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Non-Hodgkin's Lymphoma™

UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

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

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

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

The purpose of Issue 1 of *Non-Hodgkin's Lymphoma Update* is to support these global objectives by offering the perspectives of Drs Flinn, Cabanillas and Press on the integration of emerging clinical research data into the management of non-Hodgkin's lymphoma.

ACCREDITATION STATEMENT

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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. **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 **red underlined text**.

Table of Contents

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UPCOMING EDUCATIONAL EVENTS

10th National Comprehensive Cancer Network Annual Conference
March 16-20, 2005
Westin Diplomat
3555 South Ocean Drive
Hollywood, Florida
Event website: www.nccn.org/professionals/meetings/10thannual/default.asp

Lymphoma...The Next Questions
April 8-9, 2005
Ft Lauderdale, Florida
Event website:
www.imedexinc.com/ei/ltnq05set.html

96th Annual Meeting of the American Association for Cancer Research
April 16-20, 2005
Anaheim, California
Event website:
www.aacr.org/2005AM/2005AM.asp

41st American Society of Clinical Oncology Annual Meeting
May 13-17, 2005
Orange County Convention Center
Orlando, Florida
Event website: www.asco.org/ac/1,1003,_12-002092,00.asp

Breast Cancer Update Medical Oncology Educational Forum: Nonprotocol Decision-Making in the Adjuvant and Metastatic Settings
May 21, 2005
Beverly Hills, California
Event website: http://www.breastcancerupdate.com/cmemeetings/may_21_2005/default.asp

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

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

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

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

Editor's Note

The management of long-term strategies in indolent lymphoma

A 53-year-old man is diagnosed with Stage IV follicular lymphoma. The patient is asymptomatic and wishes to evaluate all available options. He seeks multiple opinions about his case.

The first oncologist explains that the disease is incurable but compatible with reasonably long survival. He recommends observation without treatment.

The second oncologist explains that the disease is incurable but compatible with reasonably long survival. He recommends rituximab.

The third oncologist explains that the disease is incurable but compatible with reasonably long survival. He recommends R-CHOP and discusses future transplantation options at relapse.

The fourth oncologist explains that the disease may be curable and is compatible with reasonably long survival. He recommends R-FND.

The fifth oncologist explains that the disease is incurable with current treatment approaches, but clinical trials are evaluating new and promising strategies. He recommends entry into E4402, an ECOG trial that randomizes between rituximab up front with indefinite maintenance or rituximab up front with re-treatment on progression.

Few clinical situations in medical oncology are more controversial than the management of indolent lymphoma. This issue includes discussion of all of the above treatment strategies and more. To launch the new year, we invited three prominent research leaders in NHL to visit our CME group in Miami during a nonsnowy week in January.

On day one, Ian Flinn, a soft-spoken, thoughtful physician and investigator, reviewed his current work at Hopkins, including a fascinating protocol investigating high-dose radioimmunotherapy for patients with relapsed indolent NHL. Like many leaders in the field, Ian's second-opinion cases often involve younger patients with indolent lymphoma, and I was surprised that he answered without hesitation when I asked him what he would do or recommend to a family member in this situation. He noted that his first-line approach would be R-CVP or R-CHOP, but he would strongly consider transplant as salvage therapy.

Two days later, Fernando Cabanillas visited our office. Our introduction to Dr C came several months earlier when he served as a faculty member for our "Meet The Professors" November recording session in New York and woke the group up faster than a Miami "colada" (large Cuban coffee) with the most controversial comment of the day.

Specifically, Dr Cabanillas postulated that a plateau occurs in the survival curve at about six to eight years after therapy for indolent lymphoma, and based on a retrospective series he first reported at ASH in 2002 (Liu 2002), he believes that the disease is in fact a curable condition. For this reason, his standard first-line approach in nonelderly patients is chemotherapy and rituximab — usually the R-FND regimen developed at MD Anderson.

The third visiting professor was Oliver Press, who was surprisingly spry and alert after taking the red-eye from Seattle. I shared Dr Cabanillas' viewpoint with Dr Press, who tactfully commented, "I would like to believe that was true and perhaps it is, but that certainly is not the consensus opinion at this time. I hope it will be in the future."

These three visiting professors had differing opinions on many issues. For example, Dr Cabanillas generally uses rituximab maintenance in indolent NHL because he perceives a positive benefit-to-risk ratio even if the only benefit turns out to be progression-free survival. The other two investigators are less certain about this strategy and use it in a minority of patients.

