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Non-Hodgkin's Lymphoma™ UPDATE

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

EDITOR

Neil Love, MD

FACULTY

Craig Moskowitz, MD

Wyndham H Wilson, MD, PhD

Anas Younes, MD

CME Certified

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

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

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

The purpose of Issue 6 of *Non-Hodgkin's Lymphoma Update* is to support these global objectives by offering the perspectives of Drs Moskowitz, Wilson and Younes on the integration of emerging clinical research data into the management of non-Hodgkin's lymphoma.

ACCREDITATION STATEMENT

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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**.

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CONTENT VALIDATION AND DISCLOSURES

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Dr Moskowitz (interview conducted on September 9, 2005) — Contracted Research: Amgen Inc, Biogen Idec, Eli Lilly and Company, Genentech BioOncology. **Dr Wilson** (interview conducted on September 10, 2005) — no financial interests or affiliations to disclose. **Dr Younes** (interview conducted on July 28, 2005) — Research Support: Amgen Inc, Biogen Idec, Eli Lilly and Company, Genentech BioOncology, GlaxoSmithKline, Millennium Pharmaceuticals Inc.

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UPCOMING EDUCATIONAL EVENTS

2006 ASCO Gastrointestinal Cancers Symposium
January 26-28, 2006
San Francisco, California
Event website: **www.asco.org/gi2006**

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

American Society of Clinical Oncology 2006 Prostate Cancer Symposium
February 24-26, 2006
San Francisco, California
Event website: **www.asco.org**

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

R-CHOP Cowboy

Many oncologists have told me that one of the most gratifying aspects of clinical practice is the opportunity to play a central role in the lives of people experiencing one of life's greatest challenges. I have always been fascinated by the relative emotional balance of cancer physicians in spite of the personal tragedies they observe every day, and part of the genesis of this strength may be the inspiration they experience partnering with people who demonstrate great courage in the face of enormous adversity.

In the previous issue of this series, we included a special pilot NHL patient education audio program, which featured interviews conducted in our recording studio in Miami with patients from the practice of Dr Lowell Hart, a medical oncologist from Naples, Florida. The first person we featured was a freckle-faced, boyish-appearing, 39-year-old man whose history included 12 years on the road as a drummer in a rock band called "Blackfish."

Mr H arranged to be interviewed on a Friday evening, and we put him up for the night in South Beach, which is just a stone's throw from our office. When I greeted him in our waiting room, my first impression was that he must have been the patient's son. He looked like just any other young man who likes young ladies and music, but Andy was indeed a hardened veteran of Dr Hart's infusion room and the rigors of therapy for chronic lymphocytic leukemia.

Below are excerpts from our conversation, which exemplify how some patients can adapt to the challenges of cancer therapy. There is a lot to learn here, and Mr H's words are a reminder that oncology healthcare professionals are truly privileged to share in the most intimate and challenging moments of their patients' lives.

— Neil Love, MD
NLove@ResearchToPractice.net
December 14, 2005

DR LOVE: What was your reaction when you learned the diagnosis?

MR H: I was freaked out — crying a lot — didn't want anyone to know. I thought I was going to die. I remember being in the hospital and thinking I

wouldn't wake up. So I would never go to sleep. They had to shoot me up with Ativan®. It just didn't seem right that I was going to die. There were so many things left in my life that I wanted to do. However, I quickly learned that either you keep living with the misery of death around the corner every day, or you become positive. And so, in the hospital, I made the decision that I was going to be positive and proactive about it and not dwell in the scary part.

Since then, I've done a lot of things I've always wanted to do. I now have my own local cable TV show. I always wanted to do that but for some reason never had the courage to do it. In general, I'm a lot more aggressive now in business and life. When you think you might die, your whole life changes. Those little problems that scared me before all went out the door. It was a real kind of freeing experience and at the same time very scary.

DR LOVE: What positive things came out of this?

MR H: Cancer drops social barriers, and that was really cool — a lot cooler than I imagined. You realize that the fear of dying really limited you before. Then suddenly, when you know you're going to die, you don't have that fear any more. I made a list of the top 10 things I wanted to do in my life, and I just went out and did them. I rode a bull. That was just the craziest thing I've ever done in my life.

DR LOVE: You rode a bull?

