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NON-HODGKIN'S LYMPHOMA

Meet The Professors

A case-based discussion on the management of non-Hodgkin's lymphoma

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from the publishers of Non-Hodgkin's Lymphoma™ UPDATE

CME Certified

Meet The Professors: A case-based discussion on the management of non-Hodgkin's lymphoma

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. In order to incorporate research advances into developing treatment strategies for patients, the CME program *Meet The Professors* utilizes case-based discussions between community oncologists and research leaders.

LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in non-Hodgkin's lymphoma (NHL) treatment and incorporate this 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 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.

EDUCATIONAL METHOD

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Faculty Disclosures

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Editor's Note

Watch and worry

In low grade lymphoma, the basis for the "watch and wait" approach is that the disease is considered incurable. First, we need to clarify that the lack of curability holds mostly for Stage IV presentations, which are the majority of cases. Second, the other rationale is that if you cannot cure the disease and you don't need to palliate anything because the patient is asymptomatic, why treat early?

I'm going to say something controversial and no one is going to believe it, but data from the various studies we did over the last 25 years at MD Anderson indicate a plateau in the curve for low grade lymphomas, and that plateau has been increasing through the years as we modified the regimens.

The plateau occurs at approximately eight years, and at 15 years, 40 percent of the patients are alive without evidence of disease. I think people have not realized that there is a plateau, mostly because they've been using single agents or palliative types of therapy, but also because they haven't followed the patients long enough. If you stop your observation period at five to 10 years, you fail to see that the tail end of the curve plateaus.

I believe that if you treat Stage IV low grade lymphoma appropriately, you can cure a fraction of the patients — not necessarily the majority — but more or less about the same that you cure with large cell lymphoma. Sandy Horning has a slide she shows that indicates that the survival of low grade lymphoma has not changed for 20 years, which is true at Stanford. But they've been doing the same thing over and over again. Why would you expect to see a change? We've been changing the regimens every four to five years. When I evaluated our data, I was surprised that we are now seeing a definite plateau in the curve.

— Fernando Cabanillas, MD

Upon meeting Fernando Cabanillas just prior to the audio recording session for this program, I immediately thought of my childhood hero, Sigmund Freud. Like Dr F, Dr C enjoys challenging long-held paradigms, as evidenced by the above comment.

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Sigmund Freud, 1910

As in our prior Meet The Professors adventures, I had gathered a group of very astute, regionally based medical oncologists to present de-identified cases from their practices to our learned faculty of Fernando, John Hainsworth, John Leonard and Mitchell Smith.

Many of the metropolitan NYC-based community docs at this meeting had worked with us on our prior breast cancer MTPs and knew the drill. As in the past, these docs more than did their jobs by identifying a variety of vexing clinical situations with no perfect solutions but plenty to fuel lively debate.

Many of the cases discussed were indolent lymphoma, for which patients with asymptomatic disease now have a relatively nontoxic alternative (rituximab) to observation. Prior to the emergence of this fascinating monoclonal antibody, the perception that survival is not improved with earlier therapy meant that chemotherapy only offered asymptomatic patients the option of side effects and perhaps the psychological comfort of taking an active step against a known cancer. Both researchers and practitioners agree that before rituximab, the logical but highly unrealistic strategy of "watch and wait" — as in other tumors, including prostate cancer — was seriously problematic. Community panelist Dr Charles Farber calls it "watch and worry."

Both the faculty and community docs agreed that it is important in this situation to carefully clarify whether the patient is truly asymptomatic. This can be challenging in an era when a symptom such as fatigue might also be the result of stress, sleeplessness or lack of exercise. John Hainsworth suggests a practical assessment of whether the patient's activity level has changed. In the case that sparked Dr C's bombshell comment, an avid golfer was incidentally diagnosed with Stage IV low grade lymphoma during arthroscopy. A related question would be whether the patient's frequency of hitting the links had decreased.

If Dr Cabanillas's assertion is true, and eradication of clinical disease is possible, then this is a semi-moot point. Dr Hainsworth and others are not nearly as convinced that this is the case, but patients and physicians should be informed that at least some experienced research leaders believe early therapy with rituximab plus chemotherapy might eradicate the disease in a significant number of patients.

Sometimes it seems that we are carrying the torch of evidence-based medicine a bit too far. We will never have large randomized trials to address every possible clinical question in oncology. As noted by onco-provocateur, Barry Kaplan, in indolent lymphoma, by the time a trial's survival endpoint is met, the principal investigator is likely to be retired or dead. The search for intermediary endpoints to predict survival may change this someday, but currently we must rely on experienced, thoughtful, unbiased mavens like our faculty to lead the way.

I love to see people stick out their necks and challenge existing dogma. Usually this is some variation on the obvious, and Dr Cabanillas' postulation on the potential curability of indolent NHL is not more difficult to believe than Dr Freud's notion that our thoughts and behaviors are expressions of a much more complex maelstrom beneath the surface.

Perhaps at some point in our lifetimes, another freethinker will simplify the mysteries of NHL and other tumors, but for the moment, patients and their physicians will struggle with painful decisions that are often based on evidence that may not totally clarify the best path to take in many common oncologic situations.

—Neil Love, MD
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Select publications

Fisher RI et al. **New treatment options have changed the natural history of follicular lymphoma.** *Blood* 2004;104(11);**Abstract 583**.

Ha CS et al. **Stage III follicular lymphoma: Long term follow-up and patterns of failure.** *Int J Radiat Oncl Biol Phys* 2003;57(3):748-54. **Abstract**

Horning SJ. **Natural history of and therapy for the indolent non-Hodgkin's lymphomas.** *Semin Oncol* 1993;20(5 Suppl 5):29-34. No abstract available

Seymour JF et al. **Long-term follow-up of a prospective study of combined modality for stage I-II indolent non-Hodgkin's lymphoma.** *J Clin Oncol* 2003;21(11):2215-22. **Abstract**

CASE 1: An 80-year-old woman with retroperitoneal lymphadenopathy and an axillary lymph node demonstrating Grade I follicular lymphoma (from the practice of Dr Pamela Drullinsky)

Edited excerpt from the discussion:

DR DRULLINSKY: I evaluated an 80-year-old woman who presented with vaginal bleeding. She went to see her gynecologist and was found to have endometrial hyperplasia. Incidentally, massive retroperitoneal adenopathy was noted. The largest nodal mass was 22 centimeters in diameter. Physical examination revealed a two-centimeter right axillary lymph node. She had many other medical problems, including severe peripheral vascular disease, coronary artery disease, hypertension and an anxiety disorder.

A staging CAT scan revealed small mediastinal lymph nodes, but most of the disease was in the abdomen. Bone marrow biopsy was negative, but immediately after the biopsy, she developed chest pain and was admitted to the hospital. Cardiac catheterization revealed mild coronary artery disease but it did not require emergency therapy.

Biopsy of the lymph node revealed a Grade I follicular lymphoma that was positive for CD20, CD10 and Bcl-2, negative for Bcl-1, and focally staining for Bcl-6. Her LDH and CBC were normal.

DR SMITH: I would want to leave this lady alone. She has a low grade lymphoma and presented incidentally with vaginal bleeding, which is presumably unrelated. Despite the size of her retroperitoneal nodes, the first question is always how much harm you're going to do with any treatment.

So what are your choices? You could give her single-agent rituximab or an oral alkylater and some steroids. Leukoran/prednisone is not a bad treatment for an 80-year-old patient. I can think of the usual laundry list of things, but in patients who are as frail as this woman, my first decision is: Do I need to treat? And I don't see any indication that she must be treated right away. You could wait a couple of months and see if it's clearly progressing. I would probably start with an oral alkylater and prednisone to keep her in check as long as possible.

DR KAPLAN: I'm reluctant to leave a large retroperitoneal mass alone because the next thing you've got is either edema of one of the legs, which won't go away, or renal shutdown. I think if you split the dose of rituximab and give her lots of premedication you're not going to wind up with a lot of reaction, and you'll probably achieve a better response than you would with an alkylating agent and prednisone.

DR SMITH: You have to make that decision based on the individual patient, and if I were going to administer rituximab, I would give her a small dose on day one and then the rest of the dose. I would certainly use premedication. Even a low grade lymphoma can be pretty large without causing a lot of the problems you mentioned. Obviously, I'm more comfortable if the mass seems to be pushing the arteries out of the way than if it's encasing them.

If you repeat the scan in three months and the mass is bigger, you're not going to be able to watch and wait, but at this point, you don't know how long it has been growing. But I share your concern. This is not someone I'd say, "Come back in a year and we'll see how you're doing." I think you have to monitor her closely for those problems.

Again, it's always a balance with toxicity, but in the absence of any clear need to treat right away, I like to get a sense of the pace of a disease.

DR RADER: What's her cardiac status?

DR DRULLINSKY: I think anxiety was more the cause of the atypical chest pain. Maybe it was false confidence, but after the cardiac catheterization, I felt that although she had coronary artery disease, it wasn't left main disease and I didn't think she was about to infarct.

DR LOVE: How did you end up treating this patient?

DR DRULLINSKY: I work in Long Island at a big hospital, and we have a disproportionate number of elderly patients. In our weekly meetings, we discuss the fact that in the main research centers, patients are 40 to 50 years old. We have 80-year-old patients, yet they want aggressive therapy.

This patient appeared younger than her actual age. We decided to treat her with rituximab/CVP (1.1) and up-front pegfilgrastim. She completed all six cycles, and the only complication was severe bone pain from the pegfilgrastim. She has had complete resolution of all adenopathy.

Where I work, people tend to want aggressive therapy. Patients are living longer and longer, into their eighties and nineties, and sometimes it's difficult to determine how much therapy someone that age can tolerate. Treating 80- and 90-year-old patients can be anxiety provoking, but sometimes I'm surprised — especially in the new era with growth factor support. I'm just amazed at what you can do with pegfilgrastim and how well patients tolerate therapy.

DR L FARBER: I use a lot of pegfilgrastim — a lot of growth factors in general — but CVP is not a regimen I would automatically put in the category of requiring these. I just wonder if she could have gotten away without the pegfilgrastim. In an elderly person, I may start out with a reduced dose of cyclophosphamide and work my way up.

1.1 Phase III Trial of CVP versus R-CVP in Previously Untreated Patients with Stage III/IV CD20-Positive Follicular NHL (N=321)

	R-CVP (n=162)	CVP (n=159)	*p*-value
Overall response rate	81%	57%	<0.0001
Complete response rate	41%	11%	—
Median time to treatment failure	27 months	7 months	<0.0001
Time to progression	32 months	15 months	<0.0001

"90% of patients had follicular small cell or follicular mixed NHL, and 9% follicular large cell NHL. According to the FLIP index 49% of patients had poor and 41% intermediate prognosis disease. Both regimens were well tolerated. The incidence of AEs was similar in both groups except for rituximab infusion related reactions in the R-CVP group. There were no differences in infection rates between the treatment arms and no treatment related deaths."

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

SOURCE: Marcus R et al. **An international multi-centre, randomized, open-label, phase III trial comparing rituximab added to CVP chemotherapy to CVP chemotherapy alone in untreated stage III/IV follicular non-Hodgkins Lymphoma.** *Proc ASH* 2003;**Abstract 87**.

Marcus R et al. **CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma.** *Blood* 2004;[Epub ahead of print]. **Abstract**

DR LEONARD: This treatment regimen is certainly reasonable and justifiable and it worked well. Part of this is the art of oncology — evaluating the patient and giving something a try. There will be times we will look at a patient and say, "This patient will do fine," and often get surprised. Some people tolerate chemotherapy much better than others. I have treated elderly patients who tolerated R-CHOP, and other patients who said, "Don't bother to do it." I've also had patients whom I thought were going to tolerate chemotherapy but they didn't because of the toxicities.

We're not perfect and a lot of this is trial and error. You have to choose a treatment that agrees with your judgment and the patient's wishes. If it works, just stick with it. In this case, it worked, but sometimes it doesn't and you have to cut back. If she had not tolerated the CVP, you could have eliminated that and given her rituximab, or cut back to the oral alkylater with or without rituximab.

