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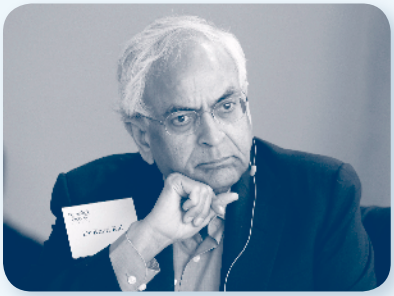
Integrating Emerging Clinical Research into the Practical Management of Non-Hodgkin Lymphomas and Chronic Lymphocytic Leukemia

Proceedings from a Clinical Investigator Journal Club



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Hematologic Oncology™ UPDATE

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Integrating Emerging Clinical Research into the Practical Management of Non-Hodgkin Lymphomas and Chronic Lymphocytic Leukemia

A Continuing Medical Education Activity

OVERVIEW OF ACTIVITY

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of lymphoproliferative disorders and is one of the most rapidly evolving fields in hematology and oncology. Published results from ongoing clinical trials lead to the continual emergence of new therapeutic agents and changes in the utilization of existing treatments. To offer optimal patient care — including the option of clinical trial participation — practicing medical oncologists, hematologists and hematology-oncology fellows must be well informed of these advances. This program uses relevant case-based discussions among clinical investigators to assist practicing clinicians with the incorporation of newly published data into optimal treatment algorithms for NHL and chronic lymphocytic leukemia.

LEARNING OBJECTIVES

- Develop an algorithm for the evaluation and treatment of newly diagnosed or relapsed/refractory chronic lymphocytic leukemia.
- Apply the results of emerging research to effectively and safely integrate novel agents and regimens into the management of relapsed/refractory indolent lymphoma.
- Counsel patients with follicular lymphoma about the risks and benefits associated with maintenance therapy.
- Assess the utility of clinical and molecular biomarkers in the selection of first-line therapy for diffuse large B-cell lymphoma (DLBCL).
- Identify investigational agents under evaluation for relapsed/refractory DLBCL.
- Communicate the existing and emerging roles of proteasome inhibitors and IMiDs® to patients with mantle-cell lymphomas.
- Integrate currently available therapeutic strategies into the management of advanced cutaneous T-cell lymphoma.

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Integrating Emerging Clinical Research into the Practical Management of Non-Hodgkin Lymphomas and Chronic Lymphocytic Leukemia — Issue 1, 2009

TABLE OF CONTENTS

TOPICS/JOURNAL CLUB PAPERS

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Journal Club Paper

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

DR RAI: At ASH 2008 Dr Ferrajoli presented a Phase II trial of front-line therapy with lenalidomide for elderly patients (≥65 years old) with chronic lymphocytic leukemia (CLL).

The dosing of lenalidomide is important. For patients with previously treated CLL, higher doses of lenalidomide were effective (Ferrajoli 2008b; Chanan-Khan 2006). However, when Christine Chen started a study for previously untreated CLL, with a high dose, the first two patients developed tumor lysis syndrome and infection. She therefore restarted the protocol at a dose of 2.5 milligrams (Chen 2008).

Ferrajoli started with a dose of five milligrams and found that for the 43 patients who enrolled, all the toxicities were tolerable. Little tumor flare occurred, and all events were Grade I or II. No tumor lysis syndrome was observed. The 35 patients with evaluable disease had a 54 percent partial response rate (Ferrajoli 2008a; [1.1]).

This is an important observation — that elderly patients with CLL can benefit from front-line therapy with lenalidomide. Because the patients achieved only partial remissions, I believe subsequent trials would involve combinations with lenalidomide as front-line therapy.

DR LOVE: Are those trials ongoing?

DR RAI: The CLL Research Consortium has recently started a trial of rituximab in combination with lenalidomide as front-line therapy for

1.1

Lenalidomide as Initial Therapy for Elderly Patients (Older than Age 65) with CLL

"Thirty-five patients are evaluable for response having received treatment for at least 3 months. Nineteen patients achieved a partial response according to the 1996 NCIWG criteria for an overall response rate of 54%, 14 patients (40%) had stable disease and 2 patients (6%) experienced disease progression after 4 and 5 months respectively. Treatment with lenalidomide rapidly reduced the number of circulating lymphocytes: 47% of the patients achieved a blood CR and 38% a blood PR...

In conclusion, our early results indicate that lenalidomide given as continuous therapy at a start dose of 5 mg followed by slow dose escalation is safe and well-tolerated as initial therapy by elderly patients with CLL."

CR = complete response; PR = partial response

SOURCE: Ferrajoli A et al. *Proc ASH* 2008a;**Abstract 45**.

all ages. The University of California, San Diego, has already enrolled eight or nine patients, and they are experiencing impressive responses.

