Second Opinion

Case-Based Discussions on the Management of Non-Hodgkin Lymphomas and Chronic Lymphocytic Leukemia

Proceedings from a Satellite Symposium Preceding the 50th ASH Annual Meeting

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OVERVIEW OF ACTIVITY

Non-Hodgkin lymphomas (NHL) constitute a heterogeneous group of lymphoproliferative disorders. NHL is an area of active research and represents a rapidly evolving field in medical oncology. Published results from ongoing clinical trials lead to the continual emergence of new therapeutic agents and strategies. To bridge the gap between research and patient care, these proceedings from a case-based CME satellite symposium at the 2008 American Society of Hematology Annual Meeting utilize the perspectives of clinical investigators, in addition to the interactive exchange between these individuals, to apply evidence-based concepts to routine clinical care. By providing access to the latest research developments and expert opinions on the disease, this activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of up-to-date clinical management strategies for NHL and chronic lymphocytic leukemia (CLL).

LEARNING OBJECTIVES

- Recount the natural history of CLL, and assess the rational indications for initiation of medical intervention with cytotoxics, monoclonal antibodies and immunomodulatory agents.
- Develop a treatment algorithm to optimize clinical outcomes and quality of life for patients with newly diagnosed or relapsed/refractory follicular lymphoma.
- Identify tolerable and efficacious systemic regimens for patients with diffuse large B-cell lymphoma (DLBCL) and advanced age or preexisting comorbidities.
- Discuss treatment options, including standard or intensive induction therapy and autologous stem cell transplant, with patients who have newly diagnosed mantle-cell lymphoma.
- Counsel patients with indolent or aggressive lymphoma about the risks and benefits associated with maintenance therapy.
- Assess the utility of current systemic therapies and/or allogeneic stem cell transplant in the management of advanced cutaneous T-cell lymphoma (CTCL).

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This program is supported by an educational grant from Genentech BioOncology/Biogen Idec.

Last review date: March 2009; Release date: March 2009; Expiration date: March 2010

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Bonus case discussion available on the audio CD and online at www.ResearchToPractice.com.

A 77-year-old man with a 20-year history of cutaneous T-cell lymphoma has undergone successful photophoresis for the past five years. Six months ago, swelling and ulceration of multiple plaques appeared and the patient no longer responded to photophoresis or topical agents. The base of one of the skin lesions was biopsied and was found to be diffuse large T-cell lymphoma (from the practice of Charles M Farber, MD, PhD)

Case 1 from the practice of Michael A Schwartz, MD

A 53-year-old man presented with an incidental white blood cell (WBC) count of 16,000/mm^3. Flow cytometry was consistent with CLL (positive for CD5 and CD23 coexpression). No palpable lymphadenopathy, splenomegaly, anemia or thrombocytopenia were present. His absolute neutrophil count was 1,000 to 1,500/mm^3. Immunoglobulin levels were normal, along with an absence of ZAP-70 expression and chromosome 13 deletion.

For three years the patient was observed off treatment with a slowly rising WBC count. Some months later he was hospitalized for pneumonia with neutropenia. WBC was 174,000/mm^3, hemoglobin 12 g/dL with a normal platelet count.

The plan was to treat him with fludarabine/cyclophosphamide/rituximab (FCR). In light of his elevated WBC count, he did not receive rituximab with the first cycle. On the second cycle of treatment, he developed Sweet syndrome — acute febrile neutrophilic dermatosis.

SOURCE: Track 1

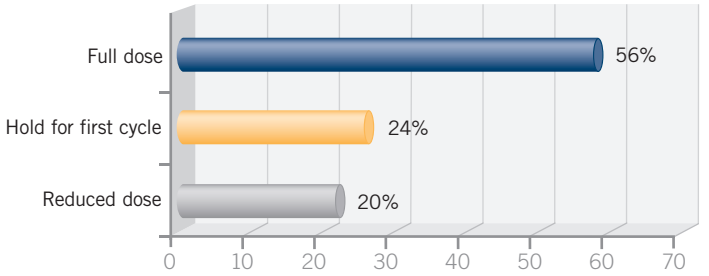
Tracks 2, 4

DR LOVE: Stephanie, can you comment on the issue of use of rituximab with the first cycle of FCR in this patient?

DR GREGORY: I believe many of us have been able to administer the full dose of rituximab in this situation (1.1). Some of the clinical trials administered 100 mg/m^2 initially and the rest during the first week. Sometimes, if I have a patient with an extremely high WBC count and a large tumor burden, I may administer the chemotherapy and then the rituximab after.

1.1

Which of the following would be your most likely approach for the first treatment cycle of FCR with regard to the administration of rituximab?



SOURCE: National Survey of 75 US-Based Medical Oncologists, November 2008.

DR LOVE: What is the specific concern?

DR GREGORY: With the early data on rituximab in patients with high WBC counts, some developed a cytokine release syndrome (Winkler 1999).

You have to be cautious in delivering rituximab to patients with a notably high tumor burden and a high WBC count. The same syndrome occurs in patients with mantle-cell lymphoma who have a leukemic phase.

DR LOVE: What are some of the new agents being studied in CLL?

DR GREGORY: Many new drugs are available. Chlorambucil has been the standard for these patients. Many drugs have been compared to it in the front-line setting, and they appear to be better, but probably not with a difference in overall survival.