MR H: Yep. Entered a rodeo in the Professional Bull Riders Association, the PBA. I had a buddy who was a rider, and he got me in. I didn't do any training — just did it — walked up to the rodeo, signed up and did it. It was by far the scariest thing I've ever done, but the coolest thing. You don't expect it to be fun. You expect it to be horrifying and that you might die — and that fear was definitely there — but suddenly I was sitting on a bull, and the crowd was screaming. It was a really cool experience. I rode it for a few seconds, and it threw me. But riding it for those few seconds was a cool moment that I would never have experienced before. And I was on chemo at the time.

DR LOVE: Any fears or concerns about the future?

MR H: Yeah, definitely. I could die. I could get the flu, and that could get real complicated. But it doesn't bother me. I could also walk out of here and get hit by a piano coming out of the building, or a car could run me over. We all have that in our lives. It's funny. I see more people dying from stuff like that than people like me dying with cancer. Why worry about it? I've become pretty positive about the future and in a weird way enjoyed the whole cancer process. I don't know if you've ever heard this before, but it's been kind of fun. It's been a bunch of new experiences for me, and it's opened doors.

I wrote a column for our newspaper, and they edited it because I was too cheerful about my condition. They cut out some of my jokes because they thought I was being too lighthearted about getting cancer and stuff. The column I wrote was a true story. In the hospital, I kept seeing this 19-year-old girl who was really hot. One of the nurses said, "Oh, she has leukemia, too."

Every time she'd walk by my room with her little pump and bags hanging, I got mobile with mine — but I could never catch up to her. So here I am — bald and about to die — in my hospital dress, walking around, trying to find this girl. I imagined we'd meet in the library and our chemo bags would entangle and I'd have some funny line to say to her.

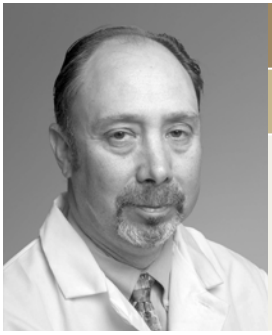
DR LOVE: Has your reaction to this whole experience surprised you?

MR H: Yeah, it has. But it's true to my person. I was pretty positive before and pretty optimistic. I didn't let things bog me down, and I didn't stress out about stuff. But it surprised me a little bit that I've done so well through this, because you think that when you get cancer, you're going to die. That's not the case. You can beat things and get through them. Fortunately, I have a disease that's treatable. So in that sense, I feel lucky that it's not some rare disorder that is only seen one in a million times. I've been lucky to get the type of cancer that I have.

DR LOVE: It seems as if you see things differently now.

MR H: Definitely. My first night out of the hospital, I went to the beach and saw a sunset. It was just like seeing it for the first time. After being in that neutropenic bubble environment, it is now just so nice and freeing to sit in a park and be the happiest dork there because I'm just happy to be alive. ■

September 2004: Mr H — who was soon to complete a six-month regimen of R-CHOP — briefly participates in a Professional Bull Riders Association rodeo.



INTERVIEW

Craig Moskowitz, MD

Dr Moskowitz is an Associate Member of Lymphoma and Hematology Services at Memorial Sloan-Kettering Cancer Center and is an Associate Professor of Medicine at Cornell University Medical College in New York, New York.

CD 1, Tracks 1-19

Select Excerpts from the Interview

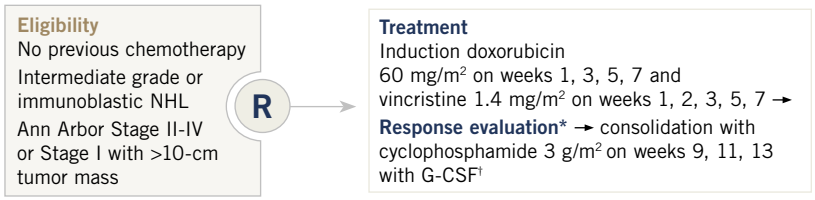
CD 1, Track 2

DR LOVE: Would you provide an overview of research in dose-dense chemotherapy for lymphoma?

1.1

Phase II Study of Sequential Dose-Dense, Dose-Intense Doxorubicin, Vincristine and High-Dose Cyclophosphamide for Aggressive Non-Hodgkin's Lymphoma (NHL-15)

Protocol ID: NHL-15
Accrual: 165 (Closed)



* Patients demonstrating no response did not receive consolidation
† G-CSF administered on days 3-10 following each cyclophosphamide treatment

SOURCE: Portlock CS et al. *Ann Oncol* 2004;15(10):1495-503. **Abstract**

DR MOSKOWITZ: We have been administering dose-dense chemotherapy to patients with untreated diffuse large B-cell lymphoma, peripheral T-cell lymphoma or aplastic large cell lymphoma since 1993. Initially, we administered induction therapy with 60 mg/m^2 of doxorubicin and 1.4 mg/m^2 of vincristine, not capped (1.1). We repeated the imaging studies, and patients who had an excellent response received consolidation therapy with high-dose cyclophosphamide every two weeks times three — very similar to the dose-dense treatment with AC in breast cancer.