DR MORRISON: This abstract is important in terms of evaluating lenalidomide in the front-line setting, but another way the drug could potentially be used is in the maintenance setting. I believe that lenalidomide will have activity in CLL, but the issue will be at what point it can be best placed to help patients. Also, in the real world setting, in which we have older patients who are frailer and can't tolerate FCR, are other treatment options available? Lenalidomide might be one of those.

Journal Club Paper

Fischer K et al. **Bendamustine in combination with rituximab (BR) for patients with relapsed chronic lymphocytic leukemia (CLL): A multicentre Phase II trial of the German CLL Study Group (GCLLSG).** Oral presentation. *Proc ASH* 2008;Abstract 330.

DR RAI: Dr Fischer reported on a Phase II trial of the combination of bendamustine and rituximab for patients who were previously treated with one to three regimens for CLL (Fischer 2008). In vitro data had suggested synergy between bendamustine and rituximab in primary CLL cells, and bendamustine has been approved for CLL.

Patients received 70 mg/m^2 of bendamustine on days one and two, and 375 mg/m^2 of rituximab in cycle one and 500 mg/m^2 from cycle two onward. Of the 81 patients enrolled, 62 were evaluable for response and demonstrated a 77 percent overall response rate with a 14.5 percent complete remission rate and a 62.9 percent partial response rate (Fischer 2008).

Across the board, the patients with poor prognostic markers experienced good responses (Fischer 2008; [1.2]). My take-home message is that bendamustine/rituximab is effective and feasible for relapsed/refractory, poor-prognosis CLL.

DR SMITH: This paper and others have demonstrated activity for this agent. My experience with bendamustine for refractory CLL is that it can be impressive. Often, especially with elderly patients, you can't administer cycle after cycle, but if they show a good response to a couple of cycles and you have to hold treatment, that's okay. You've helped the patient.

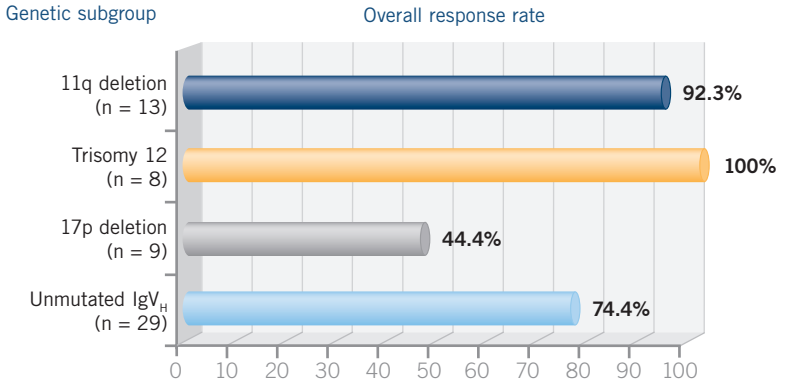
DR LOVE: How would you compare bendamustine to lenalidomide for CLL?

DR SMITH: I believe the data with bendamustine are more mature and solid. Lenalidomide is an exciting drug, but we need to know a little more about how to use it. As a single agent, I believe bendamustine is better in the long term. Combining bendamustine with other drugs is problematic because of myelosuppres-

sion. Lenalidomide may be easier to combine. As we learn more, lenalidomide may prove in the long run to be better, but today I believe bendamustine is further ahead.

1.2

Phase II Trial of Bendamustine/Rituximab for Relapsed CLL: Response Rate According to Genetic Subgroup



SOURCE: Fischer K et al. Oral presentation. *Proc ASH* 2008;**Abstract 330**.

Journal Club Paper

Osterborg A et al. **Ofatumumab (HuMax-CD20), a novel CD20 monoclonal antibody, is an active treatment for patients with CLL refractory to both fludarabine and alemtuzumab or bulky fludarabine-refractory disease: Results from the planned interim analysis of an international pivotal trial.** *Proc ASH* 2008;Abstract 328.

DR RAI: Dr Osterborg and colleagues reported a trial evaluating ofatumumab, an anti-CD20 monoclonal antibody. The trial enrolled patients with previously treated CLL, who they divided into two broad categories. One group had disease that was refractory to fludarabine and alemtuzumab — the double-refractory (DR) group (59 percent received prior rituximab). Patients in the second group had disease that was refractory to fludarabine, but because of the bulky size of their lymph node enlargement, they were not candidates for alemtuzumab (54 percent received prior rituximab). This was the bulky fludarabine-refractory (BFR) group (Osterborg 2008).

The trial population included 59 patients in the DR group and 79 patients in the BFR group. The overall response rate was close to 50 percent in both groups, and the

median time to the next treatment was approximately nine months across the board in the two arms. The median overall survival was a little more than 14 months (Osterborg 2008).

In summary, ofatumumab is emerging as a "new kid on the block" that is ready to compete with rituximab. The next order of business will be to find out how effective it is for CLL when combined with other agents and to determine the dose that is equivalent to the dose of rituximab. Those issues are currently under investigation.