It is interesting to consider that patients interfacing with the five oncologists in the theoretical case scenario would have very different experiences over the ensuing months. Some would suffer from treatment-related side effects like fatigue, alopecia and neuropathy, while others would remain asymptomatic. As with every controversial situation in medical oncology, patients and physicians must sift through the options and together arrive at the best individualized decision based on current available research evidence.

All three speakers agree on one issue: Clinical trials must be efficiently designed and executed, so that in the future we will have perhaps fewer but more effective and less toxic treatment options available for these patients.

— Neil Love, MD
NLove@ResearchToPractice.net

Select publications

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

Malek SN, Flinn IW. **Incorporating monoclonal antibodies in blood and marrow transplantation.** *Semin Oncol* 2003;30(4):520-30. **Abstract**

Press OW. **Radioimmunotherapy for non-Hodgkin's lymphomas: A historical perspective.** *Semin Oncol* 2003;30(2 Suppl 4):10-21. **Abstract**

Ian W Flinn, MD, PhD

EDITED COMMENTS

ECOG-E4402: Phase III randomized study of rituximab in patients with low tumor burden, indolent non-Hodgkin's lymphoma

In the ECOG-E4402 trial, patients are treated up front with rituximab in an attempt to delay or prevent administration of chemotherapy. The study has an interesting design. All patients receive four standard doses of weekly rituximab.

Patients are then randomly assigned to either maintenance rituximab, during which a dose is given every three months until progression, or observation, during which they are monitored closely and receive salvage rituximab at the first sign of progression. Treatment continues until the patient is no longer responsive.

Patients are excited about the opportunity to participate in this study. Many patients in my practice have just been diagnosed with low-grade lymphoma. Telling them, "We think you should watch and wait," is unsatisfactory. Every public service announcement on television — and common sense — tells them that early treatment of cancer is the key to success. With ECOG-E4402 we can tell the patient, "We are not certain that maintenance is going to help you, but it has few side effects and may be beneficial." That approach is appealing to patients.

Algorithm for transplantation at relapse of indolent lymphoma

For a patient who has had minimal prior therapy and has a matched sibling donor, we would perform a fully ablative transplant. We do a relative T-cell depletion — not a complete T-cell depletion — so it markedly reduces the incidence of graft-versus-host disease. Furthermore, it eliminates many of the infection problems associated with other forms of T-cell depletion. It may also reduce the risk of relapse and the risk of death from the procedure.

For the preparative regimen, we treat with busulfan and cyclophosphamide or cyclophosphamide and total body irradiation, and then the patient receives a graft from the matched sibling (Berdeja 2001). If the patient does not have a matched sibling, we perform an autologous transplant.

Dr Flinn is the Director of the Lymphoma Program and Associate Professor of Oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, Maryland.

Outside of a clinical trial, we utilize rituximab to purge the stem-cell graft after a high-dose preparatory regimen. Then we administer four doses of rituximab post-transplant. This regimen is offered only to patients in early remissions because patients in later remissions have a very high risk of morbidity and mortality from the procedure.

For patients in later remissions, we are developing a new preparative regimen using radioimmunotherapy. This Phase I study employs high doses of Zevalin® (yttrium 90-labeled ibritumomab tiuxetan) and stem cell transplant (1.1).

1.1 Phase I Study of Rituximab Followed by Dose-Escalated Zevalin and Peripheral Stem Cell Transplantation

Protocol IDs: JHOC-J0004, NCI-970, NCT00017381
Accrual: 10-30 (Open)

Eligibility:
Indolent non-Hodgkin's lymphoma or diffuse B-cell lymphoma; 1-5 prior chemotherapy regimens for NHL required

R → Treatment outline:
Rituximab qwk x 4 + cyclophosphamide → G-CSF → Zevalin* → peripheral blood stem cell transplant x 4-6 wk

* Initial three patients receive the same dose of Zevalin. Subsequent cohorts of three to five patients receive escalating doses until maximum tolerated dose is determined.

G-CSF = filgrastim daily

Study Contact:
Ian W Flinn, MD, PhD
Protocol Chair
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Tel: 410-614-4557

SOURCE: NCI Physician Data Query, January 2005.

Nontransplant rituximab/cyclophosphamide regimen

The schema for our nontransplant regimen was based on the ECOG-E2499 trial and previous studies of autologous transplantation in patients with low-grade lymphoma. The regimen consists of four doses of rituximab followed by four doses of cyclophosphamide, using the same dosing regimen we use in patients who receive transplants.