Select publications

Advani R et al. **Stage I and II follicular non-Hodgkin's lymphoma: Long-term follow-up of no initial therapy.** *J Clin Oncol* 2004;22(8):1454-9. **Abstract**

George S et al. **Fixed-dose pegfilgrastim is safe and allows neotrophil recovery in patients with non-Hodgkin's lymphoma.** *Leuk Lymphoma* 2003;44(10);1691-6. **Abstract**

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

Grigg A et al. **Open-label, randomized study of pegfilgrastim vs daily filgrastim as an adjunct to chemotherapy in elderly patients with non-Hodgkin's lymphoma.** *Leuk Lymphoma* 2003;44(9):1503-8. **Abstract**

Hainsworth JD et al. **Rituximab plus short-duration chemotherapy as first-line treatment for follicular non-Hodgkin's lymphoma: A Phase II trial of the Minnie Pearl Cancer Research Network.** *J Clin Oncol* 2005;23(7);[Epub ahead of print]. **Abstract**

Honecker F et al. **Chemotherapy in elderly patients with advanced lung cancer. Part I: General aspects and treatment of small cell lung cancer (SCLC).** *Onkologie* 2004;27(5):500-5.

Marcus R et al. **An international multi-centre, randomized, open-label, phase III trial comparing rituximab added to CVP chemotherapy to CVP chemotherapy alone in untreated stage III/IV follicular non-Hodgkins lymphoma.** *Proc ASH* 2003;**Abstract 87**.

Marcus R et al. **CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma.** *Blood* 2004;[Epub ahead of print]. **Abstract**

Morrison VA et al. **A model to predict chemotherapy-related severe or febrile neutropenia in cycle one among breast cancer and lymphoma patients.** *J Clin Oncol* 2004;22(14S):8068.

Ozer H et al. **2000 update of recommendations for the use of hematopoietic colony-stimulating factors: Evidence-based, clinical practice guidelines.** *J Clin Oncol* 2000;18(20):3558-85. No abstract available

Repetto L. **Greater risks of chemotherapy toxicity in elderly patients with cancer.** *J Support Oncol* 2003;1(s2):18-24.

Vose JM et al. **Randomized, multicenter, open-label study of pegfilgrastim compared with daily filgrastim after chemotherapy for lymphoma.** *J Clin Oncol* 2003;21(3):514-9. **Abstract**

CASE 2: A 43-year-old woman with Grade III follicular large cell non-Hodgkin's lymphoma (from the practice of Dr Charles Farber)

Edited excerpt from the discussion:

DR SMITH: This is clearly an area that's in a state of flux. Typically, in the working formulation, follicular large cell or what we now call follicular Grade III was considered an intermediate grade. We would have given R-CHOP based on the large cell data, which is probably not a bad idea; however, her disease is behaving a little more indolently.

If you review the literature on follicular large cell from over the years, Stanford published a paper in which they defined follicular large cell lymphoma as more than 50 percent large cells. According to the Nebraska data, follicular large cell lymphoma looks more like follicular Grade I and II. Patients in Nebraska are diagnosed with follicular large cell lymphoma a lot more often than patients at Stanford because they use more of the so-called formal criteria.

Follicular Grade III is probably a mix of diseases. People have tried to divide it into follicular Grade IIIA and B, with the A being a mixture of small and large cells, and the B being sheets of large cells. The IIIA/IIIB distinction has not been formally demonstrated with prospective data but it makes intuitive sense.

This is a long-winded prologue to saying that you can give R-CHOP and say, "Well, it's not a bad treatment for low grade lymphoma. It's a good treatment for aggressive lymphoma, and we won't be undertreating her."

If she's had this node for a long period and the gallium is negative, then you might do a PET scan to convince yourself that no areas of high uptake exist, in which case you might be comfortable in watching and observing the pace of the disease. I think you could go either way. It's sort of a gestalt, and the patient may need to be involved in the discussions by telling her, "Here's what we know. Here's what we don't know." R-CHOP would be a good therapy for either of these. I think the ultimate prognosis — whether you have a curable disease — is still up in the air.

DR LEONARD: In aggressive lymphomas, I'm a big fan of the International Prognostic Index (2.1). I sit with the patient and go through their IPI risk factors and tell the patient what their chance of cure is. Now that the follicular lymphoma IPI (2.1) has come out, I think we know less about what to do with a patient with a bad- or good-risk FLIPI; however, I think it's a good idea to at least go through it.

The FLIPI, or the five criteria that were established based on a group of about 4,000 patients, was published in *Blood* in September 2004. The five factors are described by the acronym, NoLASH: (1) more than four nodal areas; (2) elevated LDH; (3) age greater than 60 years; (4) Stage III or IV; and (5) hemoglobin level less than 120 g/L (12 g/dL). [Leonard JP. *Blood* 2004;104(5):1233-4]. Based on what you said, this patient has two of the five factors.

The point is that if she has three of the five factors, the five-year survival rate is about 50 percent. We don't know whether or not treating those patients differently or more aggressively is going to help things, but if that's the case, then we're not necessarily doing her a favor by holding off on therapy. If you think about it, a 50 percent five-year survival rate is poor.

So how do we act on that? We don't know. We need randomized trials to evaluate whether or not patients at high risk who

are treated with a specific regimen do well or don't do well. I'm hoping that all of the up-front regimens that are being tested and have been tested will evaluate this retrospectively so we can determine whether a given regimen works well in patients at high risk versus patients at low risk. My point is that she doesn't fall in the best-risk group. She may well be in the worst-risk group and, if so, I would consider more therapy.

2.1 Prognostic Indices for non-Hodgkin's Lymphoma (NHL)

The International Prognostic Index (IPI) for aggressive NHL[1]

This index identifies five significant risk factors determined to be prognostic of overall survival. There is an increased risk of relapse for each positive factor.

- Age — greater than 60 years
- Serum lactate dehydrogenase (LDH) — greater than the upper limit of normal
- Performance status — 2-4*
- Ann Arbor Stage — III or IV
- Extranodal sites — greater than 1

Patients positive for two or more risk factors have less than a 50 percent chance of relapse-free survival at five years.

* Performance status:
0 = normal activity
1 = symptomatic; fully ambulatory
2 = symptomatic; > 50% ambulatory
3 = symptomatic; < 50% ambulatory
4 = 100% bedridden

The International Prognostic Index for Follicular Lymphoma (FLIPI)[2]

Patients are assigned to a risk group based on the number of positive factors.

- Age — greater than or equal to 60
- Ann Arbor Stage — III or IV
- Hemoglobin level — less than 120 g/L
- Serum lactate dehydrogenase (LDH) — greater than the upper limit of normal
- Nodal sites — greater than 4

Overall survival (OS) according to risk group by IPI for patients with available data for the FLIPI and IPI

Risk group	Number of positive factors	Percent 5-year OS	Percent 10-year OS
Low	0-1	88.1	67.3
Low-intermediate	2	70.9	49.5
High-intermediate	3	57.4	27.6
High	4-5	43.6	35.8

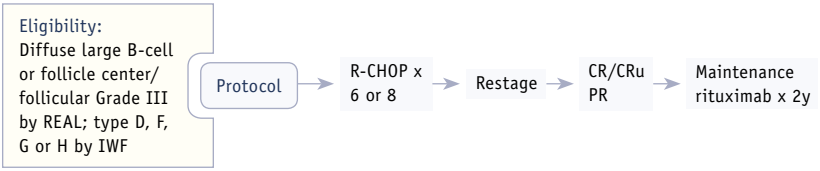
OS = overall survival

SOURCES: [1] **A predictive model for aggressive non-Hodgkin's lymphoma: The International Non-Hodgkin's Lymphoma Prognostic Factors Project.** *N Engl J Med* 1993;329(14):987-94. **Abstract**

[2] Solal-Celigny et al. **Follicular lymphoma international prognostic index.** *Blood* 2004;140(5):1258-65. **Abstract**

2.2 Phase II Trial Evaluating R-CHOP Followed by Maintenance Rituximab as First-Line Therapy in Patients with Aggressive NHL

Accrual: 105 (Closed)



Outcomes with R-CHOP (n=105)

Overall Response Rate	80.0%
CR/CRu	51.4%
Progressive disease	1.9%
Serious adverse event	33.0%
Febrile neutropenia	14.3%

CR/CRu = complete remission/unconfirmed complete remission

SOURCE: Huang JE et al. **Rituximab plus CHOP followed by maintenance rituximab as initial therapy for aggressive non-Hodgkin's lymphoma (NHL); Initial results of induction therapy, including rituximab pharmacokinetics, in a phase II study.** *Blood* 2004:104(11);**Abstract 4616**.

The question is: What is a little bit more? R-CHOP as an up-front regimen is at the stronger end of the spectrum. We have good data with that regimen, and randomized trial data indicate some benefit. Whether that is the answer for patients with high-risk FLIPIs, we don't know at this time. We haven't seen those data.

Given this patient's young age, the options of investigational trials and transplant — whether it is autologous or allogenic — may move up the list because she has some adverse factors. I agree with everything that Mitch said, but I would reiterate that based on the prognostic factors, this may not be a follicular lymphoma that putters along for 10 years. This patient may require additional treatment relatively soon and, therefore, you work your way down a treatment list relatively rapidly.

DR C FARBER: I treated her on a clinical trial that was somewhat novel at that time (2.2). She received six cycles of R-CHOP followed by two years of maintenance rituximab, a la Hainsworth, with four consecutive weekly infusions every six months for two years.

After the initial R-CHOP, she achieved a complete remission with resolution of her adenopathy. I did a bone marrow biopsy after the sixth cycle and, although the large cells were cleared, she had some residual small cleaved cells. She's remained in remission since that point in time.

Over the last three and a half years, with close follow-up, she has not had any clinical recurrence. I have not repeated any bone marrow biopsies, but her CBC has remained in good range.

What's the significance of the residual small cells? If you read the long-term data in low grade lymphoma, whether or not they have involvement is not prognostic; patients tend to have the same survival.

DR LEONARD: The one scenario in which residual small cells may be an issue

— relative to the prognostic issue — is collecting her stem cells. It becomes more difficult to collect stem cells if you want to "bank them for a rainy day." It's debatable whether you need to do that, but certainly it's worth doing if the insurance companies will allow it.

The prognostic significance of a CR versus a PR in a population-based study evaluating hundreds of patients is that the CR patients do better. For an individual patient, I'm not sure that's the make-or-break thing.

Another thing to consider is that it's not rare to see lymphoid aggregates in the marrow after rituximab treatment — these may be residual T cells. I have had debates with our pathologist over this issue because often what appear to be apoptotic B cells are actually T cells, so it doesn't necessarily represent lymphoma. If there is any question, it is worth performing a CD-3 stain to ensure that it's not a residual T cell.

I would continue observing her at this point. I agree with this management in that you treated her on a trial, which is appropriate, and she received more treatment, rather than less, on this trial. Patients in this situation often want to do as little as possible. Some trials and regimens offer less, rather than more treatment. With this patient I would err toward more, as you did, rather than less.

DR MALHOTRA: Considering that her marrow is positive, if you want to collect her stem cells, would you think about doing any purging?

DR LEONARD: My understanding is that the benefits of purging are debatable. The CUP trial, which is a randomized trial evaluating autologous transplant in follicular lymphoma, did not show a difference between purging and not purging; however, that was a different situation and the study was underpowered to evaluate that outcome.

Intuitively, purging makes a lot of sense. Even though you have marrow involvement, you can still mobilize stem cells that are free of tumor. I would not necessarily rule out a stem cell collection, and I would probably offer purging if it were readily available.

DR SMITH: Can I clarify whether the positive bone marrow biopsy was at the end of the R-CHOP or the end of the two years of maintenance rituximab?

DR C FARBER: It was at the end of the R-CHOP, not at the end of the maintenance rituximab.

DR SMITH: So it's possible that the additional rituximab has cleared her marrow. In low grade lymphomas, we don't know where the response rate improves over time. Perhaps she's negative now in terms of her small cell component. That should not impact management now, but it might be of interest in the event she needs a transplant. R-CHOP was designed to take care of the large and small cells. The small cells can continue to survive after they're damaged and don't die until much later.