This is the first positive report with a large sample size, which tells us that ofatumumab is here to stay. We'll just have to watch the scene. ■

ADDITIONAL PUBLICATIONS DISCUSSED

Chanan-Khan A et al. **Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: Results of a phase II study.** *J Clin Oncol* 2006;24(34):5343-9.

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 induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia.** *Blood* 2008b;111(11):5291-7.

Follicular Lymphoma

Journal Club Paper

Friedberg JW et al. **Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: Results from a Phase II multicenter, single-agent study.** *J Clin Oncol* 2008;26(2):204-10.

DR CZUCZMAN: This was a Phase II, multicenter, single-agent study of bendamustine for rituximab-refractory, indolent or transformed non-Hodgkin lymphoma (NHL). Patients received 120 mg/m^2 of bendamustine on days one and two every 21 days.

These patients had rituximab-resistant disease, meaning that they had not achieved a response with rituximab or that they had experienced relapse within six months of completing therapy with rituximab (Friedberg 2008).

Out of 76 patients enrolled, 74 were evaluable for response. The overall response rate was a respectable 77 percent, including a 34 percent complete response or unconfirmed complete response (CR/CRu) rate. The median duration of response for the responders was 6.7 months. Of interest, patients with indolent lymphoma fared better, with a nine-month median duration of response, whereas those with transformed NHL had a median duration of response of only 2.3 months (Friedberg 2008).

In a Phase II multicenter study in relapsed, indolent B-cell or mantle-

cell lymphoma, patients received bendamustine and rituximab. A 92 percent overall response rate was reported, with a 55 percent CR/CRu rate. The median progression-free survival rate was about two years. This was not a population with rituximab-resistant disease. A significant number of patients (44 percent) were rituximab naïve, and 56 percent had received rituximab but did not have resistant disease (Robinson 2008).

The major toxicity was myelosuppression. They used 90 mg/m^2 of bendamustine on days two and three on a 28-day cycle.

Journal Club Paper

Robinson KS et al. **Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma.** *J Clin Oncol* 2008;26(27):4473-9.

DR LOVE: John, how do you use bendamustine for NHL and what dose do you use?

DR LEONARD: I believe that it's a potentially useful drug. I've been using it primarily for relapsed follicular lymphoma and for some patients with relapsed CLL or relapsed mantle-cell lymphoma. The dose depends on the situation. I use anywhere from 90 to 120 mg/m^2 depending on the patient's bone marrow reserve, age and other factors.

DR LOVE: Myron, what do we know about how rituximab/bendamustine (R-B) compares to R-CHOP?

DR CZUCZMAN: The last two ASH meetings included presentations of the first and second interim analyses of a large German study evaluating R-CHOP versus R-B as first-line therapy for follicular, indolent or mantle-cell lymphoma. According to the data, R-B is not inferior to R-CHOP. These groups of patients had similar overall and complete response rates (Rummel 2008; [2.1]).

I don't believe that we can assess durability of response because it's still early in the course. I want to see more data and details to understand whether someday we will replace R-CHOP with R-B.

DR MOSKOWITZ: I agree with Myron. It seems almost too good to be true — the equivalency of R-B and R-CHOP and the lack of toxicity with R-B (2.1). I'll be happy to use it after the results are peer reviewed and reported in a way that demonstrates this equivalency. I am still concerned about long-term side effects of a drug that we don't know enough about.

Some of the physicians who remember bendamustine from the olden days in Europe are concerned about long-term myelodysplastic syndrome. So I — and others may disagree — will be hard pressed to use bendamustine for a younger patient who may receive a transplant in the future.

2.1

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%

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

Journal Club Paper

Blum KA et al. **A Phase II trial of induction plus maintenance rituximab and bortezomib in patients with relapsed/refractory mantle cell (MCL) and follicular (FL) non-Hodgkin's lymphoma.** *Proc ASH* 2008;Abstract 3053.

DR CZUCZMAN: This was a Phase II trial of rituximab/bortezomib for patients with relapsed/refractory mantle-cell or follicular lymphoma. The trial enrolled only 23 patients — 10 with follicular and 13 with mantle-cell lymphoma. The median age of the patients was 66. Initially, patients received rituximab and bortezomib. Patients who responded were then to receive maintenance rituximab and bortezomib (Blum 2008).

Investigators reported a reasonable overall response rate of 39 percent, including nine out of 23 patients with a CR/CRu. The median progression-free survival was approximately six months. The combination of rituximab/bortezomib has activity. However, it also brings significant toxicity (Blum 2008).

Of these patients who were previously treated, about 57 percent had Grade III autonomic, sensory or motor neuropathies despite a reduction in the dose of bortezomib from 1.5 to 1.3 mg/m^2. Because of the neurotoxicity, none of the patients who responded went on to mainte-

nance rituximab/bortezomib (Blum 2008).

DR LOVE: Rick, do you have any comments about bortezomib-related neuropathy?

DR HAGEMEISTER: After a year or so, it seems to resolve completely in the majority of patients who complain of more significant neuropathy. So, fortunately, it eventually does go away.