After the patients receive the rituximab and cyclophosphamide, they receive one dose of pegfilgrastim. When their counts return to normal and their platelets recover, they receive two additional doses of rituximab approximately one week apart starting on day 45.

Patients are treated in the outpatient setting and are only admitted if they experience hematologic toxicity. When this occurs, the duration is generally short. This regimen is well tolerated. In fact, I received an email from a patient who was upset that she did not experience side effects and was worried that she was not receiving enough therapy.

Survival benefit with rituximab-containing regimens

Two trials presented at ASH 2004 suggested, for the first time, a survival advantage associated with rituximab-containing chemotherapy regimens. These are preliminary studies and although they do not meet the required level of statistical significance, they suggest a survival advantage. This is big news.

The first trial presented (Herold 2004) is a Phase III study comparing rituximab plus mitoxantrone, chlorambucil and prednisone chemotherapy (R-MCP) to MCP alone. Eligible patients had previously untreated symptomatic Stage III or IV follicular lymphoma, mantle cell lymphoma or lymphoplasmacytic lymphoma. The patients received six cycles of either R-MCP or MCP and were then restaged. Patients who responded received two additional cycles of that respective chemotherapy.

The overall response rate and CR rate were superior with R-MCP compared to MCP; however, the big news was the increase in two-year event-free survival — 83 percent with R-MCP versus 43 percent with MCP alone. Updated results presented at the last ASH meeting suggested an increase in overall survival. Median event-free survival for patients on the rituximab-containing arm had not yet been met.

Although this trial did not use a standard chemotherapy regimen, the principle that combining rituximab with chemotherapy improved survival is important. We need further follow-up from this trial, but this is the first hint of an overall survival advantage with rituximab (Herold 2004).

The second presentation (Van Oers 2004) was a Phase III randomized trial of rituximab in remission induction and maintenance treatment for patients with relapsed or resistant follicular lymphoma. Eligible patients for this two-by-two study had Stage III or Stage IV follicular lymphoma and had previously undergone a maximum of two anthracycline-containing regimens. Patients received R-CHOP or CHOP alone for six cycles. The benefit in CR rate for R-CHOP versus CHOP was highly statistically significant.

The next phase of the trial evaluated maintenance rituximab. The patients evaluable for maintenance were split evenly between the initial groups (CHOP and R-CHOP) and underwent a second randomization to maintenance rituximab or observation. Patients who received maintenance rituximab had a prolonged progression-free survival compared to the control, which is consistent with previous reports.

What was novel about this trial was a trend toward a higher overall survival in patients receiving rituximab maintenance compared with patients randomly assigned to observation. The difference appears to be statistically significant at $p = 0.03$. However, because it was an early evaluation of a complex study it is not considered statistically significant (Van Oers 2004). This is a large study with enough patients to answer some of the questions that have not been asked in other studies. Ultimately, these findings could change the way physicians practice.

ECOG-E1496: Maintenance rituximab prolongs PFS in advanced indolent NHL

ECOG-E1496 (Hochster 2004) was originally designed to evaluate CVP versus fludarabine plus cyclophosphamide. The fludarabine/cyclophosphamide arm was dropped due to excessive toxicity, and as a result everyone received CVP. Patients were restaged and eligible patients underwent a second randomization to maintenance rituximab or observation. That study demonstrated an increase in progression-free survival but has not shown an overall survival benefit to maintenance; however, it is early, so a difference in overall survival may eventually become evident.

If maintenance rituximab improves progression-free survival, and not overall survival, then I believe the decision of whether or not to administer it is a "dealer's choice." On one hand, some patients benefit psychologically by prolonged remission. On the other hand, maintenance therapy leads to time in the infusion chair and is expensive.

Published data suggest that maintenance rituximab will prolong progression-free survival, and emerging data suggest that an overall survival advantage may occur; however, those data are preliminary and are not sufficient for me to use standard maintenance rituximab. When I do use maintenance rituximab, I administer four doses — one every six months for approximately two years.

Select publications

Berdeja JG et al. **Allogeneic bone marrow transplantation in patients with sensitive low-grade lymphoma or mantle cell lymphoma.** *Biol Blood Marrow Transplant* 2001;7(10)561-7. **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**

Flinn IW et al. **Immunotherapy with rituximab during peripheral blood stem cell transplantation for non-Hodgkin's lymphoma.** *Biol Blood Marrow Transplant* 2000;6(6):628-32. **Abstract**

Flinn IW, Lazarus HM. **Monoclonal antibodies and autologous stem cell transplantation for lymphoma.** *Bone Marrow Transplant* 2001;27(6):565-9. **Abstract**

Herold M et al. **Results of a prospective randomized open label phase III study comparing rituximab plus mitoxantrone, chlorambucil, prednisone chemotherapy (R-MCP) versus MCP alone in untreated advanced indolent non-Hodgkin's lymphoma (NHL) and mantle-cell lymphoma (MCL).** *Blood* 2004;104(11);**Abstract 584**.