The one exception is the patient with a 17p deletion. If this deletion is found in a young patient, you should consider alemtuzumab and early transplant. For an older patient, perhaps alemtuzumab should be considered. Alemtuzumab has been somewhat effective against a 17p abnormality (Lozanski 2004).

Many physicians prefer fludarabine-based regimens with or without rituximab, and most will add rituximab. Bendamustine was recently approved for the treatment of CLL. It was compared to chlorambucil as front-line therapy (Knauf 2008).

Of all the regimens, FCR has certainly been found to be highly effective (Hallek 2008; [1.2]). I'd like to point out that pentostatin/cyclophosphamide/rituximab (PCR) is also a highly effective regimen (Kay 2007; Lamanna 2006) in this setting.

DR LOVE: Ian, any comments about bendamustine for CLL?

DR FLINN: In the United States, we are now getting our first experience with bendamustine, and it's not clear how the toxicity will play out. Personally, I am not using it in the front-line setting, but I use it in the salvage setting.

DR LOVE: What about alemtuzumab, John?

DR LEONARD: When it was initially developed, alemtuzumab was recommended for patients with highly refractory or heavily pretreated disease. So a lot of immune dysfunction, infections and complications occurred. These issues are being addressed with improved supportive care and the use of alemtuzumab in earlier-stage disease. I believe we're still sorting out how we should use it in combination with other treatments. I've used alemtuzumab primarily as a single agent rather than in combinations.

DR LOVE: Mitch, what about lenalidomide?

DR SMITH: Lenalidomide has activity in lymphoma and CLL. The concern is how to use it. We thought we knew how to use it for myeloma. However, when that approach was transferred to CLL, at those doses, tumor lysis syndrome occurred. Several abstracts from this ASH meeting discuss the use

of lenalidomide at a lower dose for patients with CLL (Chen 2008; Ferrajoli 2008). ■

1.2

Phase III Randomized Trial of Fludarabine/Cyclophosphamide/ Rituximab (FCR) versus Fludarabine/Cyclophosphamide (FC) as First-Line Therapy for Advanced CLL

(Median follow-up of 25.5 months)

Efficacy

	FCR (n = 390)	FC (n = 371)	*p*-value
Overall response rate	95.0%	88.0%	0.001
Complete response rate	52.0%	27.0%	<0.0001
	FCR (n = 400)	FC (n = 387)	
Two-year PFS	76.6%	62.3%	<0.0001
Two-year OS	91.0%	88.0%	0.18

PFS = progression-free survival; OS = overall survival

"Treatment with FCR chemoimmunotherapy improves response rates and PFS when compared to the FC chemotherapy. FCR caused more neutropenia/leukopenia without increasing the incidence of severe infections. These results suggest that FCR chemoimmunotherapy might become the new standard first-line treatment for physically fit CLL patients."

SOURCE: Hallek M et al. *Proc ASH* 2008;**Abstract 325**.

SELECT PUBLICATIONS

Bidyasar S et al. **Sweet syndrome associated with granulocyte colony-stimulating factor.** *J Clin Oncol* 2008;26(26):4355-6. No abstract available

Chen C et al. **A phase II study of lenalidomide in previously untreated, symptomatic chronic lymphocytic leukemia (CLL).** *Proc ASH* 2008;**Abstract 44**.

Ferrajoli A et al. **Lenalidomide as initial treatment of elderly patients with chronic lymphocytic leukemia (CLL).** *Proc ASH* 2008;**Abstract 45**.

Hallek M et al. **Immunochemotherapy with fludarabine (F), cyclophosphamide (C), rituximab (R) (FCR) versus fludarabine and cyclophosphamide (FC) improves response rates and progression-free survival (PFS) of previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL).** *Proc ASH* 2008;**Abstract 325**.

Kay NE et al. **Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia.** *Blood* 2007;109(2):405-11. **Abstract**

Knauf WU et al. **Bendamustine versus chlorambucil as first-line treatment in B cell chronic lymphocytic leukemia: An updated analysis from an international phase III study.** *Proc ASH* 2008;**Abstract 2091**.

Lamanna N et al. **Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia.** *J Clin Oncol* 2006;24(10):1575-81. **Abstract**

Lozanski G et al. **Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions.** *Blood* 2004;103(9):3278-81. **Abstract**

Winkler U et al. **Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody rituximab, IDEC-C2B8.** *Blood* 1999;94(7):2217-24. **Abstract**

Case 2 from the practice of Charles M Farber, MD, PhD

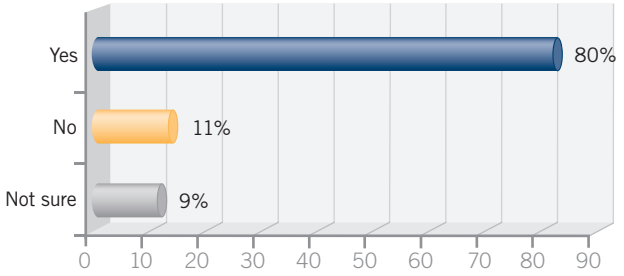
A 40-year-old physician presented with asymptomatic left neck and bilateral axillary adenopathy. An excisional node biopsy revealed follicular small cleaved and large cell NHL (follicular center cell, Grade II). The bone marrow had minimal involvement with small cleaved lymphocytes. The patient was observed closely off treatment for two years but was then lost to follow-up for one year.