Journal Club Paper

Van Oers MHJ et al. **Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: Long-term outcome of the EORTC-20981 Phase III randomized Intergroup study.** *Proc ASH* 2008;Abstract 836.

DR GREGORY: EORTC-20981 was a large Intergroup study with randomization to CHOP versus R-CHOP for patients with relapsed follicular lymphoma who had not received more than two prior treatments or an anthracycline.

The results were reported previously, and R-CHOP was superior. Patients who had partial or complete responses were then randomly assigned to observation or maintenance rituximab every three months for two years or until relapse. Progression-free survival was clearly better for the group who received maintenance rituximab, whether they had received CHOP or R-CHOP initially (Van Oers 2006).

At ASH 2008 the long-term follow-up of six years demonstrated that progression-free survival was much improved for the patients who received maintenance rituximab (Van Oers 2008; [2.2]).

2.2

EORTC-20981: Maintenance Rituximab versus Observation for Relapsed/Refractory Follicular Lymphoma Treated with CHOP or R-CHOP as Induction Therapy (Median Follow-Up of Six Years)

	Maintenance rituximab (n = 167)	Observation (n = 167)	Hazard ratio	*p*-value
Median progression-free survival	3.7 years	1.3 years	0.55	<0.0001
Five-year overall survival (OS)	74%	64%	—	0.07
Grade III/IV infection	9.7%	2.4%	—	0.01

SOURCE: Van Oers MHJ et al. Oral presentation. *Proc ASH* 2008;**Abstract 836**.

Journal Club Paper

Vidal L et al. **Rituximab maintenance for the treatment of patients with follicular lymphoma: Systematic review and meta-analysis of randomized trials.** *J Natl Cancer Inst* 2009;101(4):248-55.

DR GREGORY: This was a meta-analysis of five trials in which maintenance rituximab was used (Vidal 2009). Most of these trials enrolled patients who had relapsed follicular lymphoma.

Some of the studies used a rituximab/chemotherapy induction regimen before the maintenance regimen was administered. A couple of the studies used only rituximab as front-line treatment and then maintenance rituximab.

The conclusion was that in the relapsed setting, maintenance rituximab seems to confer an improvement in progression-free and overall survival (Vidal 2009; [2.3]).

DR CZUCZMAN: The meta-analysis included different types of therapies and, therefore, it is difficult to draw conclusions. In the paper by Van Oers, no difference was reported in the five-year overall survival between the two groups, although we saw a significant improvement in progression-free survival (Van Oers 2008). However, restaging practices were not standardized.

During the time that maintenance rituximab was administered, each institution followed individual standards. So not every patient received a scan at six months or one year, which is problematic when using progression-free survival as an endpoint. ■

2.3

Meta-Analysis of Trials Evaluating Maintenance Rituximab for Relapsed/Refractory Follicular Lymphoma

"Five trials including 1143 adult patients were included in this meta-analysis. Data for 985 patients with follicular lymphoma were available for the meta-analysis of overall survival. Patients treated with maintenance rituximab had statistically significantly better overall survival than patients in the observation arm or patients treated at relapse (hazard ratio [HR] for death = 0.60, 95% confidence interval [CI] = 0.45 to 0.79). The rate of infection-related adverse events was higher with rituximab maintenance treatment (HR = 1.99, 95% CI = 1.21 to 3.27). Patients with refractory or relapsed (ie, previously treated) follicular lymphoma had a survival benefit with maintenance rituximab therapy (HR for death = 0.58, 95% CI = 0.42 to 0.79), whereas previously untreated patients did not (HR for death = 0.68, 95% CI = 0.37 to 1.25). Conclusions: These results suggest that maintenance therapy with rituximab, either as four weekly infusions every 6 months or as a single infusion every 2–3 months, should be added to standard therapy for patients with relapsed or refractory (ie, previously treated) follicular lymphoma after successful induction therapy. The higher rate of infections with rituximab therapy should be taken into consideration when making treatment decisions."

SOURCE: Vidal L et al. *J Natl Cancer Inst* 2009;101(4):248-55.

ADDITIONAL PUBLICATIONS DISCUSSED

David KA et al. **A Phase II trial of combination bortezomib (Velcade®) and rituximab for untreated "high tumor burden" indolent non-Hodgkin lymphoma (NHL).** *Proc ASH* 2008;**Abstract 2004**.

Hochster **H et al. Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: Results of the randomized phase III ECOG1496 study.** *J Clin Oncol* 2009;27(10):1607-14.

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**.

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.

Diffuse Large B-Cell Lymphoma (DLBCL)

Journal Club Paper

Czuczman MS et al. **Confirmation of the efficacy and safety of lenalidomide oral monotherapy in patients with relapsed or refractory diffuse large-B-cell lymphoma: Results of an international study (NHL-003).** *Proc ASH* 2008;Abstract 268.

