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Visiting Professors

A case-based discussion on the management of non-Hodgkin lymphomas and chronic lymphocytic leukemia

CLINICAL INVESTIGATORS

John P Leonard, MD

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EDITOR

Neil Love, MD

COMMUNITY ONCOLOGISTS

Neil Morganstein, MD

Margaret A Deutsch, MD

Featuring two clinical investigators' perspectives on their time spent visiting patients with non-Hodgkin lymphomas and chronic lymphocytic leukemia in the clinics of community oncologists

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OVERVIEW OF ACTIVITY

Non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) comprise a heterogeneous group of lymphoproliferative disorders and belong to 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 use of existing treatments. Individualized treatment decisions are driven by disease-specific and patient-specific characteristics. In order to offer optimal patient care — including the option of clinical trial participation — practicing medical oncologists and hematologists must be well informed of these advances.

To provide clinicians with therapeutic strategies to address the disparate needs of patients with NHL or CLL, the *Visiting Professors* audio series employs an innovative case-based approach that unites the perspectives of leading NHL/CLL investigators and community oncologists as they explore the intricacies of making treatment decisions. Upon completion of this CME activity, medical oncologists and hematologists should be able to formulate an up-to-date and more complete approach to the care of patients with NHL or CLL.

LEARNING OBJECTIVES

- Use case-based learning, innovative communication strategies and shared clinical insight to provide comprehensive and compassionate oncology care.
- Refine current treatment approaches through appraisal of therapeutic advances in NHL and CLL.
- Communicate the existing and emerging therapeutic roles of proteasome inhibitors and IMiDs® to patients with NHL.
- Summarize the clinical results of combinations including novel alkylating agents such as bendamustine in the up-front treatment of mantle-cell lymphoma.
- Recall the rationale for and design of clinical trials investigating proteasome inhibitors as part of initial therapy in diffuse large B-cell lymphoma.
- Use prognostic and predictive clinical and molecular markers to aid in treatment decision-making for NHL and CLL.
- Counsel appropriately selected patients about the availability of ongoing clinical trial participation.

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CME INFORMATION

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Patients Discussed in This Program

Case 3: A 90-year-old woman is diagnosed with early-stage colon cancer after a positive PET scan performed as follow-up of FL treated with R-CVP (*from the practice of Dr Deutsch*)

Case 6: A 43-year-old man is diagnosed with Grade I FL after undergoing surgery for a large epidural mass (*from the practice of Dr Morganstein*)

Bendamustine/Rituximab (BR) as a Front-Line Option in FL

DR LOVE: Bruce, would you discuss the choice of up-front therapy in FL?

DR CHESON: Traditionally, R-CHOP has been the standard therapy in front-line FL. Recently, BR was compared to R-CHOP in a large randomized study for patients with FL, indolent lymphomas or MCL. It was a courageous study because R-CHOP has traditionally been the big gun in this area. Efficacy results demonstrated that not only was the response rate in these patients with previously untreated disease higher than 90 percent in both arms, but the complete remission rate and progression-free survival were also significantly better in the BR arm. In addition, considerably less toxicity was seen with BR (Rummel 2009; [1.1, 2.1]).

Bendamustine is an effective agent, and BR is a good alternative to a regimen such as R-CHOP or R-CVP, especially for older patients with FL, because it is well tolerated for the most part and not metabolized through the kidneys. With increasing age, patients tend to develop age-related renal dysfunction. Full doses of other drugs such as fludarabine cannot be administered to the elderly, but full doses of bendamustine can always be administered.

DR LOVE: Maggie, what experience, if any, do you have with bendamustine?

DR DEUTSCH: I have used bendamustine on occasion. I agree that it is relatively easy to use and is tolerable. Patients don't become particularly sick from it, and I believe my patient (Case 3) would have tolerated it better than R-CVP. We would not have had to worry about the growth factor issue, which was probably the thing that bothered her the most. I believe BR is an attractive alternative and certainly less toxic. It makes sense to consider first-line BR simply in terms of the overall toxicity profile.