The long-term follow-up was published last year in the *Annals of Oncology* (Portlock 2004). In general, we were not enamored with the high-dose cyclophosphamide component, and at that time we were doing gallium scanning. Patients who still had gallium-avid disease after the doxorubicin-based chemotherapy rarely went into remission with cyclophosphamide.

Therefore, we developed a new strategy utilizing CHOP administered every 14 days. It was not an uncommon treatment program — it was also being studied in a German lymphoma study group. In general, we administered standard-dose CHOP every two weeks, and again we did not cap the vincristine dose. We administered growth factors, usually on days six through 10, and we found that the regimen was well tolerated.

The patients were a mixed population, but the long-term event-free survival was more than 60 percent. The regimen took only 12 weeks to administer, and at that time — in the pre-rituximab era — we considered using accelerated chemotherapy for all patients with diffuse large B-cell lymphoma.

DR LOVE: How was it tolerated in older patients?

DR MOSKOWITZ: We didn't recommend it for older patients. However, in a landmark paper published in *Blood* last year (Pfreundschuh 2004), the German lymphoma study group reported that CHOP-14 administered for six cycles is the standard treatment, at least in Germany, for older patients with diffuse large B-cell lymphoma. It turned out to be the winner compared to CHOP every 21 days or CHOP with etoposide. So it's well tolerated in the older patient population.

CD 1, Tracks 3-4

DR LOVE: When do you believe patients with lymphoma experience the maximum benefit from dose-dense chemotherapy?

DR MOSKOWITZ: We believe that if you can get the chemotherapy in on time at full dose, patients will probably derive the maximal benefit early on in their treatment. The definition of maximal benefit has been in a state of flux.

We are conducting a study at Memorial Sloan-Kettering right now that incorporates rituximab-based treatment, dose-dense chemotherapy, and ifosfamide/carboplatin/etoposide (ICE) chemotherapy in the up-front setting. In order to be eligible, a patient must have at least one risk factor in the age-adjusted International Prognostic Index: advanced stage disease, elevated LDH or a poor performance status.

With that background, we chose an induction regimen of R-CHOP administered every 14 days. We previously piloted that regimen and published those findings this year in *Leukemia and Lymphoma* (Halaas 2005). No difference appeared between the side-effect profiles of R-CHOP every 14 days and R-CHOP every 21 days. Once again, in a mixed population of patients, long-term event-free survival approached 80 percent with diffuse large B-cell lymphoma.

Thus far, our study has accrued approximately 60 patients. The primary endpoint was to bring ICE — which is currently the most common second-line regimen used in the United States — up front. We've administered it to almost 700 patients with aggressive lymphoma and Hodgkin's lymphoma, and we believe it's ready for prime time. So the standard treatment arm in this particular study receives R-CHOP-14 for four cycles followed by three cycles of ICE consolidation. In order to receive that treatment, a patient's PET scan must be negative after R-CHOP-14 has been administered four times.

DR LOVE: What do we know about follow-up on patients from your study?

DR MOSKOWITZ: Of the first 60 patients, we had one patient who progressed on R-CHOP-14, so we have 59 patients left. Of the 59 remaining patients, 40 had a negative PET scan after the R-CHOP-14. Of those 40 patients, 36 patients remain progression-free. Only four patients who had a positive interim restaging PET scan progressed.

It's interesting that the positive predictive value of an interim restaging PET

scan at this time is poor — it's in the 30 percent range. That means it makes no sense to change your treatment based on this interim restaging PET scan.

The other thing that's interesting with this dose-dense treatment is that diffuse large B-cell lymphoma turns out to be more than one disease. The best way of thinking about it is that B-cell lymphoma derives from a certain cell within the lymph node — we call that the cell of origin. To simplify, B-cell lymphoma derives from either a germinal center B cell or a nongerminal center B cell. Among patients who receive CHOP chemotherapy for de novo diffuse large B-cell lymphoma, there's evidence in the literature that those whose cell of origin is of the germinal center do much better than those whose cell of origin is of the nongerminal center (Hans 2004).