He subsequently presented with left inguinal swelling and CT/PET evidence of bulky mediastinal, abdominal and retroperitoneal adenopathy. A biopsy of the left inguinal node showed the same follicular histology as the previous pathology results. He achieved a complete remission after six cycles of R-CHOP. He then received four weekly treatments of maintenance rituximab every six months for two years and has NED three years later.

SOURCE: Track 5

2.1

For those who would treat this patient with a rituximab-containing regimen, would you recommend maintenance rituximab?



SOURCE: National Survey of Medical Oncologists, November 2008.

Tracks 6-7

DR LOVE: David, would you review what we know about maintenance rituximab for follicular lymphoma (2.1)?

DR MALONEY: The best data are from Dr Ghielmini's SAKK trial, in which a single course of rituximab was used for untreated or previously treated follicular lymphoma. If patients had stable disease or better, they were randomly assigned to observation or four additional doses of rituximab during the next year (Ghielmini 2004; [2.2]).

A benefit was clearly evident with additional rituximab. So if you use single-agent rituximab up front, you can prolong progression-free survival by using additional rituximab.

How much more is not completely proven yet, but at least four more doses during the next year can clearly prolong the time to disease progression (Ghielmini 2004; [2.2]). This practice, however, has not been proven to affect overall survival.

For patients with newly diagnosed disease, rituximab adds benefit to all the chemotherapy regimens that have been tested. Four randomized trials — R-CHOP versus CHOP (Hiddemann 2005), R-CVP versus CVP (Marcus 2008), R-MCP versus MCP (Herold 2007) and R-CHVP/interferon versus CHVP/interferon (Salles 2008) — demonstrated that rituximab adds benefit in terms of time to progression.

Data being presented at this ASH meeting confirm that the overall response rate was higher and the time to treatment failure was prolonged with R-CHOP versus CHOP. The five-year time to treatment failure was 65 percent with R-CHOP versus 32 percent with CHOP (Buske 2008).

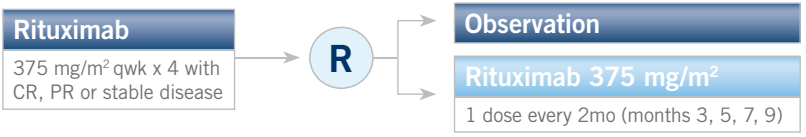
What about maintenance rituximab after rituximab and chemotherapy? No data are available yet for patients with newly diagnosed disease, but we do have data from a salvage trial evaluating maintenance rituximab after either CHOP or R-CHOP. Maintenance rituximab was of benefit in terms of progression-free survival for patients who received either CHOP or R-CHOP (van Oers 2006; [2.3]).

DR LOVE: Ian, what's your opinion about maintenance rituximab after induction with rituximab/chemotherapy for patients with newly diagnosed follicular lymphoma?

DR FLINN: I believe it's a tough question and an important one. I tend to use maintenance rituximab for two years after a rituximab-containing regimen, with all the caveats that Dave mentioned.

2.2

Phase III Randomized Trial Comparing Maintenance Rituximab to Observation in Patients with Follicular Lymphoma



	Maintenance rituximab (n = 73)	Observation (n = 78)	*p*-value
Median event-free survival (mo)	23.2	11.8	0.024
Chemotherapy-naïve patients	36	19	0.009
Pretreated patients	15	10	0.081
Median remission duration (mo)	36	16	0.004

CR = complete response; PR = partial response

SOURCE: Ghielmini M et al. *Blood* 2004;103(12):4416-23. **Abstract**

I follow this approach because I like the data in the relapse setting indicating that maintenance rituximab prolongs progression-free survival (van Oers 2006; [2.3]). I believe it's a low-toxicity approach, and it improves the patient's quality of life.

DR LEONARD: I believe it's an individualized decision. I certainly use maintenance rituximab for some patients, probably a little less often with bendamustine than Ian does. I believe it's of value to use a defined treatment and then let the disease declare itself. Some patients prefer being on treatment. It's a security blanket that makes them feel more comfortable. Others like to be finished with treatment.

It also depends on how worried I am about the patient. For an older patient who will not tolerate the next therapy well or a patient with a high-risk FLIPI score, I might be a little more inclined to use maintenance rituximab. But I believe we need additional data.

DR SMITH: I discuss the data with the patient and say, "Here's what we know. Do you feel better being on treatment or not? We're probably not going to cure you." If the patient has residual disease, it's not maintenance. It's ongoing treatment.

I tend to administer maintenance rituximab on one day every three months because that fits with when I'm seeing the patients, rather than for four weeks every six months. As long as they're not experiencing toxicity, I usually stop at two years, but again, some remain on it beyond that point.

2.3

Phase III Randomized Trial of CHOP versus R-CHOP with or without Rituximab (R) Maintenance for Patients with Relapsed Follicular Lymphoma (FL)

"The final analysis of the European Organisation for Research and Treatment of Cancer (EORTC) 20981 Intergroup study has shown several important findings. Firstly, in patients with relapsed/resistant FL, remission induction with R-CHOP results in a highly significant increase in CR rate as compared with CHOP; secondly, R maintenance treatment significantly improves PFS and OS in patients responding to induction treatment; thirdly, R maintenance treatment achieves a considerable increase in PFS not only after remission induction with chemotherapy (CHOP) but also after immunochemotherapy (R-CHOP)."

