission rate was _____.
   a. 25 percent
   b. 50 percent
   c. 75 percent
   d. 90 percent
6. The ACVBP regimen consists of the following:
   a. Dose-dense, dose-intense CHOP followed by sequential consolidation
   b. Low-dose CHOP followed by sequential consolidation
   c. Dose-dense, dose-intense CHOP alone
7. During a randomized study of ACVBP in patients with newly diagnosed aggressive lymphoma, five-year event-free survival was _____.
   a. 72 percent
   b. 82 percent
   c. 92 percent
   d. 80 percent
8. In the first analysis of the MInT trial, the addition of rituximab to CHOP-like regimens in young patients at low risk with DLBCL was associated with significant improvements in _____.
   a. Complete remission rates
   b. Event-free rates
   c. Overall survival
   d. All the above
9. The event-free survival among patients from the MInT trial with no risk factors and no bulky disease was _____.
   a. 75 percent
   b. 80 percent
   c. 90 percent
   d. 85 percent
10. McLaughlin reported that in a study conducted at MD Anderson, GM-CSF given with rituximab in treating non-Hodgkin's lymphoma had the following effects:
    a. Efficacy was improved
    b. Efficacy was reduced
    c. Toxicity was similar to rituximab monotherapy
    d. Toxicity was significantly worse than rituximab monotherapy
    e. Both a and c
    f. Both a and d
    g. Both b and c

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

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

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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
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Mark S Kaminski, MD	5 4 3 2 1	5 4 3 2 1
Bertrand Coiffier, MD, PhD	5 4 3 2 1	5 4 3 2 1
Michael Pfreundschuh, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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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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