However, in this particular study, dose-dense, aggressive chemotherapy can overcome the prognostic significance of the cell of origin, so patients with nongerminal center-derived, diffuse large B-cell lymphoma have experienced exactly the same benefits as patients whose cell of origin arose from the germinal center.

Right now, the follow-up in the study is short — it's only 18 months — but the event-free survival is 87 percent. It's a 100-patient study, and we're on patient 65. I am reluctant to present the data until we have accrued nearly all of the patients. Considering the accrual trend, I suspect the data will be presented during ASH 2006. ■

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**

Halaas JL et al. **R-CHOP-14 in patients with diffuse large B-cell lymphoma: Feasibility and preliminary efficacy.** *Leuk Lymphoma* 2005;46(4):541-7. **Abstract**

Hans CP et al. **Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray.** *Blood* 2004;103(1):275-82. **Abstract**

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Moskowitz CH et al. **Cell of origin, germinal center versus nongerminal center, determined by immunohistochemistry on tissue microarray, does not correlate with outcome in patients with relapsed and refractory DLBCL.** *Blood* 2005;106(10):3383-5. **Abstract**

Norton L, Simon R. **The Norton-Simon Hypothesis revisited.** *Cancer Treat Rep* 1986;70(1):163-9. No abstract available

Pfreundschuh M et al; German High-Grade Non-Hodgkin's Lymphoma Study. **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* 2004;104(3):634-41. **Abstract**

Portlock CS et al. **The NHL-15 protocol for aggressive non-Hodgkin's lymphomas: A sequential dose-dense, dose-intense regimen of doxorubicin, vincristine and high-dose cyclophosphamide.** *Ann Oncol* 2004;15(10):1495-503. **Abstract**

INTERVIEW

Wyndham H Wilson, MD, PhD

Dr Wilson is a Senior Investigator and Chief of the Lymphoma Therapeutics Section in the Metabolism Branch at the National Cancer Institute's Center for Cancer Research in Bethesda, Maryland.

CD 1, Tracks 20-24 — CD 2, Tracks 1-10

CD 1

Track 20 Introduction by Dr Love

Track 21 Development of therapeutic regimens and schedules for diffuse large B-cell lymphoma

Track 22 Pharmacokinetics of chemotherapy and rituximab

Track 23 Identification of diffuse large B-cell subtypes via gene array and implications for treatment

Track 24 Initial therapy options for patients with diffuse large B-cell lymphoma

CD 2

Track 1 Clinical trial evaluating R-CHOP versus R-CHOEP every two weeks versus every three weeks

Track 2 Importance of dose and schedule with etoposide

Track 3 Importance of therapeutic rigor in treating diffuse large B-cell lymphoma

Track 4 Clinical trial of idiotype vaccine following EPOCH-R in patients with mantle cell lymphoma

Track 5 Current status of randomized trials evaluating vaccines in non-Hodgkin's lymphoma

Track 6 Event-free survival as a surrogate clinical endpoint

Track 7 Rituximab as maintenance therapy versus treatment upon disease progression

Track 8 Options for first-line therapy in patients with mantle cell lymphoma

Track 9 Selection of patients with mantle cell lymphoma for watchful waiting

Track 10 Watchful waiting for patients with mantle cell lymphoma

Select Excerpts from the Interview

CD 1, Track 24

DR LOVE: What are the reasonable options for initial therapy for patients with diffuse large B-cell lymphoma with adverse prognostic features?

DR WILSON: I think it's clear that R-CHOP is the standard. But even with R-CHOP, we know from the GELA study (Feugier 2005; Coiffier 2003) that patients who are over the age of 60 with a poor prognosis do relatively poorly. We don't know about people under 60 with poor prognosis, because MInT

(Pfreundschuh 2004a; [3.1, page 15]) involved people who had a favorable prognosis.

We've been very interested in the development of better therapies. That's why we developed dose-adjusted EPOCH-R. With this regimen, the poor-prognosis groups have event-free survivals over 50 percent. Therefore, I would say that a regimen like EPOCH-R probably should be considered.

Patients who have a good prognosis will also benefit from this regimen. According to the results from our trial at the NCI, in which we have around 70 patients (Wilson 2004), and the CALGB study (Wilson 2005), neither of which involves radiation, event-free survival is 94 percent in patients over 60. In our study, we've never seen a single failure beyond 17 months.