DR LOVE: What do we know about long-term outcome for patients like this, Dr Smith?

DR SMITH: In this patient, you have the benefit of time. I suspect her large cell component is not likely to come back; however, her low grade small cell component is likely to come back. If her disease progresses, she needs to undergo biopsy to verify the histology and be treated for low grade lymphoma at that point.

DR C FARBER: This patient was treated on a study, so her maintenance was predicated and known. How would you manage her off study? Would you have endorsed maintenance therapy and, if so, would you have followed the Swiss approach or the Hainsworth approach? What duration of maintenance would you advocate?

DR SMITH: In low grade lymphoma, data indicates that rituximab either as a single agent or with CVP is beneficial when administered as prolonged maintenance or scheduled re-treatment. In contrast, we have little data regarding treatment of large cell lymphoma. The ECOG E-4494 trial suggested that if a patient received rituximab with CHOP, then maintenance rituximab did not

add any benefit to the treatment of large cell lymphoma; however, that trial was a two-by-two-design not a four-arm trial.

When treating patients, I tend to use the Swiss 1-3-5-7-9 regimen, which has now been adopted by ECOG in their up-front trial for low tumor-burden disease, into an every three-month schedule. We see patients every three months, which makes it easier to give them their treatment; therefore, I find it technically easier. I think the Hainsworth schedule certainly has a lot of support, and I don't have a strong feeling as to which one is better. I think it is whichever one is easier.

DR LOVE: Dr Leonard, if it turns out that all we are dealing with is progression-free survival as a benefit of maintenance rituximab, do you think that this is a positive benefit-to-risk ratio?

DR LEONARD: That is a difficult question. In indolent lymphoma, patients can have disease that putters on a long time before becoming symptomatic. Even if you're not extending survival, having prettier CAT scans may be psychologically meaningful for some people. For other people, it's not a big deal. From my perspective, if that's the only benefit of maintenance versus re-treatment with rituximab at progression, then it's an individualized decision.

I believe some patients like to come back to be treated because it is a security blanket, while others prefer to stay away as long as possible. Relatively few of the diseases we encounter offer us the luxury of leaving these decisions up to the patient and allowing us to tailor the treatment to their preferences and comfort levels.

DR VOGEL: If you were a medical director of an insurance company, what would you say? You have to pay a certain amount of money for treatment. How are you going to advise the physicians who call you in terms of the efficacy of maintenance rituximab?

DR SMITH: Dr Hainsworth's trial evaluating scheduled maintenance versus re-treatment at relapse resulted in only about a 20 percent difference in total drug delivered. It wasn't a huge difference, and that difference may be counteracted by fewer scans and tests. I don't think the cost is as much an issue as some people first thought. You might think, "Oh, this is a huge difference, giving scheduled maintenance, and we're going to use so much more drug that an insurance company would never want to do it." However, if you evaluate the numbers, it's not a huge difference.

DR LOVE: Fifteen years ago, a similar question was on the table in breast cancer. We thought that tamoxifen was only going to delay progression-free survival. At that point, we were saying, "The side effects and toxicity of tamoxifen are not much of a price to pay to delay progression." Dr Farber, how does it play out in terms of rituximab?

DR C FARBER: I believe patients enjoy receiving maintenance therapy because it gives them a significant degree of reassurance. They feel they're being proactive with their treatment. I explain to them up front that it's a two-year commitment and it doesn't go beyond that, but deep down inside I wonder if maybe it should be extended beyond two years. I realize that it's a tremendous financial cost and no data exist to support it.

DR LEONARD: The bottom line is your comfort level. It parallels using five years of tamoxifen for breast cancer before we knew whether or not it made a difference. The fear is that, as soon as you stop whatever you're doing, the patient may relapse.

They probably would have relapsed regardless of whether or not you were continuing your maintenance therapy, but it just makes everybody feel lousy about stopping the drug. It's reasonable to have these discussions with the patient and say, "We don't have the data."

If the patient is comfortable continuing with the therapy, great, and if they're not, then stop. On some level we like to participate in clinical trials. I presume that eventually trials will evaluate rituximab beyond two years; however, I think you have to evaluate the patient's situation.

On one hand, if the patient has done well for two years and everything's quiet, on some level you don't want to rock the boat. On the other hand, it's been two years and they haven't progressed. If the patient progresses after two years of maintenance rituximab, I would expect they'd have a beautiful response to rituximab when they relapse, so in my opinion you probably haven't lost a whole lot. I've given a long-winded answer, but the bottom line is that I don't think a right answer exists — either way is reasonable.

DR LOVE: Dr Smith, I'm guessing we aren't going to have randomized trial data on two versus five years of rituximab. Do you offer the option of continuing beyond two years?

DR SMITH: Again, without any data, that involves a long discussion with the patient. If you evaluate what Dr Hainsworth has presented from their trials with patients who have been on rituximab for two years and then stopped, what strikes me is that the patients with follicular lymphoma who are doing well at that point seem to do well for another couple of years.

The patients with the small, lymphocytic lymphomas don't do as well in the relapse setting, and they seem to fall off a lot faster. I would be more hesitant about stopping rituximab in someone who has a small lymphocytic lymphoma and has done well for two years, because I am concerned that they will progress. Perhaps we are just holding them in check and haven't addressed the disease as well as we have with the follicular lymphoma.

Right now, looking at the curves, that's sort of where I'm leaning. In patients with follicular lymphomas, I tend to stop and say, "Why don't we give you a break and when you relapse you'll probably respond well." If a patient has a small lymphocytic lymphoma, I'm a little more concerned and lean toward continuing treatment.

DR RADER: You're involved in research in this field every day. Why do you think clinical trials are not evaluating five years versus two years of rituximab?

DR SMITH: When Dr Hainsworth first proposed his two-year maintenance trial, people thought he was crazy for giving that much rituximab. Now they say, "Why did you stop?" I think we're just beginning to realize that we should ask that question. However, you'd have to be in your first year as an assistant professor to design that trial, launch it and expect an answer in your lifetime. No pharmaceutical company wants to do that either. I think it's difficult to take on such long-term projects.

DR LEONARD: I think that question will be obsolete by the time it is answered. We probably will no longer be giving maintenance rituximab as we are now. We'll be giving it in combination, using receptor polymorphisms to subset patients. I think five years down the line — which would be the earliest that we could answer that question — we'll be way ahead of that result with other drugs, regimens and subclassification of patients.

DR LOVE: It's fascinating to see these oncologic issues discussed across tumor lines. In breast cancer, bevacizumab is going to be evaluated in adjuvant clinical trials. How long do you use that therapy in that setting? In evaluating the aromatase inhibitors, we picked five years because of tamoxifen, yet bevacizumab utilizes a much different mechanism.

DR KAPLAN: The problem is the median survival of these patients is eight or 10 years. If you design a trial, you're going to be dead or retired before the trial is finished, so we're doing this purely by feel.

I don't use maintenance rituximab because I'm not convinced that it makes any difference over the long term. No data exist either way. However, I think that if you are going to give maintenance rituximab, you ought to continue indefinitely. These tumors are not like breast cancer, in which you are going to eradicate the tumor. With lymphoma, you're sitting on it, and if you're going to sit on it, you have to continue the maintenance therapy — if that's your philosophy. I can understand that philosophy, but

I don't believe in it; however, I can't understand why you would stop at two years.

DR LOVE: If we are only going to focus on the endpoint of overall survival, trials like this probably aren't going to be done, or by the time we learn the answer we'll be on to something else. Dr Leonard, what other endpoints should we be evaluating? Progression-free survival is obviously an option, but will anything else give us a quicker answer?

DR LEONARD: Trying to come up with a surrogate for survival is challenging. Certainly, progression-free survival is an objective endpoint. We can design criteria and evaluate the same patient and say, "Yes, that person has progressed."

I think the problem is that when the patient progresses, he or she can go another two months, two years or sometimes longer, feeling fine and not needing any clinical treatment. To me, that is the "Catch 22." If progression meant the patient was sick or needed treatment, then I believe we would agree it is a meaningful endpoint. In most tumors, that is the case. That is why progression is a valid endpoint; however, in indolent lymphoma, progression is not necessarily a bad thing.

We've tried to evaluate time to next treatment, which is a nice endpoint. The problem is that everyone sitting around this table could evaluate the same patient and have different opinions, or have two different patients with the exact same clinical scenario and not agree on whether the patient needed treatment. Because progression is a subjective issue, it may not be a valid endpoint.

The psychology of indolent lymphoma and the use of rituximab are fascinating. It's a unique situation in oncology when a patient wants to come back for more treatment even though it may not necessarily be helpful in the long run. You have to think that a psychological benefit occurs for some people.

Chuck put the hammer on the nail's head. For some patients, being proactive helps their quality of life because they feel like they're doing something; however, we need some objective scales. Whether it's variations on the quality of life or the psychology of the stress of these chronic disorders in which the patient has a tumor sitting there like a time bomb. I think it's a pretty unique situation in oncology.

DR SCHER: I have a quick question. In the past, we were concerned about the infusion reactions with rituximab, especially up front. After a discussion with Mitchell, we started using dexamethasone 20 mg right before each rituximab dose. Since then we haven't seen any toxicity. I think a lot of controversy exists about whether that's bad or good. I was wondering what your input would be about that now.

DR SMITH: Steroids were prohibited in the original trials, because they would have confounded the interpretation of responses. I think the theoretic concern is that you're immunosuppressing the patient, regardless of how rituximab works, whether it's ADCC or complement activation or direct apoptosis.

A dose of steroids with each infusion is probably not detrimental given the long half-life of the antibody. I believe it reduces the incidence of infusion-related toxicity; therefore, I do it in most patients.

DR LOVE: Len, how does the issue of patient age relate to the decision to use maintenance rituximab? One of the fascinating developments in breast cancer is the Adjuvant! online model. You input patient characteristics and can then obtain quantitative estimates on the effects of therapy.

One of the most interesting things about that model is when you put in the patient's age and you start to factor in co-morbidities. In NHL, we sort of do this by the seat of our pants. When we use Adjuvant! in breast cancer, the numbers are right in front of us. How does age factor into the decision to use maintenance rituximab?

DR L FARBER: I think age relates to the decision in two ways. One is the difficulty older patients may have with transportation to the office. If you have a treatment that is

not clearly beneficial in the patient, and the patient's son has to take a day off from work once a week for four weeks, then you're not necessarily going to be as inclined to recommend this option as you would in another scenario. If the patient is retired and has an open schedule and transportation, it's not as big an issue. I think the practicalities of frequent office visits affect the decision.

While the data for maintenance rituximab is less clear and, in fact, does not exist in large cell lymphoma, intuitively part of me says, "Well, gee, that's a scenario in which I might be more inclined to use it, despite negative data."

Again, I'm not advocating the use because there are no supporting data. However, the consequences of a relapse for a patient with large cell lymphoma, who may not be a candidate for intensive treatment or transplant, certainly make the concept of maintenance particularly more attractive as an effort to avoid or delay a toxic treatment. I believe that's the psychology some physicians follow when using rituximab in that setting despite the lack of data.

Select publications

Davis TA et al. **Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: Safety and efficacy of re-treatment.** *J Clin Oncol* 2000;18(17):3135-43. **Abstract**

Davis TA et al. **Single-agent monoclonal antibody efficacy in bulky non-Hodgkin's lymphoma: Results of a Phase II trial of rituximab.** *J Clin Oncol* 1999;17(6):1851-7. **Abstract**

Gordon LN et al. **Phase II trial of individualized rituximab dosing for patients with CD20-positive lymphoproliferative disorders.** *J Clin Oncol* 2005;23(6);[Epub ahead of print]. **Abstract**

Hainsworth JD. **Prolonging remission with rituximab maintenance therapy.** *Semin Oncol* 2004;31(1 Suppl 2):17-21. **Abstract**

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

Hochster HS et al. **Results of E1496: A phase III trial of CVP with or without maintenance rituximab in advanced indolent lymphoma (NHL).** *J Clin Oncol* 2004;22(14 Suppl); **Abstract 6502**.