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

Kasamon YL et al. **Outcomes of autologous and allogeneic blood or marrow transplantation for mantle cell lymphoma.** *Biol Blood Marrow Transplant* 2005;11(1):39-46. **Abstract**

Malek SN, Flinn IW. **Incorporating monoclonal antibodies in blood and marrow transplantation.** *Semin Oncol* 2003;30(4):520-30. **Abstract**

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

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

Phase III trial of rituximab/FND in patients with Stage IV indolent lymphoma

Our institution accrued the largest number of patients to the initial multi-institutional, single-agent pivotal trial of rituximab (McLaughlin 1998). We then conducted a trial combining rituximab with FND, and that proved to be the most active combination we've ever tried in the front-line management of Stage IV indolent lymphoma (McLaughlin 2000).

Not only did we see a higher clinical complete response rate, but the molecular response rate, as measured by the PCR test for Bcl-2 rearrangement, was also high.

Both arms of the trial included rituximab and FND, but in the first arm the agents were administered simultaneously, whereas the second arm began with eight courses of FND followed by rituximab one year later.

The molecular response rate was 90 percent in the patients who received the agents simultaneously, versus 70 percent in the delayed rituximab arm — and that was statistically significant. Essentially, the molecular responses were good in both arms, but it appears that administering rituximab simultaneously is superior in terms of molecular response.

An important outcome of this study was that, for the first time, we were able to show that molecular remissions are attainable with rituximab combined with chemotherapy in the vast majority of cases. With CHOP alone, few patients achieved a molecular remission — only 15 percent at best. Although we didn't conduct a randomized study against CHOP, we believe the rituximab/FND regimen is superior based on the high molecular response rate.

Dr Zinzani conducted a trial in Italy comparing CHOP to a combination of fludarabine and mitoxantrone and demonstrated a higher molecular response rate with the fludarabine/mitoxantrone combination. I believe it's becoming clear that fludarabine in combination is superior to CHOP, at least in terms of the quality of the responses.

Dr Cabanillas is a Clinical Professor of Medicine at the University of Texas MD Anderson Cancer Center in Houston, Texas and Medical Director of the Auxilio Mutuo Cancer Center in San Juan, Puerto Rico.

Role of the immune system in the prognosis of patients with indolent lymphomas

Investigators are beginning to focus more on benign or normal cells, such as macrophages and lymphocytes, rather than malignant cells. Studies now show that the gene profile of normal cells in patients who do well is different from that of patients who do poorly, and the immune system appears to play an important role (Annuska 2004).

Also, data derived from children with acute lymphoblastic leukemia show that patients who have been in remission for years and are considered cured still have residual tumor cells that are detectable by techniques such as PCR. It appears that, at least in the lymphoid disorders, patients can actually live with a small amount of residual lymphoma or lymphoid leukemia cells, which the immune system is able to keep in check.

Immunologic mechanisms of action of rituximab

We all believe rituximab works through the immune system, but multiple mechanisms may exist. The one that most people agree with is the antibody-dependent cell-mediated cytotoxicity (ADCC) mechanism, which depends a lot on the immune system. In this case, rituximab appears to attach to the tumor cell through the Fab fragment of the antibody molecule. The Fc portion then sticks out and is recognized by the immune effector cells that have Fc receptors. These cells are then eliminated from the system.

Other mechanisms may include direct lysis of the tumor cells. Some people even believe that the CD-20 molecule might play an important biological role in keeping the cell alive, and that interfering with this molecule might also lead to cell death, although that's not been proven.

Development of rituximab in the treatment of NHL

At the time of the pivotal trial of rituximab, it was the first antibody ever used in oncology. We had no experience with any like it, and I was surprised not only that it worked but also that it worked in the majority of patients with follicular lymphoma. We saw approximately a 60 percent response rate with rituximab in the salvage setting, and the rate was even higher in the front-line setting.

In addition, rituximab has a completely different mechanism of action than chemotherapy, and generally we can combine it with chemotherapy without having to compromise the dose of chemotherapy. That's something we can't do with most chemotherapy agents because the majority of them are myelotoxic.