CD 2, Track 1

DR LOVE: What are your thoughts about the dose-dense approach in terms of both the clinical data and the theoretical considerations?

DR WILSON: Dr Pfreundschuh conducted a four-arm study that compared CHOEP and CHOP administered either every 14 or every 21 days. The patients were divided into one study for those over 60 years of age and one study for those 60 years of age and under. What was a little bit unclear was that in the patients over 60, CHOP-14 worked (Pfreundschuh 2004b; [3.2, page 16]), but in the patients under 60 years of age, dose density didn't have an impact, but receiving etoposide improved event-free survival (Pfreundschuh 2004c; [2.1]).

2.1

NHL-B1: Efficacy of CHOP-14 or CHOP-21 with or without Etoposide in Young Patients with Aggressive Lymphomas and Good Prognosis

	CHOP-21 n = 176	CHOP-14 n = 172	CHOEP-21 n = 185	CHOEP-14 n = 177
Complete remission	80.1%	78.5%	84.9%	90.4%
Partial remission	3.4%	6.4%	3.2%	2.8%
Stable disease	1.1%	2.9%	1.6%	0%
Five-year EFS*†	54.7%	60.8%	69.2%	69.4%
Five-year OS*‡	74.9%	85.0%	83.3%	85.1%

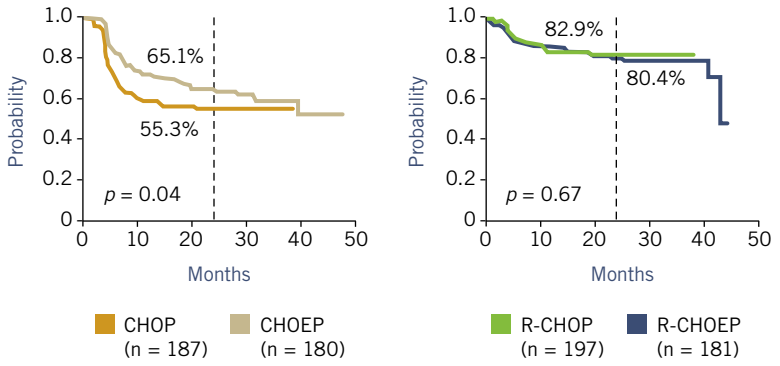
EFS = event-free survival; OS = overall survival
* Estimated at a median time of 58 months
† Addition of etoposide (relative risk = 0.70 [95% CI, 0.54-0.89], $p = 0.004$) interval reduction (relative risk = 0.93 [95% CI, 0.73-1.20], $p = 0.588$)
‡ Addition of etoposide (relative risk = 0.83 [95% CI, 0.59-1.16], $p = 0.276$) interval reduction (relative risk = 0.70 [95% CI, 0.50-0.99], $p = 0.044$)

SOURCE: Pfreundschuh M et al; German High-Grade Non-Hodgkin's Lymphoma Study Group. *Blood* 2004c;104(3):626-33. **Abstract**

The biology of the tumors is not radically different between people over and under 60 years of age. So it was not clear why dose density was not effective in people 60 years and younger and did work in people older than 60. Furthermore, a Japanese study of dose density didn't show a benefit. In fact, they stopped the study (Hotta 2003). Then Dr Pfreundschuh looked at R-CHOEP versus R-CHOP and noted that rituximab was the "great equalizer" (Pfreundschuh 2005; [2.2]).

2.2

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



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

CD 2, Track 8

DR LOVE: What do you think are reasonable options in the clinical setting for first-line treatment of patients with mantle-cell lymphoma?

DR WILSON: One of the things people don't realize is that mantle-cell disease is a disease you can sometimes watch. It's also a disease with a median age of approximately 60 years, and it can be indolent in a fair number of patients. So, depending upon the patient's age and the tempo of the disease, it's certainly reasonable to consider "watch and wait" for some folks. When it comes to treating patients, this is going to depend also on the doctor's goals. For younger patients, emerging evidence suggests that allogeneic transplant may be able to provide some benefit.

As far as choice of therapy, I think it's dealer's choice. I'm quite excited by the results that have been reported with bortezomib (O'Connor 2005; Goy 2005). In fact, we have just begun a new study using that drug up front. I believe we will begin to see bortezomib/rituximab combinations. We also have the report from the Austrian group of rituximab and thalidomide (Kaufmann 2004). And, of course, there's the old standby, R-CHOP. While R-CHOP has

a median event-free survival of about 18 months (Lenz 2005), if a patient has bulky disease, you may want to use bigger guns. ■

SELECT PUBLICATIONS

Coiffier B et al. **GELA study comparing CHOP and R-CHOP in elderly patients with DLCL: 3-year median follow-up with an analysis according to comorbidity factors.** Presentation. ASCO 2003;**Abstract 2395**.