Horning S. **Something old, something few, something subjective, something déjà vu.** *J Clin Oncol* 2003;21(1):1-2. No abstract available

Huang JE et al. **Rituximab plus CHOP followed by maintenance rituximab as initial therapy for aggressive non-Hodgkin's lymphoma (NHL): Initial results of induction therapy, including rituximab pharmacokinetics, in a Phase II study.** *Blood* 2004;104(11);**Abstract 4616**.

Leonard JP. **The "FLIPI" is no "FLOPI".** *Blood* 2004;104(5):1233-4. No abstract available

Martin AR et al. **Prognostic value of cellular proliferation and histologic grade in follicular lymphoma.** *Blood* 1995;85(12):3671-8. **Abstract**

Schouten HC et al. **The CUP trial: A randomized study analyzing the efficacy of high dose therapy and purging in low-grade non-Hodgkin's lymphoma (NHL).** *Ann Oncol* 2000;11(Suppl 1):91-4. **Abstract**

Vose JM et al. **Phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma.** *J Clin Oncol* 2001;19(2):389-97. **Abstract**

CASE 3: A 72-year-old asymptomatic man with Stage IV low grade lymphoma after knee replacement surgery (from the practice of Dr Richard Scher)

Edited excerpt from the discussion:

DR HAINSWORTH: This is an asymptomatic patient with high-stage disease, extranodal sites and minimal adenopathy who has bone marrow and bone involvement and a subcutaneous nodule.

He's elderly, but otherwise in good health. This patient would be in a relatively low-risk group according to either the IPI or the FLIPI index. This is a patient for whom you could predict a relatively indolent course despite having Stage IV disease and bone involvement in L-4.

DR LOVE: Dr Cabanillas, what are some evidence-based options that you might have presented to this patient, and how do you think you would have sorted through that?

DR CABANILLAS: I'm concerned about the presentation of this patient. Having three extranodal sites is unusual for a patient with low grade lymphoma. This patient presents with bone marrow involvement and the PET scan showed bone involvement.

He also has a soft-tissue lesion in the scalp. One of the first things I would like to clarify before giving this patient my opinion is that he doesn't have transformed lymphoma, or what we call "divergent histologies," which is probably a better term.

Some patients with low grade lymphoma could have had the disease for years and it might have been undiagnosed. At some point, it might have evolved into a large cell lymphoma.

When I see extranodal areas that are not common as a presentation for low grade lymphoma, I consider the possibility of a transformation.

You mentioned that the scalp lesion was biopsied and it showed the same diagnosis. I assume that it was called small cleaved cell lymphoma?

DR SCHER: Yes, the scalp lesion had the same diagnosis.

DR CABANILLAS: That's a bit unusual. Even if it's low grade lymphoma in those areas, having three extranodal sites is an adverse feature.

The patient's flow cytometry was positive for CD20 and CD10 and negative for CD5. That indicates a follicular lymphoma, perhaps Grade I.

I would like to know about the PET scan in this patient. I pay a lot of attention to the PET scan because it not only tells you where the disease might be located, but it gives you something that no other test will give you, which is an idea about how avid the various lesions are for fluorodeoxyglucose (FDG), which is a manifestation of the metabolic rate of that tumor.

Seeing an area like the one on the scalp, which has a low standard uptake value (SUV) — the method that nuclear medicine physicians use to calculate the amount of uptake in each tumor site — I would be convinced that the area is a low grade lymphoma. If other areas have a high SUV, then I would consider the possibility of transformation in those areas.

You could biopsy one of the areas that have a high SUV to ensure that the patient is not treated for a low grade lymphoma when he might actually have a more aggressive lymphoma. I would make that clarification before giving my opinion.

DR LOVE: What do we know about PET scan activity and disease type?

DR CABANILLAS: There are data indicating that low grade lymphomas have a lower SUV, and more aggressive lymphomas have a higher SUV. The complication is with the low grade lymphomas, which we always think of as one disease. For example, in follicular lymphomas, you can biopsy one node and find follicular small cleaved cell lymphoma; however, a biopsy from a different place might indicate that the patient has follicular large cell, follicular Grade II or even diffuse large cell lymphoma. Because we rely on one biopsy, I think we frequently miss those cases.

DR LOVE: John, is that something you've also observed in your patients — a correlation between activity on PET scan and transformation or disease activity?

DR HAINSWORTH: In general, the low grade lymphomas are less hot on PET than the large cell lymphomas. The pattern that would be worrisome in a patient like this is variation in intensity in different areas. If everything was uniform except that one area is much hotter than the others, that would be a tip-off that you might have a transformation, and should biopsy that area. I'm not aware of any data in low grade lymphomas that suggests that patients with hotter PET scans do worse.

DR CABANILLAS: No, it is not that they do worse, nor did I say that PET is a prognostic factor. What I said is that it correlates with the histology. If you treat patients with low grade lymphoma using R-CHOP, then you're going to be covering the possibility of a transformation; however, other types of treatment, such as RFND, specifically target the low grade lymphomas.

We know that FND is not a good combination for large cell lymphoma, particularly diffuse large cell lymphoma, because fludarabine as a single agent did not exhibit much activity. In fact, it was a poor agent in diffuse large cell lymphoma. We don't use FND in that situation. Whenever I use a combination that is primarily designed for low grade lymphoma, I want to be sure the patient doesn't have transformation.

DR LOVE: John, how would you have approached therapy for this patient?

DR HAINSWORTH: A number of legitimate treatment options exist for this patient because he seems to be completely asymptomatic. One option would be to observe the patient. I might be a little worried about the vertebral body involvement, although usually when you see that in a low grade lymphoma and it's a sclerotic-type lesion, it doesn't correlate with future skeletal problems, so I'm not sure that is a reason to pursue treatment. Other options include single-agent rituximab or combination chemotherapy/rituximab. I think arguments can be made for each of those.

DR LOVE: Dr Cabanillas, what do you think would be your management in this situation?

DR CABANILLAS: When you're treating a patient who is in his seventies, certainly watch-and-wait is a possibility, even though I have not been inclined to manage patients with a watch-and-wait approach. We put patients on clinical trials regardless of whether or not they have symptoms. A patient who is 72 and active might have a relatively long life expectancy if you can eradicate his disease.

I usually use the watch-and-wait approach only for patients who have a lot of comorbidity and whose life expectancy is not long. I let the patient decide, but you have to give the patient the necessary information to enable them to make the decision. The prognostic factors associated with outcome in low grade lymphoma play an important role in making that decision.

This can be done in various ways. The IPI (2.1), which was designed for aggressive lymphomas, has been applied to low grade lymphomas and it predicts the outcome. More recently, we have the follicular lymphoma IPI (2.1) that John mentioned, which gives you a better idea.

When I use the IPI, I always use the acronym APLES to remember the factors. The first consideration is A, which stands for age over 60. This patient scores one point for

that. The P stands for performance status; this patient's performance status appears to be adequate, so he doesn't score a point for that. The L stands for LDH, which was normal. The E stands for the number of extranodal sites, and his was more than one (it was three), so he scores one point for that. The S stands for stage, and because he has Stage IV disease, he scores a point for that. His overall score is three factors out of five, which puts him in an intermediate category.

The FLIPI utilizes the acronym NoLASH. This patient had one nodal area involved and his LDH was okay, so he doesn't score points in those areas. He scores one point for age and another point for stage, and the last consideration is hemoglobin level, which was normal.

So with the FLIPI he only scores two points out of the five, which does not place him in the best category, but not in the worst category, either.

One prognostic factor that has not been included in any of these methods is beta-2 microglobulin. I think the reason it's not being used is because the investigators who supply the prognostic factors to the trial investigators did not have information on the serum beta-2 microglobulin; however, we have found that beta-2 microglobulin is a powerful prognostic factor, not only for large cell lymphoma but also for Hodgkin's disease and low grade lymphoma. To me, beta-2 is as important, or maybe even more important, than LDH; therefore, I would like to know his beta-2 level. In our laboratory, the cutoff is 2.0, but we accept up to 3.0 for large cell lymphoma. As soon as it reaches 3.0 it is considered a poor or adverse factor.

In low grade lymphoma, we use 2.5 as the cutoff because the median beta-2 microglobulin for low grade lymphoma is lower than for large cell lymphoma.

This patient is active, his life expectancy is good, and he doesn't have a lot of comorbidity, and although I'm a bit concerned that his prognostic factors are not excellent, I would be inclined to offer him treatment.

DR LOVE: I want to ask John first, and then I want some feedback from the group in terms of how you handle similar patients in your practice. John, of course you'd have to see the patient in person, but based on what you've heard, how do you think would likely manage this patient?

DR HAINSWORTH: I will say that I too am less and less enamored with watch-and-wait. As was just said, this patient is at low to intermediate risk, rather than high risk. It is possible that he's going to do well for a while and continue to be asymptomatic.

In general, I have recently been recommending single-agent rituximab to older patients, rather than more intensive treatment up front. I've been using chemotherapy/rituximab combinations in younger patients.

It is not a hard and fast rule, but you can predict that someone who is 72 and at relatively low risk is going to have a course that spans several years, and it would be nice to have him consistently feeling well during that time.

DR LOVE: If the man said to you, "Can you give me some numbers in terms of what to expect over the next five, 10 or 20 years, without any treatment or, say, following your plan of rituximab?" What would you say to him?

DR HAINSWORTH: Those numbers are probably easier to give him with regard to no treatment or with whatever has been standard in the past, rather than with rituximab. With an IPI or a FLIPI score such as his, the 10-year survival is probably between 50 and 75 percent, and that's with traditional observation treating with sequential regimens designed to avoid toxicity.

With rituximab, I'm not sure that the bottom line is going to change but it allows you to treat someone with a minimally toxic regimen that also has a high chance of having a prolonged remission.

Many of these patients who receive rituximab first-line are either retreated or receive maintenance treatment. "Prolonged" means

for several years without doing anything else.

DR LOVE: What schedule of rituximab would you use, and would you use maintenance therapy for this patient?

DR HAINSWORTH: I would start out with a standard four-week course and see whether the patient responded. I prefer to use maintenance, rather than to wait and use re-treatment, although I think either one of those options would be reasonable. I have the most experience with the once-every-six-month courses.

DR LOVE: How long do you continue it?

DR HAINSWORTH: I sort of arbitrarily stop at two years, so I don't have much experience with longer, indefinite maintenance.

DR LOVE: Dr Cabanillas, how do you think this patient likely would have been managed in your practice?

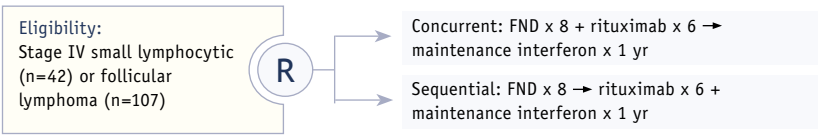
DR CABANILLAS: I offer these patients a combination of FND and rituximab, primarily based on our study results (3.1) — it was a randomized trial for patients with Stage IV low grade lymphoma — in which half of the patients were randomly assigned to receive FND plus rituximab simultaneously, and the other half received FND first, and then one year later they received rituximab. We used molecular response as the major parameter.

Most of these patients have Bcl-2 rearrangement, which you can monitor for response in their blood and bone marrow. Attaining a molecular remission with traditional chemotherapy like CHOP is uncommon.

Approximately 10 to 15 percent of the cases with Stage IV will achieve a molecular remission with CHOP, yet with FND/rituximab, we had 90 percent molecular remissions; therefore, I believe this regimen is superior to CHOP.

3.1 Randomized Trial of Fludarabine/Mitoxantrone/Dexamethasone (FND) with Concurrent or Sequential Rituximab and Maintenance Interferon in Patients with Stage IV Indolent Lymphoma

Accrual: 149 (Closed)



Outcomes for FND with Concurrent or Sequential Rituximab and Maintenance Interferon in Patients with Stage IV Indolent Lymphoma (Median Follow-Up of 30 Months)

	Concurrent (n=76)	Sequential (n=73)	*p*-value
CR + CRu	92%	85%	0.17
Partial remission	8%	10%	NS
3-Year FFS	77%	64%	0.11
3-Year Survival	95%	95%	NS

CR + CRu = complete remission + unconfirmed complete remission; NS = not significant; FFS = failure-free survival

SOURCE: McLaughlin P et al. **Stage IV indolent lymphoma: A randomized study of concurrent vs sequential use of FND chemotherapy (fludarabine, mitoxantrone, dexamethasone) and rituximab (R) monoclonal antibody therapy, with interferon maintenance.** *Proc ASCO* 2003;Abstract 2269.