DR LEONARD: A subset analysis from a previous Phase II study with lenalidomide demonstrated a 19 percent response rate for recurrent diffuse large B-cell lymphoma (DLBCL; [Wiernik 2008]).

The study by Dr Czuczman was an international, confirmatory, follow-up study with 73 patients who had recurrent DLBCL. The patients' median age was 67, and they had received a median of three prior regimens (Czuczman 2008).

The overall response rate of 29 percent is comparable to what we're starting to observe in other subtypes of lymphoma. These were mostly partial responses. An additional 15 percent of the patients had stable disease. The main toxicities were neutropenia, thrombocytopenia and anemia (Czuczman 2008).

These results suggest that lenalidomide is an active drug. The question will be how to integrate lenalidomide in the management of DLBCL. Concurrent use with chemotherapy will be complicated by cytopenias. I don't believe we will use it at the same time as chemotherapy, although that approach is being evaluated.

I believe we will see more studies evaluating chemotherapy followed by a lenalidomide-based regimen as maintenance.

Journal Club Paper

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.

DR MOSKOWITZ: We're all hoping that lenalidomide is a drug we can use and use safely. Consider a patient who is ineligible for a transplant and in his or her midseventies who receives R-CHOP and experiences a relapse 18 months later.

I would predict that oncologists would use lenalidomide/rituximab as their first choice once these results are published. It's easy to administer with no significant downside — you can always use intravenous chemotherapy thereafter.

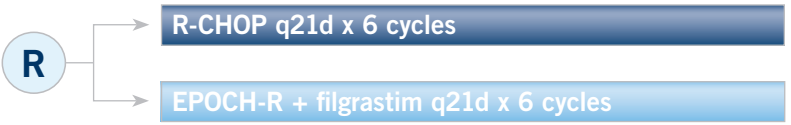
DR MOSKOWITZ: This paper was an attempt to evaluate subsets of patients in a Phase II trial who received dose-adjusted EPOCH-R for previously untreated DLBCL and also to analyze the data based on the International Prognostic Index. About three fourths of the patients had not experienced disease progression and were alive at five years (Wilson 2008).

Of the patients with low-risk or low-intermediate-risk disease, more than 90 percent were event free. However, for patients with multiple risk factors, no benefit was evident with this treatment program compared to standard R-CHOP-21, with fewer than half of the patients being free of disease progression (Wilson 2008).

Evaluating the data on MIB-1 revealed no difference in outcome. The best marker for efficacy with dose-adjusted EPOCH-R was Bcl-6 expression. Those patients with Bcl-6-positive disease fared extremely well. Of the minority of patients

3.1 **Phase III Study Comparing R-CHOP to EPOCH-R**

Protocol IDs: CALGB-50303, ECOG-50303, NCI-05-C-0252, NCT00118209
Target Accrual: 478



Eligibility

Previously untreated de novo diffuse large B-cell NHL

Study Contacts

Cancer and Leukemia Group B

Wyndham Wilson, MD	Tel: 301-435-2415
Andrew Zelenetz, MD	Tel: 212-639-2656

SOURCE: NCI Physician Data Query, July 2009.

with Bcl-6–negative disease, only half were event free (Wilson 2008).

DR LEONARD: I believe this is an interesting report, but you have to remember that it's a single-institution, 70-patient study with many retrospective subset analyses. I would emphasize the importance of the ongoing randomized study comparing CHOP-R to EPOCH-R (CALGB-50303; [3.1]), which is a prospective analysis of approximately 400 patients with gene expression profiling.

Journal Club Paper

Pfreundschuh M et al. **Improved outcome of elderly patients with poor-prognosis diffuse large B-cell lymphoma (DLBCL) after dose-dense rituximab: Results of the DENSE-R-CHOP-14 trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL).** *Proc ASCO* 2008;Abstract 8508.

DR MOSKOWITZ: This presentation makes an assumption, which I believe is without basis, that R-CHOP-14 is superior to R-CHOP-21 for DLBCL. The investigators decided to use DENSE-R-CHOP-14. The rationale is that it usually takes three to four cycles to attain an active serum concentration of rituximab, which this group believes is necessary (Reiser 2006).

Pharmacokinetic data suggested that when intensified rituximab was used in the first few cycles, a quick peak was obtained in the serum rituximab concentration and then maintained at a certain level throughout the treatment program (Poeschel 2006). This may have an effect on outcome.

Instead of using R-CHOP-14, with eight doses of rituximab, these investigators used DENSE-R-CHOP-14, with 12 doses of rituximab, for a group of elderly patients in a Phase II design. Adequate serum rituximab levels were maintained with this treatment program. The results were compared to the results with R-CHOP-14 from the RICOVER trial (Pfreundschuh 2008).

DENSE-R-CHOP-14 was more toxic than R-CHOP-14 and, similarly to R-CHOP-14, it required antibiotic prophylaxis. A significant amount of morbidity was recorded among the first 25 patients.