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**

Feugier P et al. **Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: A study by the Groupe d'Etude des Lymphomes de l'Adulte**. *J Clin Oncol* 2005;23(18):4117-26. **Abstract**

Goy A et al. **Bortezomib in patients with relapsed or refractory mantle cell lymphoma (MCL): Preliminary results of the PINNACLE study**. *Proc ASCO* 2005;**Abstract 6563**.

Hotta T et al. **Randomized phase III study of standard CHOP (S-CHOP) versus biweekly CHOP (Bi-CHOP) in aggressive non-hodgkin's lymphoma (NHL): Japan Clinical Oncology Group study, JCOG9809.** *Proc ASCO* 2003;**Abstract 2271**.

Kaufmann H et al. **Antitumor activity of rituximab plus thalidomide in patients with relapsed/refractory mantle cell lymphoma.** *Blood* 2004;104(8):2269-71. **Abstract**

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

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

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**.

Pfreundschuh M et al. **First analysis of the completed Mabthera International (MInT) Trial in young patients with low-risk diffuse large B-cell lymphoma (DLBCL): Addition of rituximab to a CHOP-like regimen significantly improves outcomes of all patients with the identification of a very favorable subgroup with IPI=0 and no bulky disease.** *Proc ASH* 2004a;**Abstract 157**.

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 elderly patients with aggressive lymphomas: Results of the NHL-B2 trial of the DSHNHL.** *Blood* 2004b;104(3):634-41. **Abstract**

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Wilson WH et al. **Phase II study of dose-adjusted EPOCH-R in untreated de novo CD20+ diffuse large B-cell lymphoma (DLBCL)-CALGB 50103.** *Proc ASCO* 2005;**Abstract 6530**.

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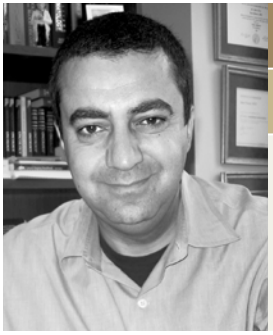

INTERVIEW

Anas Younes, MD

Dr Younes is the Director of Clinical and Translational Research and is a Professor of Medicine in the Department of Lymphoma/Myeloma at The University of Texas MD Anderson Cancer Center in Houston, Texas

CD 2, Tracks 11-27

Track 11 Introduction by Dr Love

Track 12 MInT trial: CHOP-21, CHOEP-21, MACOP-B and PMitCEBO with and without rituximab in patients with aggressive lymphomas

Track 13 Rituximab plus chemotherapy as the standard of care for patients with diffuse large B-cell lymphoma

Track 14 Therapeutic strategies to improve survival in diffuse large B-cell lymphoma

Track 15 Increased acceptance of the Follicular Lymphoma International Prognostic Index (FLIPI)

Track 16 Potential curability of follicular lymphoma

Track 17 Options for first-line therapy in patients with follicular lymphoma

Track 18 Selection of patients for rituximab monotherapy

Track 19 Selection of chemotherapy regimens in combination with rituximab

Track 20 Incorporation of radioimmunotherapy and transplant in the treatment algorithm for follicular lymphoma

Track 21 Role of rituximab as maintenance therapy

Track 22 Novel clinical research strategies in follicular lymphoma

Track 23 Clinical advances in the treatment of mantle cell lymphoma

Track 24 Treatment of patients with mantle cell lymphoma who relapsed after R-hyper-CVAD

Track 25 Efficacy and toxicity comparisons of R-hyper-CVAD and R-CHOP

Track 26 Community oncologists and the treatment of non-Hodgkin's lymphoma

Track 27 Clinical trials evaluating novel biologic agents for non-Hodgkin's lymphoma

Select Excerpts from the Interview

CD 2, Track 12

DR LOVE: Would you provide an overview of the Mabthera International Trial (MInT) and some of the trials for patients who relapse?

DR YOUNES: MInT was spearheaded by Michael Pfreundschuh from Germany (Pfreundschuh 2004a, 2004b). It was truly an international trial because it included investigators from Europe, Asia and South America. The

trial specifically looked at the role of rituximab in combination with chemotherapy. The specific regimen was chosen by the investigator, and approximately 50 percent of the investigators used CHOP, while others — particularly in Germany — used a CHOP equivalent such as CHOEP.