Zinsani, in Italy, used fludarabine/mitoxantrone (FN) plus rituximab, without the dexamethasone, and he compared the results to CHOP.

He also found that FN plus rituximab has a higher molecular response rate, so I think it's a powerful combination in indolent disease. The patients in whom we saw a molecular response have had an excellent failure-free survival. I'm more focused on failure-free survival because a good failure-free survival will result in superior survival.

I prefer that the patient continue with no evidence of disease, rather than survive seven or nine years having multiple relapses, because quality of life is compromised once they start relapsing and they have to go from one treatment to another. I think it's more traumatic for the patient psychologically, but the fact that they have to change therapy and take chemotherapy also takes away from their quality of life.

DR LOVE: Dr Scher, can you follow up in terms of your discussions with this patient?

DR SCHER: I discussed the various options with him, including watch-and-wait and the Hainsworth data using rituximab that was available at that time.

He was not anxious to start therapy because he was completely asymptomatic. He was somewhat worried about the few times we occasionally see rituximab reactions.

He was mostly concerned, as I was, that we had no sense at all regarding the pace of his disease. His approach, which I was comfortable with, was to proceed with watch and wait. I saw him in three months and he was without symptoms.

I saw him six months after that initial visit and, at that point, I was a bit concerned, because he was complaining of left arm pain.

He was playing golf every day and was perfectly active, but he had developed pain in his left arm. I repeated the CT and PET scans at that time, and they revealed essentially the same thing we saw before, with two exceptions.

An area of uptake near the left internal carotid indicated a small lymph node that was visible on the PET scan, but not on the CT scan. Uptake in the C-2 vertebral body was also noted, which was not present previously. The other vertebral bodies were the same. An MRI of the cervical spine showed evidence of what was probably lymphoma in the C-2 vertebral body, but it was not compressing any nerve and we don't believe it was contributing to his left arm pain.

His orthopedic surgeon believes his left arm pain was due to arthritis and not related to the disease. The lymph node in the left carotid region was so small that it couldn't be seen, and it was unlikely to be the cause of his left arm pain. We are now in the process of trying to make a decision as to whether we should proceed with therapy.

DR LOVE: What kind of therapy are you considering?

DR SCHER: I discussed several therapies with him, including rituximab alone, which he was most comfortable with. The alternative treatment was CVP and rituximab based on the recently published data indicating high response rates and good tolerance with that regimen. He was most comfortable with rituximab alone.

Parenthetically, he has had no other disease recurrence. The small subcutaneous lesion on his scalp has not recurred. He has not developed adenopathy elsewhere, just in those unusual sites — the C-2 vertebral body and the bone lesions.

DR LOVE: John, if this patient had come to you for a second opinion at this point, as opposed to the initial point, how would you be thinking it through?

DR HAINSWORTH: Well, I think now you have the additional data of new things happening within a relatively short time. I'd now be more worried about his bone involvement. Certainly, C-2 is a bad area to be affected by a complication or a compression fracture. I would be more intent on treating him now than I was before. I would

tell him that, at this point, continued watching and waiting is not what I would recommend.

DR LOVE: Would you be more likely to recommend rituximab alone or with chemotherapy?

DR HAINSWORTH: Either one of those options would be defensible and reasonable. I would still probably favor using the single agent.

DR LOVE: As you listen to this case, it sounds as though this patient is oriented toward not experiencing toxicity from treatment unless it's absolutely necessary.

DR CABANILLAS: We see all variations in how people respond to this situation. Some patients want to be treated immediately and aggressively, while others, like this patient, are interested in minimizing toxicity from therapy. I tell my patients that they should not only consider the toxicity of the chemotherapy, but also the toxicity of the disease itself.

If a patient is developing pain and new bone lesions within six months, I don't think it's going to be a low grade lymphoma, and if it is a low grade lymphoma, I think it's on the way to transformation.

I am concerned about this patient, and again, I would carefully evaluate the PET scan to determine whether any areas have more than seven SUV. Up to six is usually okay for low grade lymphoma. You start seeing more large cell lymphomas when the SUV is above six.

I think a needle biopsy of one of the high SUV areas might offer more information, but at this point I would not be inclined to use FND/rituximab, especially now that we know that the pace of the disease is more aggressive and that the patient is experiencing pain. Low-grade lymphomas usually don't cause pain, and they usually don't go to bone. When they do go to bone and start causing pain, that usually means something is wrong, and the patient's disease is going to evolve more rapidly than the usual course of low grade lymphoma.

I think this six-month period of time is already telling you that the tempo of the disease is not going to be that of a low grade lymphoma. If I have to make a choice, I would be more inclined to use R-CHOP, or try to make a more informed decision, perhaps by performing a biopsy of the area that has the highest SUV.

DR LOVE: Just to clarify, what was your impression of what was causing the pain?

DR SCHER: It wasn't clear to me. The MRI revealed abnormalities in the C-2 vertebral body, but they didn't appear large enough to cause pain. No pressure was exerted on any of the nerves. His orthopedic surgeon was convinced that his pain was not related to adenopathy. He felt it was restricted to his left shoulder and a result of playing golf. Over the subsequent week or two, his pain was somewhat alleviated without treatment. We weren't convinced that the pain was definitely related to his lymphoma, but I was concerned.

DR HAINSWORTH: Was the C-2 lesion another sclerotic area or was this a lytic lesion on plain films?

DR SCHER: We don't have plain films, just the PET scan. The MRI just showed an abnormal C-2. I did not actually see the scan, but I think it was probably more sclerotic. I don't think any evidence indicated it was lytic.

DR GOLDBERG: With the vertebral lesions, is anyone thinking about using radiation therapy in a localized manner?

DR HAINSWORTH: I think that would be a reasonable option. If I were starting with systemic treatment, particularly first-line treatment, I probably would not do that. I don't believe these lesions are presently at high risk of having collapse or pathologic fracture, if, indeed, they are both sclerotic. If this were a patient for whom systemic treatment was not an option, I would consider radiation therapy.

DR RADER: My understanding is that SUV values are not standard across the spectrum by various PET scan techniques and PET

scanners. Relying on one value may be OK in one institution, but do those numbers apply across various institutions?

DR CABANILLAS: Some nuclear medicine physicians are not sold on the idea of the SUV, but the data are beginning to accumulate — not only in lymphoma, but in other tumors like breast cancer, in which a correlation exists between the histologic grade and the degree of SUV uptake.

In dealing with nodal sites of biopsy, how do you feel about making a diagnosis with needle biopsy and flow cytometry, especially with transformation, versus evaluating a whole node? Do you think the science of molecular biology has changed enough that we could make a diagnosis based on a small needle biopsy of lymphoma? In the past, a single biopsy was inadequate and we always demanded a full node.

I don't like to do an FNA for the primary diagnosis, but in a patient who already has an established diagnosis for whom I am trying to establish transformation — with a good cytologist — I rely on the FNA.

I prefer to do a lymph node biopsy, if possible. That's easy to do when you have peripheral adenopathy, but if you have a bony lesion, for example, then your option is to either do an open biopsy or a needle biopsy.

If you ask the pathologist for evidence as to whether the tumor is transformed, rather than asking exactly what kind of tumor it is, you're more likely to get the right answer. An evaluation of Ki-67 can give you an idea about the proliferative rate. We have accumulated evidence regarding the correlation between Ki-67 and histologic grade, and a correlation definitely exists. I tend to rely on FNAs only when performed by a good pathologist or cytologist who has a lot of experience with lymphoma cytology. I never recommend an FNA for the primary diagnosis, only to establish a relapse and transformation.

DR BHARDWAJ: We are seeing the difference in terms of how the two faculty members would handle this patient if they decided to treat. There is the RFND school, and the other school of CVP or CHOP with rituximab. What data exist in terms of favoring one over the other and how meaningful is a molecular remission in terms of either survival or quality of life?

DR HAINSWORTH: I think we agree that the data isn't as complete as we'd like for it to be. In the pre-rituximab days, the fludarabine-based regimens were somewhat better than the alkylator-based regimens in low grade lymphoma, at least in some parameters. The data from two large randomized trials showed that complete response rate, molecular complete response rate and progression-free survival were consistently higher with fludarabine-based regimens.

What happens when you add rituximab to the mix is not clear. Certainly, in both areas, the molecular CR goes up. It will probably continue to be higher in the fludarabine combinations plus rituximab than with the alkylator combinations plus rituximab. No head-to-head comparison has been done, so it is difficult to know which chemotherapy to use with rituximab.

If you evaluate the two randomized trials that utilized straight chemotherapy with or without rituximab — which were CVP and CHOP — CHOP appears to be more active than the CVP; however, we already knew that, at least as far as initial activity and CR rate. Does that translate into a better regimen? I think the meaning of a molecular CR in low grade lymphoma is still debated. Molecular CR clearly leads to a longer remission. Does that lead to longer survival? I think we're becoming more optimistic about that, but it has not yet been proven.

DR BHARDWAJ: Does exposure to fludarabine early on in the treatment course interfere with options down the road?

DR HAINSWORTH: I think it does in some patients, but in general, the answer to that question is no. Whatever you use as initial chemotherapy interferes down the road, and patients have more bone marrow problems as you progress from first- to second- to third- to fourth-line regimen.

DR LOVE: Fernando, it seems that in this situation, the base of the therapy is the rituximab. How much benefit does chemotherapy add? What clinical trial evidence do we have, particularly in terms of survival, regarding the impact of adding chemotherapy in addition to rituximab in this situation?

DR CABANILLAS: Rituximab is a relatively new agent, so we don't have 10-year follow-up data. All we have is relatively short follow-up, perhaps not even five years, and we have molecular remission data that are associated with a longer failure-free survival. We are projecting what's going to happen in the future based on that. A lot of people are using R-CHOP based on the small series that was published by Myron Czuczman from Roswell Park.

Even though the data look intriguing with very good response rates, durations and even molecular remissions, the follow-up is not long enough and the number of patients is small. I think the larger experience is with the FND/rituximab, where more patients have been systematically staged and treated. Czuczman's data covers multiple stages, including Stage IV and earlier stages. The FND/rituximab data is purely Stage IV.

DR MALHOTRA: Fernando, what is your experience with fludurabine-based regimens in terms of immunosuppression, especially in an asymptomatic patient like this one? What do you tell them? Our practice recently almost lost two patients who had pneumocystis pneumonia. We never had that problem with CVP-based regimens.

DR CABANILLAS: That's definitely a risk, which we identified early on in the FND trial. The first FND trial was done as a salvage regimen, and we observed a couple of cases of pneumocystic carinii pneumonia, so we started using sulfamethoxazole and trimethoprim (Bactrim®) prophylaxis during the weekends. We instructed the patients to take one double-strength Bactrim twice a day on Saturdays and Sundays. They do that while they're on treatment and continue for at least three months after they finish the treatment. Since we began doing that, we haven't seen any more pneumocystis.

Now my concern is the cases of hypogammaglobulin anemia that frequently occur. If a patient is receiving a combination of chemotherapy and rituximab, and develops recurrent sinusitis that responds to antibiotics but reoccurs upon cessation of antibiotics, you can bet that the patient is most likely hypogammaglobulinemic. You can treat the patient with gammaglobulin, which will usually cure the problem for several months to a year.

We have also seen patients who have developed a parvovirus infection with marrow aplasia. Again, those cases are patients who develop hypogammaglobulin anemia, so if you give them gammaglobulin, their bone marrow will recover; however, fludarabine has a cumulative toxicity in the bone marrow independent of parvovirus, so you have to be careful to not overtreat.

It's important to stop fludarabine at the first signs of thrombocytopenia; don't wait until the patient becomes severely thrombocytopenic. If a patient develops 90,000 platelets, and they take six to eight weeks to recover, the bone marrow is already intoxicated with fludarabine. If you keep pushing, you're going to run into trouble. You have to strike a balance when you use this kind of regimen, especially in elderly patients.