DR LOVE: What would you be thinking if this patient's (Case 3) disease progressed at this point?

DR DEUTSCH: I would definitely administer BR. I would not go back to rituximab alone because she never responded to that to begin with. A bendamustine-based regimen would be my choice.

1.1 Efficacy Data from the Phase III Study Comparing Bendamustine/Rituximab (BR) to R-CHOP in the Front-Line Treatment of Follicular Lymphoma, Indolent Lymphomas and Mantle-Cell Lymphoma

	Overall response	Complete response	Progression-free survival	Time to next treatment
BR (n = 260)	93.8%	40.1%	54.8 months	Not reached
R-CHOP (n = 253)	93.5%	30.8%	34.8 months	40.7 months
p-value	—	0.0323	0.0002	0.0002

Rummel MJ et al. *Proc ASH* 2009;**Abstract 405**.

DR LOVE: John, do you have any comments on bendamustine and BR?

DR LEONARD: Bendamustine has been around since the 1960s in Germany. It has some features of an alkylating agent and of a purine analog. So some would argue that it is similar to those classes of drugs. However, clinically, it seems to be an interesting and exciting drug.

In the United States it was initially assessed in relapsed indolent lymphomas and was approved in rituximab-refractory FL, in which it had approximately an 80 percent response rate and a time to disease progression of about nine months. Since then, it has been studied in CLL and MCL in the relapsed setting, and the big buzz was at ASH 2009, when Rummel and colleagues presented the randomized trial of BR versus R-CHOP, predominantly in FL but also in other indolent lymphomas and MCL. The gist of this study is that BR seemed to be better than R-CHOP in progression-free survival and also seemed to be better tolerated — particularly, fewer infections, fewer cytopenias and less alopecia occurred (Rummel 2009; [1.1, 2.1]).

The data are still going to mature a bit, but BR is moving up front as an alternative to R-CHOP or R-CVP, especially for older patients and those for whom transformation is less of a concern. It is potentially as good as if not better than R-CHOP with less toxicity.

The question that I have about bendamustine relates to long-term marrow toxicity, so I am a little more cautious about using it for patients who are younger and to whom, down the line, I may want to administer stem cell transplant or radioimmunotherapy.

A companion report at ASH on stem cell collections looks fine, but this is an alkylating agent (Burchardt 2009; [1.2]) so I am concerned in the back of my mind about young patients. That being said, it seems to me that it is becoming harder and harder to justify using R-CVP and R-CHOP.

DR LOVE: John, have the Rummel data affected the choice of control arm in ongoing clinical trials?

DR LEONARD: The good thing is that we have other options, and the bad thing is that it does make the control arm for clinical trials more challenging. In fact, the cooperative group studies that are coming along are considering bendamustine-containing arms, in some cases as part of up-front therapies.

1.2 Stem Cell Mobilization After BR versus R-CHOP

	BR (n = 260)	R-CHOP (n = 253)
Number of patients with stem cell mobilization	23	23
Median CD34+ cell count	4.55 x 10^6/kg	6.17 x 10^6/kg
Median number of apheresis procedures	1.85	1.66
Number of patients with mobilization of <2.0 x 10^6/kg CD34+ cells	1	2

Burchardt CA et al. *Proc ASH* 2009;**Abstract 2679**.

Maintenance Rituximab After Initial Rituximab/Chemotherapy in FL

DR LOVE: John, do you have any updates on data with maintenance rituximab in FL after initial rituximab/chemotherapy induction?

DR LEONARD: In the PRIMA study, patients with FL received rituximab/chemotherapy, mostly R-CHOP or R-CVP, and were then randomly assigned to observation or maintenance rituximab. Improvement in progression-free survival with maintenance rituximab has been observed in this setting (Salles 2010; [1.3]). It is reasonable to administer maintenance rituximab after

rituximab/chemotherapy as initial therapy. I believe we need to see these data in full form with longer follow-up. We also have to be mindful of the toxicity of rituximab maintenance, which can include infections in this subset of patients. It is not quite a black and white issue, at least in my mind at this point.