Among patients with low-risk or low-intermediate-risk disease, no difference was apparent between DENSE-R-CHOP-14 and R-CHOP-14. Patients with multiple risk factors, however, had an improved event-free survival with DENSE-R-CHOP-14 (Pfreundschuh 2008; [3.2]).

I would caution community physicians about using this until we find out whether in fact R-CHOP-14 is superior to R-CHOP-21, because this is a toxic treatment program for the elderly. I'd be careful about using it in that particular patient population. ■

3.2

DENSE-R-CHOP-14 Compared to R-CHOP-14 from the RICOVER Trial for Elderly Patients with DLBCL

"Despite a less favorable study population DENSE-R-CHOP-14 resulted in a somewhat higher CR (83% vs 78%) and lower progression under therapy rate (5% vs 7%) rate, but event free and overall survival were not different compared to 8 biweekly applications of R.

However, a subgroup analysis of patients according to IPI risk group showed that DENSER-R-CHOP-14 resulted in a higher complete response rate of patients with poor-prognosis (IPI:3-5) disease (81% vs 68%) and in a better 1-year event-free survival rate (74% vs 65%) of these patients."

SOURCE: Pfreundschuh M et al. *Proc ASCO* 2008;**Abstract 8508**.

ADDITIONAL PUBLICATIONS DISCUSSED

Poeschel V et al. **Dose-dense rituximab in combination with biweekly CHOP-14 for elderly patients with diffuse large b-cell lymphoma (DLBCL): Results of a Phase-I/II and pharmacokinetic study of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL).** *Proc ASH* 2006;**Abstract 2738**.

Reiser M et al. **Serum levels and pharmacokinetic of rituximab in bi-weekly R-CHOP in elderly patients with DLBCL treated in the RICOVER-60 trial.** *Proc ASH* 2006;**Abstract 2748**.

Wiernik PH et al. **Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma.** *J Clin Oncol* 2008;26(30):4952-7.

Mantle-Cell Lymphoma

Journal Club Paper

Zinzani PL et al. **Confirmation of the efficacy and safety of lenalidomide oral monotherapy in patients with relapsed or refractory mantle-cell lymphoma: Results of an international study (NHL-003).** *Proc ASH* 2008;Abstract 262.

DR SMITH: This international study evaluated lenalidomide for patients with relapsed or refractory mantle-cell lymphoma. These patients had heavily pretreated disease: Patients had received a median of three prior treatments, and one fourth had received bortezomib.

Lenalidomide was administered daily, three weeks on, one week off, at 25 milligrams until either disease progression or toxicity.The overall response rate was 41 percent, including 13 percent CR/CRu and 28 percent partial responses (Zinzani 2008; [4.1]). Lenalidomide is active as a single agent in this heavily pretreated population. It was well tolerated, although some myelosuppression occurred, as you'd expect.

We'd like to achieve better results ultimately by perhaps evaluating lenalidomide in combination with other agents, but right now I believe that lenalidomide is a reasonable treatment to consider for relapsed mantle-cell lymphoma.

4.1

NHL-003: Efficacy and Safety of Lenalidomide Oral Monotherapy for Patients with Relapsed or Refractory Mantle-Cell Lymphoma (MCL)

Efficacy	Lenalidomide (n = 39)
Overall response rate	41%
Complete response (CR)/unconfirmed CR	13%
Partial response	28%
Adverse events (Grade III/IV)	
Neutropenia	51%
Thrombocytopenia	25%
Anemia	13%
Fatigue	10%
Febrile neutropenia	10%

SOURCE: Zinzani PL et al. *Proc ASH* 2008;**Abstract 262**.

Journal Club Paper

O'Connor O et al. **Schedule of bortezomib administration may be an important determinant of single-agent activity in patients with relapsed or refractory follicular (FL) lymphoma and mantle cell lymphoma (MCL).** *Proc ASCO* 2007;Abstract 8051.

DR SMITH: The bortezomib dosing question is interesting. From the myeloma standpoint, we administer it twice a week for two weeks, and some data evaluating rituximab/bortezomib reported that once-weekly bortezomib appeared to offer similar efficacy to twice-weekly bortezomib (De Vos 2006). Some of us tend to extrapolate that as, "You can administer it once a week at a little higher dose and do just as well, and it's easier for the patient."

The group at Memorial Sloan-Kettering had reported on a twice-weekly bortezomib schedule (O'Connor 2005), and in this study they used a once-weekly schedule. They reported that weekly dosing with bortezomib may not be as effective as twice weekly for patients with relapsed or refractory follicular lymphoma or mantle-cell lymphoma (O'Connor 2007; [4.2]), suggesting that as a single agent, bortezomib twice a week may be better than once a week.