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

SOURCE: Van Oers MH et al. *Blood* 2006;108(10):3295-301. **Abstract**

Track 8

DR LOVE: What are your thoughts about the data with bendamustine for indolent lymphoma?

DR GREGORY: I'm impressed with the rituximab/bendamustine versus R-CHOP data. I believe the side effects are less with bendamustine (Rummel 2008; [2.4]). I'm anxiously waiting to see whether rituximab/bendamustine will replace R-CHOP.

DR ZELENETZ: I believe bendamustine should be used in the relapsed and refractory setting.

Some of the major issues in the up-front setting include the following: Is there a life after bendamustine? Can you mobilize stem cells for the younger patients? How does it impact the ability to deliver effective chemotherapy later? These questions will be answered in the large randomized trial because we will evaluate its impact on overall survival. ■

2.4

Phase III Randomized Trial of Rituximab/Bendamustine (R-B) versus R-CHOP as First-Line Therapy for Follicular, Indolent or Mantle-Cell Lymphoma

Second interim analysis (median follow-up of 28 months)

Efficacy

	R-B (n = 221)	R-CHOP (n = 212)
Overall response rate	94%	93%
Complete response rate	41%	33%
Median event-free survival	Not reached	39 months*

* No statistical difference

Safety

	R-B (n = 221)	R-CHOP (n = 212)
Alopecia	0%	89%
Any grade infection	25%	37%
Grade III/IV leukopenia	19%	36%

"In this second interim analysis the combination of Bendamustine plus Rituximab appears to be non-inferior to the standard CHOP-R while showing a better tolerability profile."

SOURCE: Rummel MJ et al. *Proc ASH* 2008;**Abstract 2596**.

SELECT PUBLICATIONS

Buske C et al. **Rituximab in combination with CHOP in patients with follicular lymphoma: Analysis of treatment outcome of 552 patients treated in a randomized trial of the German Low Grade Lymphoma Study Group (GLSG) after a follow up of 58 months.** *Proc ASH* 2008;**Abstract 2599**.

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**

Herold M et al; East German Study Group Hematology and Oncology Study. **Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: An East German Study Group hematology and oncology study.** *J Clin Oncol* 2007;25(15):1986-92. **Abstract**

Hiddemann W et al. **Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group.** *Blood* 2005;106(12):3725-32. **Abstract**

Marcus R et al. **Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma.** *J Clin Oncol* 2008;26(28):4579-86. **Abstract**

Rummel MJ et al. **Bendamustine plus rituximab versus CHOP plus rituximab in the first-line-treatment of patients with follicular, indolent and mantle cell lymphomas: Results of a randomized phase III study of the study group indolent lymphomas (StiL).** *Proc ASH* 2008;**Abstract 2596**.

Salles G et al. **Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: Results of the GELA-GOELAMS FL2000 study.** *Blood* 2008;112(13):4824-31. **Abstract**

Van Oers MH et al. **Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: Results of a prospective randomized phase 3 intergroup trial.** *Blood* 2006;108(10):3295-301. **Abstract**

Case 3 from the practice of Kenneth R Hoffman, MD, MPH

A 71-year-old man with a long history of smoking presented to the emergency room with superior vena cava (SVC) syndrome. Bilateral supraclavicular adenopathy was noted on exam, and a chest x-ray demonstrated bulky mediastinal widening with tracheal deviation. A lymph node biopsy revealed diffuse large B-cell lymphoma (DLBCL), and a CT scan showed extensive involvement of mediastinal and retroperitoneal nodes. Treatment was initiated with R-CHOP.

SOURCE: Track 9

Track 10

DR LOVE: What do you think about the issue of six versus eight cycles of R-CHOP and also about dose-dense R-CHOP for DLBCL (3.1)?

DR LEONARD: I believe it remains a somewhat open question. I use six cycles of R-CHOP. We've also generally stuck with the 21-day schedule because it seems to me that rituximab will obviate some, and perhaps all, of the benefit of the 14-day schedule. The 14-day schedule clearly causes some additional toxicity, although it's often manageable (Pfreundschuh 2004).

DR LOVE: Andy, what do you see in terms of quality of life with dose-dense therapy?

DR ZELENETZ: We have a lot of experience using dose-dense therapy for the younger patient (up to age 70) with R-CHOP-14 or R-CHOP-14 followed

by RICE and ICE. These are well-tolerated regimens. You have to be a little more careful with prophylaxis. This is one situation in which you add prophylaxis with fluconazole, because thrush is a more common problem with dose-dense prednisone. If you're careful about using it, however, patients tolerate it well, and we don't see a substantially increased risk of complications.

DR LOVE: Mitch, do you offer R-CHOP-14 to your patients off protocol?

DR SMITH: Usually not, but maybe for a patient at high risk. Among the patients I've treated with R-CHOP-14, I have seen some problems with neuropathy — more than I expect with R-CHOP-21. So in the absence of clear data, I stick with R-CHOP-21.