It's been interesting to follow the development of rituximab. While we initially thought it was mostly active in follicular lymphoma, we then learned that other nonfollicular indolent lymphomas are also responsive. For example, marginal zone lymphomas respond to rituximab, and it has been shown that chronic lymphocytic leukemia is another important target for rituximab combined with chemotherapy.

My biggest surprise was with large-cell lymphoma. The single-agent data with large cell lymphoma was not promising, yet when rituximab was combined with CHOP in the front-line setting — as was done by Coiffier in France — rituximab contributed very significantly to the outcome (Coiffier 2002; [2.1]).

2.1 CHOP Chemotherapy with or without Rituximab in Elderly Patients with Diffuse Large-B-Cell Lymphoma: Efficacy Data

Response	CHOP + R (n=202)	CHOP (n=197)	*p*-value
Complete response*	76%	63%	0.005
End point†			
Progression during treatment	9%	22%	NR
Two-year event-free survival	57% (95% CI, 50-64)	38% (95% CI, 32-45)	NR
Two-year survival	70% (95% CI, 63-77)	57% (95% CI, 50-64)	NR

"In conclusion, the addition of rituximab to CHOP chemotherapy, given for eight cycles to elderly patients with newly diagnosed diffuse large-B-cell lymphoma, significantly increases the rate of complete response, decreases the rates of treatment failure and relapse, and improves event-free and overall survival as compared with standard CHOP alone. These gains were achieved without a significant increase in clinically significant toxic effects."

* Includes unconfirmed complete responses
† Results of the intention-to-treat analysis of endpoints

SOURCE: 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

Nonprotocol use of maintenance rituximab in indolent lymphoma

In the past, interferon was my drug of choice for maintenance therapy because data showed that, when combined with chemotherapy regimens like CHOP-Bleo, it prolonged failure-free survival (McLaughlin 1993); however, interferon is toxic and not easy for patients to tolerate for one or two years, so I was interested in the idea of maintenance rituximab.

Data demonstrate that rituximab definitely prolongs failure-free survival, but we don't know whether it prolongs overall survival. Many things can occur after patients relapse on (or after completion of) rituximab that can effect survival.

In addition, the median survival with standard therapy is seven years, and the disease is so indolent it takes a long time to demonstrate an impact on survival.

Although we don't know whether maintenance rituximab prolongs survival, increasing the duration of failure-free survival is an achievement from a quality-of-life standpoint. I believe an improvement in failure-free survival usually translates into an improvement in overall survival, so I'm not waiting to see if anyone proves that point — I'm already using maintenance rituximab instead

of interferon. I administer four weekly doses of rituximab every six months for two years.

Rituximab/FND plus oxaliplatin in patients with relapsed follicular lymphoma

We just began a trial for patients with relapsed follicular lymphoma using a combination of rituximab, fludarabine, oxaliplatin, mitoxantrone and dexamethasone. Basically, it's an extension of the rituximab/FND regimen that we've utilized as salvage therapy and, more recently, in the front-line setting. We added oxaliplatin to try to exploit synergism with fludarabine.

The schedule of administration is similar to the FND/rituximab regimen: fludarabine daily for three days, mitoxantrone and oxaliplatin on day one, and dexamethasone for four days. Rituximab is given the day before.

We don't know if separating rituximab from chemotherapy is necessary, but if we postulate that the immune system is critical in the mechanism of action of rituximab, then administering rituximab first might be important. The schedule is repeated every 28 days, ideally for eight courses.

This trial is like a Phase I/II study because, in addition to trying to improve response rates, we want to determine the dose of oxaliplatin that can be combined with fludarabine. We began with a low dose that we are now escalating. We're not using growth factors because neutropenia is not generally pronounced with fludarabine.

The major cumulative toxicity caused by fludarabine involves platelets. After four courses, we sometimes see a delayed drop in platelet counts, which may then stay down and decline with each additional course. Thrombocytopenia is generally in the range of 75,000 to 90,000. It remains at that level for a long time, so sometimes we are only able to give patients, especially elderly patients, six or even four courses.

Duration of rituximab in treating indolent lymphoma

Six cycles has been the magic number for the treatment of aggressive lymphoma, but with indolent lymphomas the response rate is more gradual so we aim for eight cycles. For example, with Burkitt's lymphoma the majority of patients experience a complete remission with just one course; however, with indolent lymphomas it sometimes takes six courses or more to produce a complete remission. Rituximab has a long half-life, which may explain why some patients take longer to achieve the maximum response.