DR MOSKOWITZ: When administered with chemotherapy, it may be different than as a single agent administered once a week. ■

4.2

Schedule of Single-Agent Bortezomib for Patients with Relapsed or Refractory Follicular Lymphoma or Mantle-Cell Lymphoma

"These data suggest weekly dosing with bortezomib may not be as effective as twice weekly. One difference in the schedules is the dose intensity and dose density. A cycle of twice weekly bortezomib administers 1.7 mg/m^2/week, while a weekly schedule administers only 1.2 mg/m^2/week, a 30% difference in dose intensity and a 100% difference in dose density (1.33 × per week vs 0.67 × per week).

What remains unclear from a pharmacologic perspective is the relative importance of high Cmax vs high AUC exposures, and their impact on both toxicity and efficacy. These data suggest that schedule is critical in the activity of bortezomib."

SOURCE: O'Connor O et al. *Proc ASCO* 2007;**Abstract 8051**.

ADDITIONAL PUBLICATIONS DISCUSSED

De Vos S et al. **Phase 2 study of bortezomib weekly or twice weekly plus rituximab in patients with follicular (FL) or marginal zone (MZL) lymphoma: Final results.** *Proc ASH* 2006;**Abstract 694**.

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

Cutaneous T-Cell Lymphoma (CTCL)

Journal Club Paper

Negro-Vilar A et al. **Efficacy and safety of denileukin diftitox (Dd) in cutaneous T-cell lymphoma (CTCL) patients: Integrated analysis of three large phase III trials.** *Proc ASCO* 2008;Abstract 8551.

DR HAGEMEISTER: Dr Negro-Vilar reported at ASCO 2008 on the efficacy and safety of denileukin diftitox in the treatment of CTCL. This report was an analysis involving patients receiving denileukin diftitox in three different trials.

The first trial included patients with CD25-positive, Stage IB through Stage IVA disease treated with nine µg/kg of denileukin diftitox for five days or 18 µg/kg for five days. The second was a three-arm study evaluating the same schedules of treatment versus placebo for patients with CD25-positive Stage IA through Stage III disease who'd received three or fewer prior treatments — a little earlier than the first trial. The third study

evaluated denileukin diftitox at 18 µg/kg for patients with CD25-positive disease that responded on previous trials and patients with CD25-negative, previously untreated disease.

Not surprisingly, overall, patients who received denileukin diftitox always fared better than patients who received placebo (Negro-Vilar 2008; [5.1]).

A question that was not addressed was that of the correct dose. It appeared to me that patients receiving the higher dose probably fared better as far as overall response was concerned. Also, patients with CD25-positive CTCL fared better than those with CD25-negative disease, although patients with CD25-negative disease still demonstrated responses (5.1).

The package insert states that patients must have CD25-positive disease, but these data indicate patient responses to denileukin diftitox independent of CD25 status.

I believe that the most important toxicity factor is that of capillary leaks requiring discontinuation of the drug. This occurred in only three percent of the patients.

The authors didn't report the overall risk of capillary leak or the severity in this entire set of trials. Grade III to Grade IV capillary leaks occurred in six percent of the patients, but only three percent discontinued therapy.

DR GREGORY: I've had success using denileukin diftitox earlier for patients with CTCL who were referred to me by dermatologists after standard treatments had failed. Patients with heavily pretreated disease don't tolerate this drug well. ■

5.1

Efficacy and Safety of Denileukin Diftitox (Dd) in Patients with CTCL: An Integrated Analysis of Three Phase III Trials

Efficacy	Dd treated (all) n = 263	Dd HD CD25+ n = 118	Dd HD CD25- n = 36	Placebo n = 44
Median PFS	794 days*	870 days*	>487 days*	124 days
ORR	38.0%*	47.5%*	30.6%	15.9%
CR/CCR	9.1%	11.0%	8.3%	2.3%
PR	28.9%	36.4%	22.2%	13.6%
PD	17.5%	11.0%	25.0%	52.3%

* $p < 0.02$ or better compared to placebo

HD = high dose; PFS = progression-free survival; ORR = overall response rate; CR = complete response; CCR = clinical complete response; PR = partial response; PD = progressive disease

SOURCE: Negro-Vilar A et al. *Proc ASCO* 2008;**Abstract 8551**.