Track 11

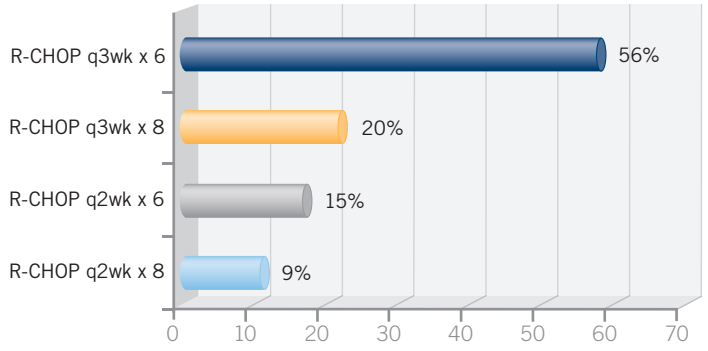
DR LOVE: Dave, any comments on new research initiatives in DLBCL?

DR MALONEY: We are trying to figure out what to add to R-CHOP. Attempts have been made to add bortezomib. The question is, should we drop vincristine? I use R-CHOP-14 relatively frequently in this population. With pegfilgrastim, it's surprising how easy it is to administer R-CHOP on a two-week cycle, and treatment is completed faster.

For this particular patient, however, I would probably recommend dose-adjusted EPOCH-R, based on the data showing that cardiac toxicity does not occur with the long infusion of the anthracycline (Wilson 2008). An infusional regimen in this kind of comorbid patient population makes a lot of sense. A randomized study is evaluating dose-adjusted EPOCH-R versus R-CHOP.

3.1

Which systemic treatment would you most likely recommend for this patient?



SOURCE: National Survey of Medical Oncologists, November 2008.

DR LOVE: John, what about the use of bortezomib for these patients?

DR LEONARD: We've conducted a small study evaluating bortezomib in combination with R-CHOP (Leonard 2007). We do observe probably more neuropathy than what we see with R-CHOP. We're evaluating whether bortezomib adds anything to R-CHOP in large cell and in mantle-cell lymphoma. It's an interesting concept, but I would rely on a randomized trial to demonstrate it.

Track 13

DR LOVE: Andy, what's your standard approach to DLBCL?

DR ZELENETZ: R-CHOP-21 is the standard treatment for patients with DLBCL. For patients older than age 60, this conclusion is based on prospective randomized trials demonstrating that R-CHOP-21 is superior to CHOP-21 (Feugier 2005; [3.2]; Habermann 2006). For patients younger than age 60, the data are a little thinner because the MInT study applies only to patients with low-risk disease (Pfreundschuh 2006; [3.3]). No randomized trial data support the use of R-CHOP-21 for the patient who is younger and has poor-risk disease, although it does remain the standard regimen. ■

3.2 GELA Trial: R-CHOP versus CHOP for the Treatment of Elderly Patients with DLBCL

"The updated analysis with a median 5-year follow-up confirmed previous results showing a significant prolongation of EFS, PFS, DFS, and OS for patients treated with R-CHOP compared with those treated with CHOP alone. The longer survivals observed in the R-CHOP group is due to lower rates of disease progression during therapy and lower rates of relapse after reaching a CR.

Importantly, the EFS, PFS, DFS, and OS curves for R-CHOP and CHOP alone remained separated throughout the follow-up period, indicating that the benefit of combining rituximab with CHOP is durable and translates into an increase in the number of patients who are cured of their lymphoma. After a median follow-up of 5 years, 26% more patients were alive in the R-CHOP arm than in the CHOP arm."

SOURCE: Feugier P et al. *J Clin Oncol* 2005;23(18):4117-26. **Abstract**

3.3 MInT: R-CHOP-Like Chemotherapy versus CHOP-Like Chemotherapy for Young Patients with Good-Prognosis DLBCL

"We have shown that the addition of rituximab to six cycles of a CHOP-like chemotherapy improves the outcome of all subgroups of patients with good-prognosis diffuse large-B-cell lymphoma without increased toxic effects. To our knowledge, these findings are the best reported for this group of patients to date in a randomised trial."

SOURCE: Pfreundschuh M et al; MabThera International Trial Group. *Lancet Oncol* 2006;7(5):379-91. **Abstract**

SELECT PUBLICATIONS

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

Habermann TM et al. **Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma.** *J Clin Oncol* 2006;24(19):3121-7. **Abstract**

Hsi ED et al. **Biologic prognostic markers in diffuse large B-cell lymphoma patients treated with dose adjusted EPOCH-R: A CALGB 50103 correlative science study.** *Proc ASH* 2008;**Abstract 476**.

Leonard JP et al. **CHOP-R + bortezomib as initial therapy for diffuse large B-cell lymphoma (DLBCL).** *Proc ASCO* 2007;**Abstract 8031**.

Pfreundschuh M et al; MabThera International Trial Group. **CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: A randomized controlled trial by the MabThera International Trial (MInT) Group.** *Lancet Oncol* 2006;7(5):379-91. **Abstract**

Pfreundschuh M et al; German High-Grade Non-Hodgkin's Lymphoma Study Group. **Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: Results of the NHL-B2 trial of the DSHNHL.** *Blood* 2004;104(3):634-41. **Abstract**

Wilson WH et al. **Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers.** *J Clin Oncol* 2008;26(16):2717-24. **Abstract**

Case 4 from the practice of Lowell L Hart, MD

A 66-year-old man presented in 2005 with a right axillary mass. A biopsy demonstrated mantle-cell lymphoma (positive for CD20 and cyclin D1). No disease was found outside the axilla, and a bone marrow biopsy was negative. The patient also had a well-controlled seizure disorder. He had a complete response after six cycles of R-CHOP. Two years later, he presents with a recurrence of the axillary mass and extension to the chest wall.