We have seen patients treated with rituximab, and six months later the lymph nodes were still decreasing in size. I've seen one patient whose lymph nodes were still shrinking one year later. In addition, rituximab adheres to tumor cells and is released into circulation as they die.

Curability of Stage IV indolent lymphoma

We have reviewed our research experience at MD Anderson in the last 30 years in the treatment of Stage IV indolent lymphomas, motivated by the belief in the oncology community that little progress has been made in the management of this disease. The idea actually came from Stanford. They plotted three decades of their experience in the treatment of indolent lymphoma, and it shows overlapping curves with no improvement at all. Of course, the treatment didn't change in those 30 years, so I don't see how outcome could have improved.

We looked at four different studies that we have conducted in the last 30 years and interestingly, a stepwise increase in outcome has occurred every time we opened a new trial (2.2). The survival and failure-free survival both improved, and I'm becoming increasingly convinced that this is not an incurable disorder.

2.2 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 vs 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. **Stage IV indolent lymphoma: 25 years of treatment progress.** *Proc ASH* 2003;**Abstract 1446**.

Select publications

Annuska M et al. **Gene expression profiles are best suited to assess present though not future clinical aggressiveness in follicular lymphoma.** *Proc ASH* 2004;**Abstract 698**.

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**

Liu Q et al. **Stage IV indolent lymphoma: 25 years of treatment progress.** *Proc ASH* 2003;**Abstract 1446**.

McLaughlin P et al. **CHOP-Bleo plus interferon for stage IV low-grade lymphoma.** *Ann Oncol* 1993;4(3):205-11. **Abstract**

McLaughlin P et al. **Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: Half of patients respond to a four-dose treatment program.** *J Clin Oncol* 1998;16(8):2825-33. **Abstract**

McLaughlin P et al. **Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma.** *Semin Oncol* 2000;27(6 Suppl 12):37-41. **Abstract**

Management of indolent lymphoma

My first consultation with a patient with indolent lymphoma usually involves a long discussion because no routine standard of care exists in the United States.

The treatment of indolent lymphomas is "all over the map" nation-wide. Many options are available, all of which are reasonable and none of which is currently believed to be curative.

Whether survival is prolonged remains controversial — and that is often difficult for the patient to grasp. Patients prefer simple options and one treatment that is clearly best, particularly if it's a curative treatment. Being presented with an array of options is confusing for most patients.

Off protocol, many patients are followed by observation alone for a few years or treated with a single alkylating agent, such as chlorambucil, or they may receive single-agent rituximab. In the Stanford area they commonly receive R-CVP, which is also a popular regimen in Europe. MD Anderson typically uses a fludarabine-based regimen, such as R-FND.

SWOG-S0016: CHOP plus rituximab versus CHOP plus Bexxar®

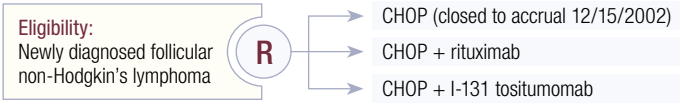
This trial is evaluating more aggressive therapies for indolent lymphoma (3.1), and was designed to develop a curative treatment or at least one that would prolong survival. It was believed that in order to accomplish that, one might need to combine a chemotherapy regimen with an immunotherapy, such as a monoclonal antibody, because these work by different mechanisms.

Currently, antibodies are generally believed to work best if the tumor burden is relatively small and the antibody doesn't have to penetrate a long distance to the center of a tumor. CHOP was chosen as the chemotherapy for that trial because it debulks faster and has a higher complete remission rate than many of the other less intense regimens.

Dr Press is a member of The Fred Hutchinson Cancer Research Center, Recipient of the Dr Penny E Petersen Memorial Chair for Lymphoma Research, Professor of Medicine and Biological Structure and Associate Director of the Medical Scientist Training Program at the University of Washington Medical Center in Seattle, Washington.

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, January 2005.

Nonprotocol therapy for patients with indolent NHL

Off protocol, I tend to be somewhat more conservative than I would be with patients enrolled in a clinical trial. If a patient is elderly, has relatively small lymph nodes and doesn't have any symptoms, I will watch and wait until the patient becomes symptomatic or develops bulky disease. Some patients are uncomfortable with watching and waiting but are also afraid of chemotherapy. In those patients, single-agent rituximab is a well-tolerated, mild treatment that often induces a meaningful response.

If patients have substantial bulk of disease and are elderly or have heart disease, I tend to use a combination chemotherapy regimen along with rituximab, such as CVP. In younger patients with rapidly growing bulky disease, I use CHOP plus rituximab.