DR C FARBER: I would like to reiterate two points that our faculty touched on. First, Dr Hainsworth mentioned that he was concerned about the location of the tumor. If you have a lymph node that grows over a period of a few months, it's not a big deal; however, a C-2 lesion could cause spinal cord compression. I think that's critical.

Second, Dr Cabanillas mentioned that it might be worth performing a fine needle aspiration (FNA). That is a relatively inexpensive, low-tech way to evaluate a tumor, and it gives you a definitive answer. If you see transformed cells, it changes your management of this patient. You would go with R-CHOP or something more aggressive.

I think the location and the unusual nature of the tumor begs to determine exactly what you're dealing with.

DR KAPLAN: Can I ask you about fludarabine in the elderly? I had a startling conversation with some folks from Memorial Sloan-Kettering, and they don't use fludarabine in patients older than 70 years of age. How do you feel about that?

DR CABANILLAS: In our trial, age 75 was the cutoff. So, we have treated patients up to age 75.

DR KAPLAN: We've used it in much older patients without much trouble; however, we don't use as much as in many of the clinical trials. We use it for three days in a row and usually give four cycles instead of six, and we rarely run into trouble.

DR CABANILLAS: Your point is well taken. The FND combination is three days of fludarabine, not five days, like with the single agent. That's one of the reasons it's relatively well tolerated.

I think time will tell you how the patient tolerates it. The toxicity is not only acute, but also cumulative, so if you start seeing cumulative toxicity, you know that the patient is heading for trouble.

DR LOVE: I would like to hear about the discussions you have with patients with asymptomatic indolent lymphoma. How do you approach decision-making in that situation, Dr Farber?

DR C FARBER: I don't know if any area of oncology is more complicated than managing low grade lymphomas. It's almost counterintuitive. You sit down with a patient who often is surprised at the diagnosis. "How could this be? I've been healthy my whole life. I've felt that lymph node for months."

The patients have a tough time understanding, and that is appropriate because it's often not curable. Of course, we need more follow-up on the issue of rituximab, but no definitive evidence indicates that early intervention translates to an improved outcome — people living longer or with a better quality of life.

For many people, observation without treatment is counterintuitive. I tell my patients it's akin to being in a war. You know at some point the battles are going to start, but they haven't started yet so there's no need to be shooting off your ammunition. This is a difficult concept for some patients, who say, "The treatment is there. Let's put me in remission."

They have a tough time with the concept of waiting for something to happen because they want to be more proactive. Some people loathe the idea of chemotherapy and would postpone it at all costs. For other people, the concept of just waiting is extremely difficult.

DR RADER: The one thing that's made a difference in the management of these patients is rituximab. I loathed treating lymphomas in the old days. I don't believe any good survival data exist, no matter what treatment you use. We have disease-free survival data but no overall survival data. Rituximab makes it easier because you have some patients who are borderline whom you want to treat.

DR CABANILLAS: In low grade lymphoma, the basis for the watch-and-wait approach is that the disease is considered incurable. First, we need to clarify that the lack of curability holds mostly for Stage IV presentations, which are the majority of cases. Second, the other rationale is that if you cannot cure the disease and you don't need to palliate anything because the patient is asymptomatic, why treat early?

I'm going to say something controversial and no one is going to believe it, but data from the various studies we did over the last 25 years at MD Anderson indicate a plateau in the curve, and that plateau has been increasing through the years as we modified the regimens.

The plateau occurs at approximately eight years, and at 15 years, 40 percent of the patients are alive without evidence of disease. I think people have not realized that there is a plateau, mostly because they've been using single agents or pallia-

tive types of therapy, but also because they haven't followed the patients long enough. If you stop your observation period at five to 10 years, you fail to see that the tail end of the curve plateaus — just as in large cell lymphomas.

I believe that if you treat Stage IV low grade lymphoma appropriately, you can cure a fraction of the patients — not necessarily the majority — but more or less about the same that you cure with large cell lymphoma.

Sandy Horning has a slide she shows that indicates that the survival of low grade lymphoma has not changed for 20 years, which is true at Stanford. But they've been doing the same thing, over and over again. Why would you expect to see a change? We've been changing the regimens every four to five years, when I evaluated our data. I was surprised that we are now seeing a definite plateau in the curve.

DR LOVE: John, agree, disagree, or in between?

DR HAINSWORTH: First, I think his statement that this would be controversial, is true. I believe that these patients have been overtreated with combination chemotherapy for years. I know I'm sounding like a nihilist, which I'm not. We have data from many years of treatment with standard combination regimens of various types, and I'm not sure anybody has, in any controlled way, shown any plateaus on the curves. I would love for that to be true, but I'm not convinced of it yet.

DR CABANILLAS: I would like to respond to that because you said precisely the right word, "standard" therapy. It became evident that when we began to try new things, such as adding interferon, that gave us a better survival and disease-free survival. Then we began alternating regimens, and now, with FND, the plateau in the curve appears better and better.

DR LOVE: What's the number in the rituximab era? Do you have that data at this point?

DR CABANILLAS: The rituximab trials don't have as long of a follow-up, but we have 90 percent of the patients alive at five years. With the simultaneous approach using FND/rituximab, the failure-free survival was around 60 percent at five years. Obviously, that is going to change, because the plateau doesn't seem to occur as early with low grade lymphoma as with large cell lymphoma. It takes approximately eight years.

DR L FARBER: If you have the opportunity to observe these patients to evaluate the pace of the disease over time, you'll have a much better feel than if you're asked to make a decision at one point in time. We all have to listen and respond to the patient, and many patients will not accept a watch-and-wait approach no matter how persuasive we try to be.

We might be able to convince them to try it for a week or two, but they come to us because they want us to do something for them now. Where I live, few patients seek second consultations and opinions, so it's a little easier. I'm a therapeutically oriented oncologist and I've always had difficulty watching and waiting. The era of rituximab makes it a lot easier to not watch and wait.

Nonetheless, I think that we have to listen to our patients. Some patients are going to accept the concept of watching and waiting, while other patients are going to say, "This is just not for me. I am not sleeping at night because I can't stand to live with this cancer." It requires a tremendous amount of persuasion and I think rituximab offers us somewhat of an out — maybe not an easy out, but an out nonetheless.

DR C FARBER: Those patients call it "watch and worry."

DR LOVE: Dr Farber, how do you approach the issue of whether to utilize chemotherapy in addition to rituximab? It reminds me a little bit of the breast cancer situation with trastuzumab. Are you going to use trastuzumab alone in metastatic disease or add in chemotherapy? Research leaders in breast cancer often start with trastuzumab alone

and then add in chemotherapy if the patient is not doing well. Is that an approach you utilize in NHL as it relates to rituximab?

DR C FARBER: I agree with that. For the patient who really needs some form of treatment, you don't want to do any harm. Fludarabine, given long term, causes immunosuppression and myelosuppression. Rituximab is a good agent to start with, and it offers the patient real response rates.

I think a relatively low morbidity occurs with rituximab, and it can be used repeatedly. In many ways, it's a good agent for use in those patients because they feel more proactive.

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CASE 4: A 73-year-old man who carries a primary diagnosis of diffuse small cell lymphoma. The patient was initially treated with CVP and subsequently FCR, but then develops worsening lymphadenopathy, anemia, fatigue and a WBC of 34,400 (from the practice of Dr Michael Rader)

Edited excerpt from the discussion:

DR LEONARD: We're facing an older gentleman who's had prior treatment. He has a combination of diffuse mixed cell and diffuse small cell lymphoma. His presentation is consistent with chronic lymphocytic leukemia (CLL). He may also have a leukemic spread of an indolent lymphoma, potentially follicular or mantle cell lymphoma.

My first question is: Are we sure of his diagnosis? Peripheral blood immunophenotyping might be helpful in that regard. My second question would be: Is his high white count the main issue? From what you have said, it sounds like the major problem is anemia and cytopenia, and not so much the nodes.

DR RADER: He also had constitutional symptoms — weight loss, but no fever or sweats. The flow cytometry was positive for CD20, CD5, CD19, CD23, CD38, CD45 and CD52. He was also noted to have some cytogenetic abnormalities — deletion of 11q and trisomy 12.

DR LEONARD: His presentation seems consistent with CLL. Are the nodes much of an issue right now or is it mainly the constitutional symptoms?

DR RADER: It's mainly the constitutional symptoms.

DR LEONARD: The issue here is how we approach him, because he has an indolent lymphoproliferative disorder. The blood counts and the bone marrow are the main issue. He's already had some pretty good treatment regimens. His last treatment was FCR, which he tolerated well. He's had several years of remission with FCR, so you could potentially treat him with that again. Another approach would be to treat him with alemtuzumab, which is approved in this population of patients. This agent is particularly effective in the blood and the bone marrow, and less effective for the nodes; therefore, if you are dealing with nodal disease, alemtuzumab might not be as effective.

I think that either of these options is quite reasonable. It's a matter of balancing out how well he tolerated FCR, and the positive and negative aspects of the regimen. Toxicities occur with the FCR regimen and with alemtuzumab. I'm not certain that one approach is better than the other. I probably would lean toward alemtuzumab.

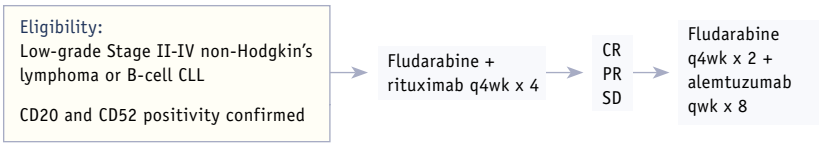
DR SMITH: I would also lean toward alemtuzumab, since he hasn't had it yet. A number of regimens could be considered: FCR again; FR without C, which may be less toxic; or prednisone/cyclophosphamide/rituximab, which is another option.

I agree, it sounds as though this patient has CLL. He has trisomy 12, which is correlative and CD-38 positivity, which is a poor prognostic factor in general. One could also evaluate patients for ZAP-70, but that won't change day-to-day treatment. These indicators put the patient in a favorable- or poor-risk group, and you still have to consider the pace of the disease.

DR RADER: We decided to enroll him in one of our active clinical trials, which offered a combination of fludarabine and rituximab (4.1). In the trial design, at the end of four months the patient would be restaged, and if there was no evidence of active disease, started on alemtuzumab.

4.1 Phase II Study of Fludarabine, Rituximab and Alemtuzumab for Indolent Lymphoma and CLL

Protocol ID: WIRB 20030625



CLL = chronic lymphocytic leukemia; CR = complete response; PR = partial response; SD = stable disease

Study Contact:
David Savage, MD
New York Presbyterian Hospital
Tel: 212-305-8615

SOURCE: Columbia Presbyterian Cancer Center Protocol, July 2004.

He was started on fludarabine/rituximab as part of that study, and at the end of the fourth cycle, his white count was really low — in the range of about 1,000 to 1,500 — with a relatively low ANC. At that point, we evaluated his bone marrow. The marrow revealed erythroid hyperplasia and persistent evidence of small-cell lymphoma/CLL in the blood. At that point we elected to continue the protocol and put him on alemtuzumab.

After approximately a month and a half of the alemtuzumab, we became concerned because his white count never increased. It remained in the 1,000 to 1,800 range, with no evidence of infection.

A repeat bone marrow biopsy at that point revealed that his cytogenetic abnormalities had cleared. The 11q and trisomy 12 had disappeared and flow cytometry was normal.

Chromosome studies on bone marrow revealed no evidence of MDS. The patient has remained persistently leukopenic to this time, with an ANC of approximately 1,000 and total white count of approximately 1,500. He is afebrile, his hemoglobin is in the 11 to 12 range, and his hematocrit is 33. Computed tomography revealed marked resolution of his lymphadenopathy.

We had him on Bactrim prophylaxis, which we usually continue until the CD4 counts return to normal. Later on, we decided to stop the Bactrim. He's currently chugging along with a mild anemia and is doing quite well. He actually had a cytogenetic remission as a result of the alemtuzumab treatment, which I thought was impressive.