SOURCE: Track 14

Tracks 15, 17

DR LOVE: Which regimens do you discuss with patients who have newly diagnosed mantle-cell lymphoma (4.1)?

DR FLINN: I certainly discuss R-CHOP and R-hyper-CVAD. I also mention the notion of autologous stem cell transplant (ASCT) as consolidation therapy. I bring to the table my own bias that the R-hyper-CVAD regimen is somewhat toxic. In fact, I believe that consolidation with ASCT is probably less toxic than a complete regimen of R-hyper-CVAD.

DR MALONEY: With R-CHOP, the median time to disease progression is less than two years on average (Lenz 2005). So I believe every patient with mantle-cell lymphoma who is younger than age 70 should receive consolidation with an autologous transplant if you use R-CHOP. If you don't do that, then you can consider using R-hyper-CVAD, but patients spend more time

in the hospital being treated with R-hyper-CVAD than for an autologous transplant. I believe the current standard approach for mantle-cell lymphoma, supported by the German data (Dreyling 2005), is consolidation with an autologous transplant after a regimen with rituximab as induction.

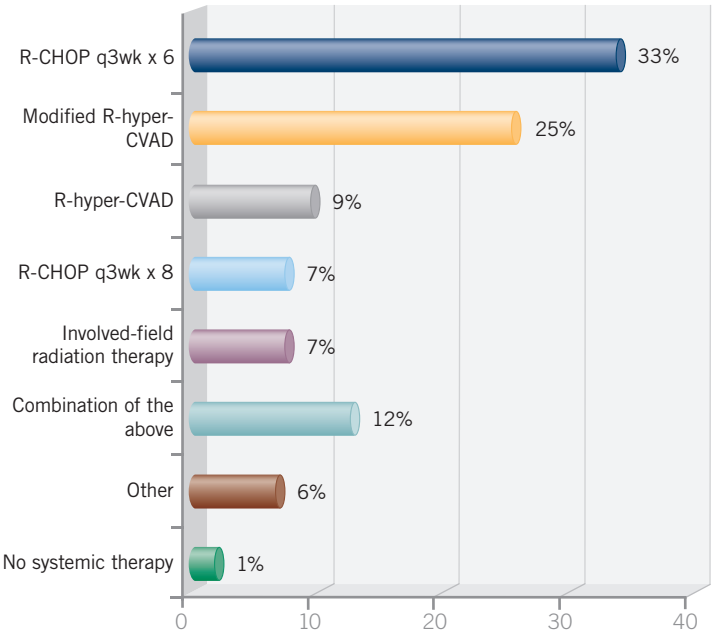
DR ZELENETZ: I agree with Ian that up-front consolidation with a transplant is less toxic than hyper-CVAD. So for a younger patient whom I want to have a durable remission, I'll use sequential treatment with dose-dense R-CHOP, ICE and transplant. For the older patient, however, we'll use other treatment strategies.

DR LOVE: Mitch, would you review the treatment options for mantle-cell lymphoma?

DR SMITH: The key questions when you approach mantle-cell lymphoma are, are you going to cure this patient, and is it an aggressive lymphoma, indicated by the short median survival? Maybe then you can consider an aggressive approach. The alternative is to say, "I can't cure it, and I'll watch and wait and be a little less aggressive." The answer is individualized, depending on the age and performance status of the patient.

4.1

What would be your most likely initial treatment approach for this 66-year-old patient?



SOURCE: National Survey of Medical Oncologists, November 2008.

What can you expect from a patient with mantle-cell lymphoma? R-CHOP has a 90 to 95 percent response rate with a median duration of response of about 1.5 years (Lenz 2005).

Data from Europe demonstrate that the median overall survival for mantle-cell lymphoma has increased, and it's now about five years (Herrmann 2009; [4.2]). If you're younger than age 65 and you tolerate R-hyper-CVAD with methotrexate and high-dose ara-C, you tend to fare well, with a median progression-free survival of about five years. If you're older than age 65 or not fit, you don't fare as well (Romaguera 2008).

During the next few years, we will have a set of protocols for young, fit patients that are more dose-intense, transplant-type regimens. For the older patients or those with comorbidities, we will try to be gentler.

In the rituximab/bendamustine data, a subset of the patients had mantle-cell lymphomas, and those data are interesting (Rummel 2008). ■

4.2

Improvements in Overall Survival for Advanced Stage Mantle-Cell Lymphoma (MCL)

"Median overall survival of patients with advanced nonblastoid MCL almost doubled during the past 30 years. Potential reasons for this apparent improvement in overall survival include the application of anthracycline-containing regimens and new approaches, such as antilymphoma antibodies or stem cell transplantation.

Advances in general supportive care, new diagnostic tools, and general improvement of life span might have also reinforced this effect."

SOURCE: Herrmann A et al. *J Clin Oncol* 2009;27(4):511-8. **Abstract**

SELECT PUBLICATIONS

Dreyling M et al. **Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: Results of a prospective randomized trial of the European MCL Network.** *Blood* 2005;105(7):2677-84. **Abstract**

Herrmann A et al. **Improvement of overall survival in advanced stage mantle cell lymphoma.** *J Clin Oncol* 2009;27(4):511-8. **Abstract**

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

Romaguera J et al. **Rituximab (R) + hyperCVAD alternating with R-methotrexate/cytarabine after 9 years: Continued high rate of failure-free survival in untreated mantle cell lymphoma (MCL).** *Proc ASH* 2008;**Abstract 833**.