ADDITIONAL PUBLICATION DISCUSSED

Gu H et al. **Phase II trial of pegylated liposomal doxorubicin (PLD), Rituxan, cyclophosphamide, vincristine, and prednisone in aggressive B-cell non-Hodgkin's lymphoma.** *Proc ASCO* 2008;**Abstract 8563**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **A trial of bendamustine/rituximab for relapsed or refractory CLL demonstrated an overall response rate of _____.**
   a. 77 percent
   b. 57 percent
   c. 37 percent
   d. None of the above
2. **A trial of bendamustine alone for rituximab-refractory indolent or transformed NHL demonstrated an overall response rate of _____.**
   a. 77 percent
   b. 57 percent
   c. 37 percent
   d. None of the above
3. **A trial of bendamustine/rituximab for relapsed or refractory indolent B-cell or mantle-cell lymphoma demonstrated an overall response rate of _____.**
   a. 92 percent
   b. 52 percent
   c. 32 percent
   d. None of the above
4. **Early results from a Phase III randomized trial comparing bendamustine/rituximab to R-CHOP as first-line therapy for follicular, indolent or mantle-cell lymphoma demonstrated that the two regimens have similar overall response rates.**
   a. True
   b. False
5. **Pulini and colleagues reported an overall response rate of _____ for patients with primary cutaneous lymphoma treated with pegylated liposomal doxorubicin.**
   a. 45 percent
   b. 68 percent
   c. 81 percent
6. **A meta-analysis of maintenance rituximab was evaluated in relapsed disease and concluded that maintenance rituximab after successful induction therapy improves _____ for relapsed follicular lymphoma.**
   a. Progression-free survival
   b. Overall survival
   c. Both a and b
7. **The NHL-003 study reported an overall response rate of _____ with lenalidomide oral monotherapy for patients with relapsed or refractory mantle-cell lymphoma.**
   a. 15 percent
   b. 25 percent
   c. 41 percent
   d. 52 percent
8. **In a Memorial Sloan-Kettering Cancer Center study for patients with relapsed or refractory mantle cell or follicular lymphoma, weekly dosing with bortezomib appeared to be as effective as twice-weekly dosing.**
   a. True
   b. False
9. **EORTC-20981, which evaluated maintenance rituximab versus observation following induction with CHOP or R-CHOP for relapsed/refractory follicular lymphoma, demonstrated that maintenance rituximab improves _____.**
   a. Progression-free survival
   b. Overall survival
   c. Both a and b
10. **An integrated analysis of three large Phase III trials evaluating efficacy and safety of denileukin diftitox (Dd) in patients with CTCL reported an overall response rate of _____ with Dd compared to placebo.**
    a. 15 percent
    b. 23 percent
    c. 38 percent
    d. 49 percent

Post-test answer key: 1a, 2a, 3a, 4a, 5c, 6c, 7c, 8b, 9a, 10c

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Integrating Emerging Clinical Research into the Practical Management of Non-Hodgkin Lymphomas and Chronic Lymphocytic Leukemia — Issue 1, 2009

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

How would you characterize your level of knowledge on the following topics?

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

	BEFORE	AFTER
Activity of bendamustine for relapsed/refractory chronic lymphocytic leukemia (CLL) or indolent lymphoma	4 3 2 1	4 3 2 1
Efficacy of ofatumumab for relapsed/refractory CLL	4 3 2 1	4 3 2 1
Maintenance rituximab following CHOP or R-CHOP for relapsed/refractory follicular lymphoma	4 3 2 1	4 3 2 1
Activity of fostamatinib or lenalidomide for relapsed/refractory diffuse large B-cell lymphoma	4 3 2 1	4 3 2 1
Dose and schedule of bortezomib for relapsed/refractory lymphoma	4 3 2 1	4 3 2 1
Denileukin diftitox for cutaneous T-cell lymphoma	4 3 2 1	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 learning objectives (LOs) by circling the appropriate selection:

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

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

- Develop an algorithm for the evaluation and treatment of newly diagnosed or relapsed/refractory chronic lymphocytic leukemia. . . . . 4 3 2 1 N/M N/A
- Apply the results of emerging research to effectively and safely integrate novel agents and regimens into the management of relapsed/refractory indolent lymphoma. . . . . 4 3 2 1 N/M N/A
- Counsel patients with follicular lymphoma about the risks and benefits associated with maintenance therapy. . . . . 4 3 2 1 N/M N/A
- Assess the utility of clinical and molecular biomarkers in the selection of first-line therapy for diffuse large B-cell lymphoma (DLBCL) . . . . . 4 3 2 1 N/M N/A
- Identify investigational agents under evaluation for relapsed/refractory DLBCL. . . 4 3 2 1 N/M N/A
- Communicate the existing and emerging roles of proteasome inhibitors and IMiDs® to patients with mantle-cell lymphomas. . . . . 4 3 2 1 N/M N/A
- Integrate currently available therapeutic strategies into the management of advanced cutaneous T-cell lymphoma. . . . . 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?

.....

Additional comments about this activity:

.....

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.

PART TWO — Please tell us about the faculty and moderator for this educational activity

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

Faculty	Knowledge of subject matter				Effectiveness as an educator			
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Stephanie A Gregory, MD	4	3	2	1	4	3	2	1
Fredrick B Hagemeister, MD	4	3	2	1	4	3	2	1
John P Leonard, MD	4	3	2	1	4	3	2	1
Vicki A Morrison, MD	4	3	2	1	4	3	2	1
Craig Moskowitz, MD	4	3	2	1	4	3	2	1
Kanti R Rai, MD	4	3	2	1	4	3	2	1
Mitchell R Smith, 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 faculty and moderator for this activity:

.....

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HOUJC109

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Hematologic Oncology™
UPDATE

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