Role of maintenance rituximab in clinical practice

Rituximab maintenance therapy is currently one of the most controversial issues in the management of indolent lymphomas. Intriguing data have demonstrated that administering either an extended course of rituximab with a dose every two months for four doses (as reported by Ghielmini 2004) or maintenance therapy with four doses every six months for two years (as reported by Hainsworth 2002) may result in a significantly protracted progression-free or event-free survival; however, neither study has shown an overall survival advantage.

If patients are not living longer, and if you're not even changing the time to rituximab refractoriness — which Hainsworth has shown — then it's not clear whether maintenance is cost effective. Some oncologists believe that even if you're not prolonging survival, it is worthwhile to prevent relapses and save patients the mental anguish. Others believe that waiting until relapse to administer rituximab is the preferred approach.

I use rituximab maintenance selectively for patients in whom I'm particularly worried about an early relapse. Perhaps the most common setting where I'll use maintenance is when a patient comes in after surfing the internet and has strong feelings about wanting rituximab maintenance. I believe the data are strong enough that if someone is inclined to receive it, I administer it.

Sequencing radioimmunotherapy in the treatment algorithm for indolent lymphoma

Off protocol, I believe the best setting for radioimmunotherapy is a patient in their second or third relapse. Like most other treatments, it works best if administered relatively early in the treatment course, and it is a treatment that most patients like because it is a single-dose treatment with few acute side effects. I've personally treated many patients who have had durable responses.

On the other hand, the concept of radioactivity is intimidating for some physicians, and the logistic issues have, until now, led oncologists to delay using this therapy until few options remain. Many physicians use it as ninth- or tenth-line therapy, and no treatment will be very effective in those patients.

This is unfortunate, and I've been surprised at the slow uptake of radioimmunotherapy. I've conducted many of the clinical trials of this approach, and it's clearly a highly effective treatment — more effective than many of the therapies being utilized more frequently. It is well tolerated and it rarely causes life-threatening toxicity, so I'm almost dumbfounded that it hasn't captured the imagination of American hematologists and oncologists.

I believe the issues causing the slow uptake involve the logistics of having to coordinate between a medical oncologist, oncologist and a nuclear medicine doctor or radiation oncologist. Reimbursement is also an issue. Additionally, I believe many patients are phobic about radioactivity, even though studies have shown the risks are small.

Active trials with lymphoma vaccines

In single-arm studies, some vaccines appear to prolong remissions. We don't yet know whether they will cure patients, but I believe the vaccines are one of the most exciting avenues of research being pursued.

Currently, at least three large trials in the United States are evaluating the efficacy of lymphoma vaccines (3.2). The largest — the Genitope trial — was completed within the past year, and the results should be available at the 2005 ASH meeting. In that trial, patients received CVP and were then randomly assigned to receive an idiotype vaccine or not.

A trial by Larry Kwak at MD Anderson is addressing a similar issue but using a doxorubicin-based chemotherapy regimen. The FAV-ID trial utilizes rituximab followed by the vaccine, which is an exciting approach.

Concern exists about whether rituximab, which depletes B-lymphocytes, may blunt the humoral immune response to vaccines, so both the Genitope trial and Larry Kwak's trial have not allowed rituximab before the vaccine administration. In marked contrast, the FAV-ID trial, or the FAVORAL trial, uses rituximab as the debulking agent before the vaccine is administered.

It will be interesting to see what humoral responses are obtained. Preliminary data from the FAVORAL trial presented at ASH 2004 suggested some patients form antibody responses despite receiving rituximab as induction therapy,

but those responses usually are not manifest until the B-lymphocyte depletion resolves (Omer 2004).

3.2 Active Clinical Trials Evaluating Vaccines in NHL

Protocol ID	N	Preprotocol treatment	Protocol
BIOVEST-BV301	563	CHOP x 6 If CR or CRu → protocol	• Autologous lymphoma idiotype vaccine and KLH + GM-CSF • KLH + GM-CSF
FAV-ID-06	342	Rituximab x 4 If CR, PR or SD → protocol	• Autologous immunoglobulin idiotype-KLH conjugate vaccine + GM-CSF • Placebo + GM-CSF
GENITOPE-2002-09	60-140	Rituximab x 4 If PR → protocol	• Autologous immunoglobulin idiotype-KLH conjugate vaccine + GM-CSF 26 weeks after rituximab x 8 • Autologous immunoglobulin idiotype-KLH conjugate vaccine + GM-CSF 13 weeks after rituximab x 8
MCC-13840	40-60	CHOP x 6 or hyper-CVAD x 3 If PR → protocol	• Vaccine of autologous tumor cells and GM-CD40L + low-dose IL-2 • Repeats q28d x 4. If stable or responding at 12 months, patients receive 4 additional booster courses. Continues in the absence of disease progression or unacceptable toxicity
GENITOPE-IND-8294	20	Hematopoietic STC 100 days or 6 months post STC → protocol	• Autologous lymphoma-derived idiotype vaccine + KLH + GM-CSF x 5