Rummel MJ et al. **Bendamustine plus rituximab versus CHOP plus rituximab in the first-line-treatment of patients with follicular, indolent and mantle cell lymphomas: Results of a randomized phase III study of the Study Group Indolent Lymphomas (StiL).** *Proc ASH* 2008;**Abstract 2596**.

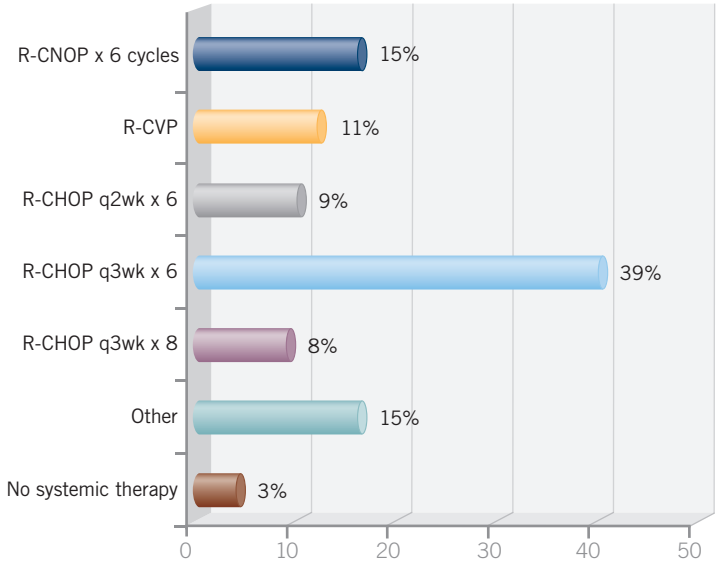
Case 5 from the practice of Abraham B Schwarzberg, MD

An 80-year-old, very fit man with no major comorbidities presented with hematuria. A CT scan revealed pelvic lymphadenopathy (largest node 1.3 centimeters) and several splenic masses (largest 2.2 centimeters). Splenic biopsy revealed DLBCL. His medical history was significant for a diagnosis of non-Hodgkin lymphoma 35 years ago for which he received a cumulative dose of 300 mg/m^2 of doxorubicin. An echocardiogram demonstrated an ejection fraction of 45 percent. After two cycles of R-CHOP with a full dose of doxorubicin that was divided over two days, he demonstrated a complete response and no change in his ejection fraction. He received four more courses of a modified R-CHOP regimen, and he has remained in complete remission for one year with a stable ejection fraction.

SOURCE: Track 18

5.1

Which systemic treatment would you most likely recommend for this patient?



SOURCE: National Survey of Medical Oncologists, November 2008.

Track 20

DR LOVE: John, what are your thoughts regarding this case?

DR LEONARD: The literature is scant and not useful for telling us what the best approach is. It's an individualized decision (5.1). The first thing is to be sure that the patient's cardiac function is truly compromised. We recently had a patient in the middle of receiving R-CHOP whose ejection fraction

appeared to decline. We repeated the study in a different way and spoke with his cardiologist — it hadn't dropped at all, so it's helpful to have the cardiologist involved.

For most of my patients with compromised cardiac function, I've administered rituximab-cyclophosphamide/etoposide/procarbazine/prednisone (R-CEPP). This is a Stanford regimen from 10 or 15 years ago (Chao 1990) and we have added the rituximab. So it is different from the prednisone/etoposide/procarbazine-cyclophosphamide (PEP-C) regimen that we've occasionally used (Coleman 2008).

Sometimes you can get away with R-CHOP for these patients. For an 80-year-old patient with an ejection fraction of 45 percent who has received a prior anthracycline, I would be hesitant about using R-CHOP, but I can't argue against using a dose reduction or doing it carefully.

Few data are available for R-CNOP in this population. Certainly, some are using R-CVP. I don't believe you're giving up the ship by omitting the anthracycline, and for some patients that is reasonable. Most of the time, I end up starting with one regimen and cutting it down as time goes on, depending on how the patient tolerates it.

Obviously, we don't watch and wait in DLBCL too often, but with a compromised patient who's sick and has comorbidities, watching for a while without symptoms might also be reasonable. However, in this case, I'd be hesitant to do that.

DR MALONEY: It's a mistake not to treat this patient aggressively. Every study that has treated elderly patients with DLBCL using kinder and gentler therapy has been associated with inferior survival or, at best, comparative survival.

If you don't use the correct dose of mitoxantrone or you drop the anthracycline, you have inferior survival. Your default position should be to try to cure this man, despite the fact that he's 80 years old and has received an anthracycline.