DR LOVE: John, could you comment on the case?

DR LEONARD: It seems like he's had a good response, but I think the real question is: Why is he persistently cytopenic? I think you've done a good job chasing after that. Obviously, residual lymphoma would be one possibility, and an autoimmune process could be another. The marrow is consistent with that, although it sounds like his biggest issue is his neutropenia more so than his erythroid lineage.

Myelodysplasia, which can be associated with the FCR regimen, is certainly in the differential diagnosis, but you have utilized cytogenetics to rule that out. The FCR regimen is obviously immunosuppressive, so it may be CMV or a related infectious process; however, it sounds like he's not systemically ill. Perhaps he has low-level myelodysplasia that you're not detecting, or

profound cytopenia, which is occasionally evident after a fludarabine-based regimen.

DR GOLDBERG: One of the problems with fludarabine is that some patients become cytopenic. It is hard to predict which ones, but even after one treatment, they can be left with profound cytopenia that becomes problematic and prevents further therapies. Do you have any evidence of which patients might be at risk for this and how you deal with it?

DR SMITH: I don't know that we have any a priori notion of whom it's going to affect. I think it relates to the number of cycles. Clearly, when you combine fludarabine with other drugs — FC or FN — the combination is a lot more myelosuppressive than fludarabine alone, and it is cumulative.

This patient was initially treated with fludarabine for six months and then, three years later, was treated for another four months. The addition of rituximab seems to enhance the myelosuppression, so this patient has had a lot of fludarabine in combination with other agents. I believe that is one of the more predisposing factors in addition to age, prior therapy, etc. I don't think we can predict it up front; however, I do see it more frequently with the fludarabine combinations.

DR VOGEL: Do you think pentostatin would have been a better choice here in terms of reducing bone marrow toxicity?

DR LEONARD: It's hard to say. I'm not aware of any randomized studies comparing these regimens. From my perspective, the choice between these approaches is based on personal preference. We all tend to become familiar with a regimen — either one learned in training or one we have a lot of experience with — and we stick with it. I believe that it is probably more important to select a regimen that you're comfortable with, rather than focus on the subtle differences between regimens.

DR LOVE: Mike, what are your concerns for the future for this patient?

DR RADER: My major concern is infection because of the low ANC. I can treat the red cell series with erythropoietin; however, I can't justify putting him on chronic white cell growth factors because he is asymptomatic and I anticipate that his CD4 counts are going to rise.

We chose this treatment regimen because it was part of a clinical trial investigating the role of alemtuzumab in CLL, which I felt was important because of associated toxicities. I find it interesting how he didn't respond initially to the repeat FR treatment, but subsequently responded to the alemtuzumab part of the trial. The trial is still accruing, so we don't have the final results, but I was extremely impressed with the reversal of cytogenetics in this patient.

DR LOVE: Dr Leonard, how do you think you would approach this patient if he does have progressive disease and is still neutropenic?

DR LEONARD: I think it's going to be very tough. I would probably re-evaluate his marrow and if he has progressive disease in the marrow I may be more inclined to treat him more intensively. Overall, I would reassess the marrow and focus on symptomatic treatment. If it were a nodal disease, perhaps I would consider radiation.

DR RADER: Now that we've had resolution of the cytogenetic abnormalities, do we have any data on how these patients do? Once again, he has poor prognostic markers. Does resolution of the cytogenetic abnormalities produce a longer-term response? What's the data on that, looking at this over the long term?

DR SMITH: I'm not sure I can quote any specific data on that. It's evident that the deeper your response, the better you do. Therefore, a patient who is PCR-negative would do better. I don't know of any data with alemtuzumab that has a long enough follow-up to indicate that the patient is going to do better. With every other disease and every other marker, the increasingly smaller proportion of patients who have reached that definition of response clearly do better.

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Smolewski P et al. **Proapoptotic activity of alemtuzumab alone and in combination with rituximab or purine nucleoside analogues in chronic lymphocytic leukemia cells.** *Leuk Lymphoma* 2005;46(1):87-100. **Abstract**

Thieblemont C et al. **Maintenance therapy with a monthly injection of alemtuzumab prolongs response duration in patients with refractory B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (B-CLL/SLL).** *Leuk Lymphoma* 2004;45(4):711-4. **Abstract**

CASE 5: A 50-year-old man with cutaneous Bcl-2-positive follicular lymphoma presenting with eight skin nodules on the chest wall; workup revealed no other evidence of lymphoma (from the practice of Dr Subhash Gulati)

Edited excerpt from the discussion:

DR LEONARD: We have a patient who has skin-only involvement with follicular lymphoma. In general, I think skin involvement of lymphoma is among the more difficult pathologic diagnoses to make. This is one scenario in which eliciting an opinion from an experienced hematopathologist or dermatopathologist is important. Pathologists often have different opinions in this situation. The type of lymphoma isn't always clear because lymphoid proliferations can arise in the skin for many reasons.

That being said, an interesting issue is MALT lymphoma (MALToma) of the skin, which is one of the more common B-cell subtypes. Some association has been made between MALToma of the skin and infectious agents; therefore, it's something I always consider. Although this patient has a follicular lymphoma, not a MALToma, I wonder whether we should chase after that a little bit.

With those kinds of sidebars, I think a patient with a follicular lymphoma of the skin who has no disease elsewhere is likely to do well in the long term. Often these patients will have disease that, for whatever reasons, recurs only in the skin. These are four-millimeter lesions, so I would be inclined to do relatively little — topical steroid treatment, local radiation or no therapy.

Whether or not you chase after the skin lesions is a clinical judgment based on the scenario. I'm not sure systemic therapy, whether it is rituximab or chemotherapy, is going to change the big picture for this patient. I don't know that we have any randomized trials showing that systemic therapy makes a difference. My inclination would be to do less, rather than more.

DR LOVE: From a psychosocial perspective, do you think the patient and his wife would have been able to accept watchful waiting?

DR GULATI: No. That was the major issue. Watchful waiting was offered to them, but they are clearly the nervous type. They chose rituximab, which we gave weekly for four weeks followed by monthly for four months, for a total of five months.

DR LOVE: What happened to the lesions?

DR GULATI: The lesions disappeared by the second treatment. The patient was doing fine, but he was obviously worried. Every time he came in, we would discuss the issue. An episode occurred during which the patient said he felt like fainting. He was rushed to the emergency room where he had a full coronary workup, but everything was normal.

I called him before this conference and he said he has a few new skin lesions near the initial site. The patient was anxious; he did not want these lesions on his skin. If a remission occurred, it lasted only about nine or 10 months. This is a Bcl-2-positive lymphoma, so I don't think that it is follicular or lymphoid hyperplasia. He's going to come in and have a biopsy, and the question will arise: What will be the next treatment?

DR C FARBER: I would be inclined to utilize electron beam radiation therapy with a wide field and an adequate margin in this patient. That would probably prevent at least a local recurrence. The lesions may keep recurring just outside the field, in which case it's almost like spot welding. Electron beam

therapy offers a low morbidity and it should be effective.

DR LOVE: What about electron beam therapy in this situation, Dr Leonard?

DR LEONARD: I think it's certainly reasonable if the lesions are in the same area. It is probably not going to change his long-term outcome. You're not going to prevent recurrence elsewhere by removing these lesions. It's a matter of just chasing after them. It may reach a point at which you question whether it is worth the effort. If you treat him and then a month later a lesion pops up somewhere else, you start to wonder if it may be easier for him to receive a couple "squirts" of rituximab and go into remission, rather than undergo re-treatment.

Again, that's a clinical judgment. I'd be inclined to do less, rather than more. If you're forced to treat him, I think it's a matter of the time and effort involved in chasing after this, which is really psychological palliation more than anything.

DR RADER: At some of the breast cancer meetings, we discuss immunohistochemistry for ER and how unreliable it is.

In patients with lymphoma, I've seen multiple different opinions on whether cells have been transformed — whether they're large or small cells — or whether the flow cytometry agrees with the histological picture. Do you believe that, routinely, most lymphomas should have a second pathology opinion. When the second opinions are widely divergent, what type of evidence do you evaluate next?

Second opinions are often 180 degrees different. These opinions influence therapy — like CHOP versus watchful waiting — so should second opinions be routine?

DR SMITH: I see a lot of patients who were referred to me for a second opinion, and when I discuss the case with the referring doctor, it's clear that I'm going to not change the oncologist's opinion. However, whether it's low grade or aggressive lymphoma, the key to a second opinion is a review of the pathology.

Approximately a third of the time we will have a change regarding pathology. Often the change is minor; however, sometimes it is major, making it low grade versus aggressive — particularly when the lymphoma is in extranodal sites, such as the stomach or skin. Second opinions are critical, but then what do you do? Is it best two out of three?

In community practices, I find that the slides are usually analyzed locally, and the flow goes to someone at an outside lab who knows nothing about the patient or the physician. At our place, after I've seen the patient, I sit down with my hematopathologist, who also does the flow. We discuss the issues, and come up with something. It's not so much that the stain or the flow is wrong, but that you have to put the whole picture together before it can make sense. That's one of the concerns, particularly if you're in a small hospital.

DR LEONARD: I agree; it is easy to ascertain a pathologic second opinion — it's simply a matter of sending the slides; the patient doesn't have to go. Generally, pathologists will discuss it with you over the phone, even if you're at another institution. It's not a big deal to do, and the pathology is key. I believe a pathologic second opinion is more important than another lymphoma subspecialist's opinion. We re-evaluate a situation based on our pathologist giving us information that the primary oncologist didn't have; therefore, I encourage patients to ascertain a pathologic second opinion. It is a relatively easy thing to do, and it gives the patients some reassurance.

I think all patients diagnosed with mantle cell lymphoma should also have a second pathology opinion. That's a hard diagnosis to make and the implications, as far as the prognosis, are enormous. Additionally, if the disease is acting like one type of lymphoma, but the pathologist is telling you it's another type of lymphoma, maybe that's a red flag that you ought to have it evaluated by someone else.

Finally, gray areas exist when you see follicular and diffuse lymphomas, and you are trying to decide if transformation has

occurred and whether you need to use an anthracycline — this is an area in which I would encourage a second opinion from the pathological standpoint.

DR BHARDWAJ: Some changes have occurred in terms of how the insurance companies are reimbursing for second opinions. At some institutions, the Pathology Department is now billing the hospital Pathology Department, and not the patient. That puts a crimp in terms of where the patients' slides are being sent.

DR LEONARD: Second-opinion slides are the best spent $300 or $500 that a patient will invest. Even if you have to tell the patient, "Insurance isn't going to cover it," this has such important implications, at least in lymphoma, that if the patient can do it, even if they have to pay out of pocket, I encourage it.

DR SMITH: A more difficult situation is when patients have large cell lymphoma isolated to the skin, because it looks ugly but often behaves indolently. Can you give rituximab as a single agent or local radiation to a patient who, histologically, has large cell lymphoma? According to the literature, large cell lymphoma in the skin tends to behave more indolently. That is a second opinion that we see often, and my reply is, "Maybe you need to be aggressive with this tumor."

DR LOVE: Any hints in terms of pathophysiology of cutaneous lymphoma in terms of why it has this natural history?

DR SMITH: As John mentioned, the MALTomas of the skin might be infection-driven. We don't know much about the lymphocytes that are normally in the skin, why they home there and how they behave day to day. There is probably something there that we should be learning about, but we don't know that much about it.

DR LOVE: Dr Gulati, how are you going to treat this patient?

DR GULATI: My previous experience with electron beam, especially for large cell lymphoma, has not been good. This is the first time I've seen a follicular Bcl-2-positive, so I'm open-minded. Rituximab worked; therefore, I am tempted to give more rituximab although the remission didn't last more than seven months. The story is incomplete. I think the workup will be important. If he has positive lymph nodes, then he's going to receive chemotherapy.