CR = complete remission; CRu = unconfirmed CR; KLH = keyhole limpet hemocyanin; PR = partial remission; SD = stable disease; STC = stem cell transplantation

SOURCE: NCI Physician Data Query, January 2005.

Select publications

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

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

Hieke K et al. **Cost evaluation of rituximab plus MCP vs MCP alone in advanced stage indolent non-Hodgkin's-lymphoma based on a randomized controlled multicenter trial.** *Proc ASH* 2004;**Abstract 87**.

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

Omer N et al. **Id/KLH vaccine (FavId™) following treatment with rituximab: An analysis of response rate improvement (RRI) and time-to-progression (TTP) in follicular lymphoma (FL).** *Proc ASH* 2004;**Abstract 587**.

Post-test:

Non-Hodgkin's Lymphoma Update — Issue 1, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The standard of care for indolent NHL in the United States is:
   a. CHOP plus rituximab
   b. CVP plus rituximab
   c. Watch and wait
   d. Radioimmunotherapy
   e. Not defined

2. ECOG trial E4402 assesses up-front single-agent rituximab therapy followed by either maintenance rituximab or observation.
   a. True
   b. False

3. The ECOG-E2499 trial examines autologous stem cell transplant with and without _____ _____ in patients with CD-20 positive B-cell lymphoma.
   a. Zevalin
   b. Busulfan
   c. Rituximab
   d. Cyclophosphamide

4. In the Phase III trial comparing simultaneous use of FND and rituximab to FND followed by rituximab, which arm was superior in achieving molecular responses?
   a. Simultaneous use of FND and rituximab
   b. FND followed by rituximab

5. In a randomized trial reported by Coiffier, comparing CHOP with or without rituximab for the treatment of elderly patients with newly diagnosed diffuse large-B-cell lymphoma, the addition of rituximab improves which of the following?
   a. Complete response rate
   b. Event-free survival rate
   c. Overall survival rate
   d. All of the above

6. Studies have shown that the gene profile of normal immune cells in patients who do well is different from that of patients who do poorly, suggesting an important role for the immune system in indolent lymphomas.
   a. True
   b. False

7. The ongoing trial of rituximab, fludarabine, oxaliplatin, mitoxantrone and dexamethasone for patients with relapsed follicular lymphoma is attempting to exploit the synergism between oxaliplatin and fludarabine.
   a. True
   b. False

8. SWOG-S0016 is a Phase III randomized trial for patients with newly diagnosed NHL that compares which of the following therapies:
   a. CHOP plus rituximab versus CHOP plus Zevalin
   b. CHOP plus rituximab versus CHOP plus Bexxar
   c. CHOP versus rituximab versus watch and wait

9. Hainsworth and colleagues demonstrated maintenance rituximab resulted in an improvement in progression-free survival.
   a. True
   b. False

10. At ASH 2004, results presented from two separate trials of rituximab/chemotherapy regimens suggested a possible survival advantage associated with rituximab.
    a. True
    b. False

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

Evaluation Form:

Non-Hodgkin's Lymphoma Update — Issue 1, 2005

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Please answer the following questions by circling the appropriate rating:

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

GLOBAL LEARNING OBJECTIVES

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

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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Ian W Flinn, MD, PhD	5 4 3 2 1	5 4 3 2 1
Fernando Cabanillas, MD	5 4 3 2 1	5 4 3 2 1
Oliver W Press, MD, PhD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity. . . . . 5 4 3 2 1 N/A
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
Avoided commercial bias or influence. . . . . 5 4 3 2 1 N/A

Evaluation Form:

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I certify my actual time spent to complete this educational activity to be _____ hour(s).

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.....

What other faculty would you like to hear interviewed in future educational programs?

.....

Degree:

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As part of our ongoing, continuous, quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

☐ Yes, I am willing to participate in a follow-up survey.

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Additional comments about this activity:

.....

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Non-Hodgkin's Lymphoma™ UPDATE

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UPDATE

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