I would use dose-adjusted EPOCH-R (Wilson 2008). You can administer infusional anthracyclines without cardiac toxicity because they don't reach the peak levels that cause the toxicity. I've done it for several patients who had already received the maximum dose of anthracyclines. If I ran into problems with toxicity, I would retreat to a more palliative approach. ■

SELECT PUBLICATIONS

Chao NJ et al. **CEPP(B): An effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma.** *Blood* 1990;76(7):1293-8. **Abstract**

Coleman M et al. **Prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C) oral combination chemotherapy regimen for recurring/refractory lymphoma: Low-dose metronomic, multidrug therapy.** *Cancer* 2008;112(10):2228-32. **Abstract**

Wilson WH et al. **Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers.** *J Clin Oncol* 2008;26(16):2717-24. **Abstract**

POST-TEST

Second Opinion: *Case-Based Discussions on the Management of Non-Hodgkin Lymphomas and Chronic Lymphocytic Leukemia*

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Sweet syndrome, also known as neutrophilic dermatosis, can be a complication of therapy with G-CSF.**
   a. True
   b. False
2. **For patients with follicular lymphoma who had stable disease or better after a course of rituximab monotherapy, maintenance rituximab improved progression-free survival.**
   a. True
   b. False
3. **For patients with relapsed follicular lymphoma who responded to induction therapy with CHOP or R-CHOP, maintenance rituximab improved progression-free survival.**
   a. True
   b. False
4. **The addition of rituximab to which of the following chemotherapy regimens has been found to improve time to progression of follicular lymphoma?**
   a. CHOP
   b. CVP
   c. MCP
   d. All of the above
   e. None of the above
5. **Which of the following regimens utilizes a prolonged infusion of an anthracycline?**
   a. R-CHOP
   b. R-CVP
   c. R-EPOCH
   d. All of the above
   e. None of the above
6. **In the MInT study, the addition of rituximab to a CHOP-like regimen was found to improve outcomes in which of the following groups?**
   a. Elderly patients with high-risk diffuse large B-cell lymphoma (DLBCL)
   b. Elderly patients with low-risk DLBCL
   c. Younger patients with high-risk DLBCL
   d. Younger patients with low-risk DLBCL
   e. All of the above
7. **On average, the median duration of response to R-CHOP in mantle-cell lymphoma is less than _____.**
   a. One year
   b. Two years
8. **Among patients with DLBCL, maintenance rituximab improves outcomes for those treated with which induction regimen?**
   a. CHOP
   b. R-CHOP
   c. Both a and b
   d. None of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Second Opinion: *Case-Based Discussions on the Management of Non-Hodgkin Lymphomas and Chronic Lymphocytic Leukemia*

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

- Dosing and administration of rituximab for patients with CLL who have a high white blood cell count 4 3 2 1
- Incidence of superior vena cava syndrome in patients with DLBCL 4 3 2 1
- Benefits and risks of dose-dense R-CHOP-14 in newly diagnosed DLBCL 4 3 2 1
- Dosing of maintenance rituximab for patients with follicular lymphoma 4 3 2 1
- Individualized selection of standard and intensive induction regimens for newly diagnosed mantle-cell lymphoma 4 3 2 1
- Emerging systemic treatment options for CTCL 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

- Dosing and administration of rituximab for patients with CLL who have a high white blood cell count 4 3 2 1
- Incidence of superior vena cava syndrome in patients with DLBCL 4 3 2 1
- Benefits and risks of dose-dense R-CHOP-14 in newly diagnosed DLBCL 4 3 2 1
- Dosing of maintenance rituximab for patients with follicular lymphoma 4 3 2 1
- Individualized selection of standard and intensive induction regimens for newly diagnosed mantle-cell lymphoma 4 3 2 1
- Emerging systemic treatment options for CTCL 4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: .....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: .....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: .....

Please respond to the following LEARNER statements by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

As a result of this activity, I will be able to:

- Recount the natural history of CLL, and assess the rational indications for initiation of medical intervention with cytotoxics, monoclonal antibodies and immunomodulatory agents. ..... 4 3 2 1 N/M N/A
- Develop a treatment algorithm to optimize clinical outcomes and quality of life for patients with newly diagnosed or relapsed/refractory follicular lymphoma. ..... 4 3 2 1 N/M N/A
- Identify tolerable and efficacious systemic regimens for patients with diffuse large B-cell lymphoma (DLBCL) and advanced age or preexisting comorbidities. ..... 4 3 2 1 N/M N/A
- Discuss treatment options, including standard or intensive induction therapy and autologous stem cell transplant, with patients who have newly diagnosed mantle-cell lymphoma. ..... 4 3 2 1 N/M N/A
- Counsel patients with indolent or aggressive lymphoma about the risks and benefits associated with maintenance therapy. ..... 4 3 2 1 N/M N/A
- Assess the utility of current systemic therapies and/or allogeneic stem cell transplant in the management of advanced cutaneous T-cell lymphoma (CTCL). ..... 4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

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Additional comments about this activity:

.....

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

☐ Yes, I am willing to participate in a follow-up survey. ☐ No, I am not willing to participate in a follow-up survey.

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4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

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Stephanie A Gregory, MD	4 3 2 1	4 3 2 1
John P Leonard, MD	4 3 2 1	4 3 2 1
David G Maloney, MD, PhD	4 3 2 1	4 3 2 1
Mitchell R Smith, MD, PhD	4 3 2 1	4 3 2 1
Andrew D Zelenetz, MD, PhD	4 3 2 1	4 3 2 1
Moderator	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the moderator and faculty for this activity:

.....

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ASH109

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Hematologic Oncology™

UPDATE

This program is supported by an educational grant from
Genentech BioOncology/Biogen Idec.

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Sponsored by Research To Practice.

Last review date: March 2009
Release date: March 2009
Expiration date: March 2010
Estimated time to complete: 1.75 hours