Select publications

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Hsi ED. **Pathology of primary cutaneous B-cell lymphomas: Diagnosis and classification.** *Clin Lymphoma* 2004;5(2):89-97. **Abstract**

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CASE 6: A 37-year-old man with a Grade I follicular lymphoma treated with CVP with an apparent allergic reaction after rituximab infusion (from the practice of Dr Sushil Bhardwaj)

Edited excerpt from the discussion:

DR LEONARD: Allergic reactions to rituximab are rare. The spectrum of what is an allergic reaction versus what is an infusion reaction overlaps. It's hard to say one way or another. Most patients will tolerate rituximab without a problem, but in this situation, the questions are: How hard do you want to work at it and how important is it?

One approach would be to admit the patient to the hospital and give the rituximab over 24 hours, which we have done on occasion. However, that is inconvenient for both the patient and physician.

I would do what John Byrd has done in CLL. Perhaps pre-medicate with a steroid and then give 40 or 50 milligrams of rituximab over three or four hours. Then give another 50 or 100 milligrams the next day, perhaps dividing the dose over three days to see how the patient responds. If the patient is tolerant, then you know that it is not an allergic reaction, and you will probably be able to give subsequent doses more quickly.

DR LOVE: What's the mechanism or pathophysiology of an infusion reaction versus an allergic reaction?

DR LEONARD: Most infusion reactions are related to complement and the fact that you are binding B cells, which activate complement. When more circulating tumor cells are present, greater complement activation by B cells occurs, which leads to more cytokine activation.

I'm not certain that steroids help much in preventing infusion reactions; however, in a patient like this, when you don't know exactly what you're dealing with, you need all of the help you can get. Give this patient plenty of diphenhydramine and some steroids.

Select publications

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CASE 7: A 55-year-old woman with mantle cell lymphoma hospitalized with neutropenic fever during the course of hyper-CVAD (from the practice of Dr Leonard R Farber)

Edited excerpt from the discussion:

DR LEONARD: The bottom line with mantle cell lymphoma is that R-CHOP is not enough as far as up-front therapy. I would consider clinical trials of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) with rituximab with or without a transplant, or R-CHOP with a transplant, unless the patient is not a candidate.

You have chosen the hyper-CVAD/rituximab path, which is reasonable and appropriate. The questions are: Do you pursue a full course of rituximab/hyper-CVAD and stop?

Do you pursue a full course of hyper-CVAD and an autologous transplant, an abbreviated course of hyper-CVAD and an autologous transplant, or either of those with an allogenic transplant or perhaps a mini-allogenic transplant?

No randomized trials exist to guide us. The MD Anderson data suggest that hyper-CVAD with an autologous transplant is similar to rituximab/hyper-CVAD without an autologous transplant, so a question arises over whether you need to do an autologous transplant if you're going to give the full course of R-hyper-CVAD.

Another question would be: Do you just stop the R-hyper-CVAD and go to an autologous transplant? To some degree, it's six of one, half a dozen of another. Knowing the problems that she's had with the hyper-CVAD, I probably would not push ahead with that treatment at this point.

There is no guarantee that she's going to continue to have these problems, but on the other hand, they may continue. Realistically, the difference is three or four months of treatment versus doing an autologous transplant, which involves spending a month in the hospital.

I would be inclined to do the autologous transplant. I think she's demonstrated that she's got chemotherapy-sensitive disease.

She's a young patient with a rapid CR and chemotherapy-sensitive disease. My inclination is that chemotherapy-sensitive patients benefit the most from autologous transplant.

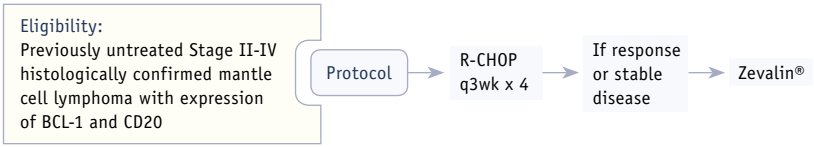
The question of an allogenic transplant is always an issue. Do you do that now? Do you do that down the line if she has a relapse after her autologous transplant? No data exist but I would lean toward stopping the hyper-CVAD, doing the autologous transplant, and hoping for the best. Probably five reasonable pathways could be followed, and it will be a complicated discussion with the patient. Given that her experience with hyper-CVAD hasn't been a picnic, how will she feel about a transplant?

DR SMITH: I want to throw in an advertisement for the ECOG E-1499 trial, which is a Phase II trial of R-CHOP for four cycles followed by ibritumomab tiuxetan (Zevalin®) (7.1). I agree that R-CHOP is not adequate in this situation; it gives you about an 18-month duration of remission; however, R-CHOP plus something — whether it is transplant or Zevalin — is a reasonable research question that should be evaluated on a research study, not off study.

As John mentioned, rituximab/hyper-CVAD probably equals hyper-CVAD followed by autologous transplant. At this point, I would agree it's a question of balancing. What's the risk of her having a complication from the methotrexate/cytarabine cycle versus complication from an autologous transplant? Again, that is a gut decision.

7.1 Phase II Study of R-CHOP followed by Zevalin®

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



R = rituximab; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone

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

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

SOURCE: NCI Physician Data Query, January 2005.

DR KAPLAN: What's the role of bortezomib in this group of patients?

DR SMITH: Evidence indicates that it's active in relapse disease. Certainly, when you have an active drug, one immediately thinks, "Well, I didn't cure the patient with R-CHOP, maybe I should give maintenance or give rituximab/bortezomib/CHOP." One could consider a lot of things, but no real data exist.

Some other interesting drugs are being investigated for use in mantle cell lymphoma. The rapamycin analog, CCI-779, has been evaluated in a couple of clinical trials. Tom Witzig did a Phase II study that showed significant activity. Some new drugs that are not typical lymphoma drugs also look interesting for treatment of mantle cell lymphoma; however, you still have the complicating factors — which combinations and when to use them, etcetera. If R-CHOP were not adequate, would you be willing to use a brand new agent up front or in combination with R-CHOP?

These are the issues we address in group discussions regarding what trial to propose next. Most of us believe that a national trial with rituximab/hyper-CVAD is not going to accrue well because even young, healthy patients have trouble tolerating that regimen.

DR LOVE: What do you think you're going to do, Len?

DR L FARBER: She's being harvested tomorrow.

Select publications

Bertoni F et al. **Mantle cell lymphoma.** *Curr Opin Hematol* 2004;11(6):411-8. **Abstract**

Ghielmini M et al. **Effect of single-agent rituximab given at the standard cycle or as a prolonged treatment in patients with mantle cell lymphoma: A study of the Swiss Group for Clinical Cancer Research (SAKK).** *J Clin Oncol* 2004;[Epub ahead of print].

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Witzig TE et al. **A phase II trial of therapamycin analog CCI-779 in previously treated mantle cell non-Hodgkin's lymphoma: Interim analysis of 18 patients.** *Proc ASH* 2003;**Abstract 2374**.

CASE 8: A 72-year-old man presented with abdominal pain. Endoscopy revealed a B-cell, diffuse large cell, non-Hodgkin's lymphoma with evidence of transformation from a helicobacter-associated MALToma, positive for Bcl-6 (from the practice of Dr Charles Farber)

Edited excerpt from the discussion:

DR HAINSWORTH: We have moved away from routine surgery for gastrointestinal lymphomas, particularly for gastric lymphomas with which we have a fair amount of experience with chemotherapy. Although no randomized trials are perfect, several large series have had similar results. The initial concern about chemotherapy and gastric perforations has not proven to be a common complication; therefore, that concern has decreased in importance in people's minds when considering initial treatment.

DR CABANILLAS: We have to be careful interpreting the data on the use of antibiotics in these cases. If you evaluate the patients with gastric lymphoma who have large cell lymphoma and MALToma, frequently the area of large cell lymphoma might be small, and the predominant tumor bulk might be low grade MALToma.

If you treat these patients with antibiotics, the tumors may shrink but you might miss an area of residual large cell lymphoma because the endoscopies are not always able to identify it.

Anecdotal data in the literature show that the antibiotics don't work when the tumor transforms into large cell lymphoma. One of the mistakes an inexperienced gastroenterologist can make when they stage these patients is obtaining only one biopsy because they might miss an area of large cell lymphoma; therefore, it is always important to obtain multiple biopsies.

I had a patient whom I managed in consultation, who had been diagnosed with MALToma, treated with antibiotics and had a response, but also had a residual tumor mass. A repeat biopsy revealed evidence of large cell lymphoma that had not been diagnosed initially, so it can be tricky.

Most patients, who have a large tumor mass, even if it's low grade MALToma, do not respond to antibiotics. The ones who respond well to antibiotics are those with a superficial gastritis type of presentation. Years ago, we published data in the *Annals of Internal Medicine*, which showed that patients who have large tumor masses or large ulcerations and have endoscopic appearance of transmural disease don't respond to antibiotics the majority of the time. I believe that approximately one third of the patients respond, but the majority of patients do not.

Even if a patient did not have large cell lymphoma — just a large tumor mass and low grade lymphoma — eventually that patient will likely require more treatment than antibiotics. It is good to start with antibiotics to treat the Helicobacter pylori and prevent the induction of some other malignancy, including gastric cancer; however, most patients will eventually require radiation.

DR C FARBER: I can tell you anecdotally that I have seen three such patients. I presented the case of one that did not respond to the anti-H pylori treatment; however, in my experience, one out of the three had full regression of the lymphoma, including the large cell component. I'm one for three, whereas the literature suggests 10 out of 15.

Select publications

Calvert R et al. **Genetic abnormalities during transition from Helicobacter-pylori-associated gastritis to low-grade MALToma.** *Lancet* 1995;345(8941):26-7. **Abstract**

Datta YH et al. **Rituximab-induced remission of a gastric MALT lymphoma.** *Leuk Lymphoma* 2004;45(6):1297-9. **Abstract**

DeJong D et al. **Histological grading with clinical relevance in gastric mucosa-associated lymphoid tissue (MALT) lymphoma.** *Recent Results Cancer Res* 2000;156:27-32. **Abstract**

Du MQ, Isaacson PG. **Gastric MALT lymphomas: From aetiology to treatment.** *Lancet Oncol* 2002;3(2):97-104. **Abstract**

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Inagaki H et al. **Gastric MALT lymphomas are divided into three groups based on responsiveness to Helicobacter pylori eradication and detection of API2-MALT1 fusion.** *Am J Surg Pathol* 2004;28(12):1560-7. **Abstract**

Isaacson PG, Du MQ. **Gastrointestinal lymphoma: Where morphology meets molecular biology.** *J Pathol* 2005;205(2):255-74. **Abstract**

Jaskiewicz K, Kobierska G. **Lymphoid aggregates in gastric biopsies: Relationship to other mucosal lesions.** *Arch Immunol Ther Exp* (Warz) 2000;48(3):201-4. **Abstract**

Marshall BJ, Windsor HM. **The relation of Helicobacter pylori to gastric adenocarcinoma and lymphoma: Pathophysiology, epidemiology, screening, clinical presentation, treatment, and prevention.** *Med Clin North Am* 2005;89(2):313-44. No abstract available

Martinelli G et al. **Clinical activity of rituximab in gastric marginal zone non-Hodgkin's lymphoma resistant to or not eligible for anti-Helicobacter pylori therapy.** *J Clin Oncol* 2005;[Epub ahead of print]. **Abstract**

Morgner A et al. **Helicobacter-induced expression of Bcl-X(L) in B lymphocytes in the mouse model: A possible step in the development of gastric mucosa-associated lymphoid tissue (MALT) lymphoma.** *Int J Cancer* 2001;92(5):634-40. **Abstract**

O'Rourke JL et al. **Gastric B-cell mucosa-associated lymphoid tissue (MALT) lymphoma in an animal model of 'Helicopacter heilmannii' infection.** *J Pathol* 2004;203(4):896-903. **Abstract**

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- Critically evaluate the clinical implications of emerging clinical trial data in non-Hodgkin's lymphoma (NHL) treatment and incorporate this 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 alone and in combination with chemotherapy for patients with NHL, and counsel appropriately selected patients about the risks and benefits of these agents. . . . . 5 4 3 2 1 N/A
- Describe and implement an algorithm for sequencing of therapies in the management of indolent and aggressive NHL. . . . . 5 4 3 2 1 N/A

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Faculty	Knowledge of subject matter	Effectiveness as an educator
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