MInT confirmed, in a randomized fashion, that the addition of rituximab to CHOP or CHOP-like regimens improves outcomes specifically in terms of complete remission rate and survival in patients who are younger than 60 years of age (3.1).

Trials have also been conducted for patients with relapsed disease. One trial from Memorial Sloan-Kettering reported on the use of rituximab with isofosfamide/carboplatin/etoposide (ICE) chemotherapy (Kewalramani 2004). This was not a randomized trial; it was a Phase II trial, but it compared data with previous experience using ICE chemotherapy — sequential trials from the same institution using similar eligibility criteria. They showed that the addition of rituximab to salvage therapy like ICE improves the complete remission rate.

Improving complete remission rate prior to transplant is a very important prognostic factor, because patients who receive transplant during complete remission have a better outcome and survival than patients who are not in complete remission at the time of transplantation.

We had similar outcomes in our institution using a regimen of paclitaxel, topotecan and rituximab (TTR). We utilized the regimen for patients with diffuse large B-cell lymphoma who failed to respond to front-line regimens — they were treated with TTR at first or second relapse. We've seen a similar improvement in overall response rate and an improvement in complete remission rate, making these patients better candidates for stem cell transplantation.

3.1 **MInT: 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. *Proc ASH* 2004;**Abstract 157**.

CD 2, Track 13

DR LOVE: What are your thoughts about dose-dense chemotherapy in patients with lymphoma?

DR YOUNES: Dose-dense therapy is an important concept that is now gaining some appeal, especially for solid tumors. In non-Hodgkin's lymphoma,

Michael Pfreundschuh spearheaded a randomized trial — published in *Blood* — that compared CHOP-14 and CHOP-21 with or without etoposide (Pfreundschuh 2004c, 2004d). The interesting thing about the data was — at least in the elderly patients — the dose-dense 14-day regimen was superior to the 21-day regimen (3.2). However, these trials were conducted before the incorporation of rituximab, so we don't know if R-CHOP-14 is superior to R-CHOP-21. Currently, randomized trials are investigating this question, but we don't know the results yet.

DR LOVE: At this time, do you think it's rational to utilize R-CHOP-14 in the clinical setting, particularly in patients with poor prognostic factors?

DR YOUNES: I don't think it's wrong to use R-CHOP-14 in selected patient populations, simply because it's not more toxic, at least based on the Pfreundschuh data. We would not be harming patients, but whether or not it's more beneficial is yet to be determined in a randomized study.

3.2

Efficacy of CHOP-14 or CHOP-21 with or without Etoposide in Elderly Patients with Aggressive Lymphomas (NHL-B2)

	CHOP-21 n = 178	CHOP-14 n = 172	CHOEP-21 n = 170	CHOEP-14 n = 169
Complete remission	60.1%	76.1%	70.0%	71.6%
Partial remission	2.8%	6.4%	5.9%	6.5%
Stable disease	1.1%	0.6%	1.2%	0.6%
Three-year EFS	41.3%	54.2%	45.5%	46.0%
Five-year EFS*	32.5%	43.8%†	41.1%	40.2%
Three-year OS	48.8%	68.5%	57.7%	56.4%
Five-year OS*	40.6%	53.3%‡	45.8%	49.8%

EFS = event-free survival; OS = overall survival

* Estimated at a median time of 58 months
† CHOP-14 versus CHOP-21 (relative risk = 0.66 [95% CI, 0.50-0.87], $p = 0.003$)
‡ CHOP-14 versus CHOP-21 (relative risk = 0.58 [95% CI, 0.43-0.79], $p < 0.001$)

SOURCE: Pfreundschuh M et al; German High-Grade Non-Hodgkin's Lymphoma Study Group. *Blood* 2004;104(3):634-41. **Abstract**

CD 2, Track 17

DR LOVE: Would you discuss your approach to patients with follicular lymphoma who present for first-line therapy?

DR YOUNES: It's complicated, particularly when you discuss these issues with the increasing number of educated patients. They're aware of what's available — a large menu of options that are all reasonable. But the majority of trials never made head-to-head comparisons to determine whether one treatment is better than the other, and that's creating confusion for the patients. We know

right now that when you add rituximab to a front-line regimen for patients with advanced-stage follicular lymphoma, you improve outcomes in terms of duration of remission and the percentage of patients whose disease enters remission. Most oncologists believe this will eventually translate into improved survival.

What's the optimal combination — chemotherapy with rituximab? No one knows. A large menu of combination chemotherapy regimens is available that you can combine with rituximab, or you can use rituximab alone. Furthermore, information is emerging about the use of radioimmunotherapy up front — at least in the experimental setting — that can demonstrate effectiveness perhaps as good as combination chemotherapy but with shortened duration of treatment and potentially fewer potential side effects (Kaminski 2005).

I am pro-clinical trial participation. Although I discuss the different options that may be used off protocol, I tend to encourage patients to participate in the clinical trials. Outside clinical trials, I use one of three combinations, depending on the patient's situation and preference. It's a mutually agreeable treatment plan. I tend to use R-CHOP, R-FND or R-CVP. I extensively discuss the pros and cons of these regimens with the patients and their families, and then we reach a mutual agreement. I think the majority of oncologists in North America use R-CHOP or R-CVP for patients with advanced-stage follicular lymphoma. ■

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**

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

Kewalramani T et al. **Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma**. *Blood* 2004;103(10):3684-8. **Abstract**

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-CD20 antibody rituximab — Early stopping after the first interim analysis.** Presentation. ASCO 2004a;**Abstract 6500**.

Pfreundschuh MG et al. **First analysis of the completed Mabthera International (MInT) Trial in young patients with low-risk diffuse large B-cell lymphoma (DLBCL): Addition of rituximab to a CHOP-like regimen significantly improves outcomes of all patients with the identification of a very favorable subgroup with IPI=0 and no bulky disease.** Presentation. ASH 2004b;**Abstract 157**.

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QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In an ongoing study at Memorial Sloan-Kettering, induction chemotherapy includes _____ followed by ICE consolidation in responders.**
   a. R-CHOP-21
   b. R-CHOP-14
   c. CHOP-14
   d. CHOP-21

2. **The likelihood that patients with diffuse large B-cell lymphoma will not suffer a relapse if they have a negative PET scan after treatment is 92 percent.**
   a. True
   b. False

3. **In patients with diffuse large B-cell lymphoma, the cell of origin (germinal or nongerminal) is determined using the following immunohistochemistry markers:**
   a. CD10
   b. BCL-6
   c. MUM1
   d. All the above

4. **Dose-dense, aggressive chemotherapy abrogates the prognostic significance of the cell of origin, which can be used to predict response to standard-dose regimens in de novo B cell lymphoma.**
   a. True
   b. False

5. **Which pharmacodynamic endpoint is used to titrate the doses of the drugs in the dose-adjusted EPOCH-R regimen?**
   a. Platelet nadir
   b. Neutrophil nadir
   c. Red blood cell nadir
   d. All of the above
   e. None of the above

6. **In the four-arm trial comparing CHOP-14, CHOP-21, CHOEP-14 and CHOEP-21, CHOP-14 was better in _____ patients with aggressive lymphomas.**
   a. All
   b. Younger
   c. Older
   d. No

7. **Mantle-cell lymphoma in select patients can be managed initially with watchful waiting.**
   a. True
   b. False

8. **Which of the following agents have shown activity in patients with mantle-cell lymphoma?**
   a. Bortezomib
   b. Thalidomide
   c. Rituximab
   d. All of the above
   e. None of the above

9. **MInT demonstrated that the addition of rituximab to CHOP-like regimens was associated with significant improvements in complete remission rates and survival among young (<60 years of age) patients at low risk with aggressive lymphoma.**
   a. True
   b. False

10. **R-CHOP or R-chemotherapy is the standard of care for patients with newly diagnosed DLBCL, regardless of age or prognostic factors.**
    a. True
    b. False

11. **In elderly patients with aggressive lymphomas, the German trial (NHL-B2) headed by Pfreundschuh reported that dose-dense CHOP therapy resulted in higher rates of _____ compared to CHOP-21.**
    a. CR
    b. PR
    c. EFS and OS
    d. All of the above

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

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Non-Hodgkin's Lymphoma Update — Issue 6, 2005

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued upon receipt of your completed evaluation form.

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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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Anas Younes, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
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Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
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Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: NLove@ResearchToPractice.net
For CME Information	Melissa Vives, CME Coordinator Email: MVives@ResearchToPractice.net

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Non-Hodgkin's Lymphoma™

UPDATE

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