1.3 PRIMA: Rituximab Maintenance for Two Years After Initial Response to Rituximab/Chemotherapy Induction in Untreated FL

	Observation (n = 513)	Rituximab maintenance (n = 505)	*p*-value	Hazard ratio
Two-year progression-free survival	66%	82%	<0.0001	0.50

Salles GA et al. *Proc ASCO* 2010;**Abstract 8004**.

Emerging Role of Immunomodulatory Agents in FL

DR LOVE: Bruce, what about immunomodulatory agents in FL?

DR CHESON: Lenalidomide is a second-generation IMiD® that has been approved for 5q-minus myelodysplastic syndromes and multiple myeloma.

A series of Phase II studies has shown that lenalidomide is active in FL and DLBCL, with a response rate of approximately 25 percent in each. A Phase II study in indolent lymphomas has demonstrated impressive activity with the combination of lenalidomide and rituximab, with an astounding response rate of 84 percent, and most of those responses were complete remissions (Fowler 2009a; [1.4]).

The CALGB is embarking on a confirmatory trial of this regimen in front-line FL.

1.4 Efficacy of Lenalidomide/Rituximab in the Front-Line Treatment of Indolent B-Cell Non-Hodgkin Lymphomas

OR	CR/CRu	PR
84%	79%	5%

OR = overall response; CR = complete response; CRu = unconfirmed complete response; PR = partial response

Fowler N et al. *Proc ASH* 2009a;**Abstract 1714**.

Encouraging Activity of Proteasome Inhibitors in FL

DR LOVE: Bruce, what about proteasome inhibition in FL?

DR CHESON: We have some interesting data with the proteasome inhibitors, particularly bortezomib. As a single agent, the response rate is in the range of 30 percent. However, the combination of bortezomib with rituximab is of interest.

A randomized Phase II trial in relapsed/refractory indolent lymphomas, evaluating a combination of rituximab with the standard schedule of bortezomib on days one, four, eight and 11 or with weekly bortezomib, has been published (de Vos 2009; [1.5]). The regimen with weekly bortezomib was equally efficacious and much less toxic.

Another approach has been to combine proteasome inhibition with bendamustine-based regimens. The Phase II VERTICAL study of weekly bortezomib/bendamustine/

rituximab (VBR) in relapsed or refractory FL has shown responses in excess of 80 percent (Fowler 2009b; [1.6]). We now plan to take this regimen to the front line to see if we can do even better.

1.5 Efficacy and Safety of Weekly or Twice-Weekly Bortezomib with Rituximab in Patients with Relapsed/Refractory Follicular or Marginal Zone B-Cell Lymphoma

	Arm A (rituximab with bortezomib 1.3 mg/m² twice weekly) N = 41	Arm B (rituximab with bortezomib 1.6 mg/m² weekly) N = 40
Overall response	49%	43%
Complete response/ unconfirmed complete response	14%	10%
Partial response	35%	33%
Time to disease progression	7.0 months	10.0 months
≥Grade III neutropenia	10%	3%
≥Grade III thrombocytopenia	10%	0%
≥Grade III nausea	10%	0%
≥Grade III neuropathy	10%	5%

De Vos S et al. *J Clin Oncol* 2009;27(30):5023-30.

1.6 VERTICAL Study: Efficacy and Safety of VBR in Relapsed/Refractory FL

OR	CR	PR	≥Grade III peripheral neuropathy
84%	47%	37%	6%

OR = overall response; CR = complete response; PR = partial response

Fowler N et al. *Proc ASH* 2009b;**Abstract 933**.

Select publications

Burchardt CA et al. **Peripheral blood stem cell mobilization after bendamustine containing chemotherapy in indolent lymphomas is possible. Results from the phase III study of B-R vs CHOP-R (NHL 1-2003 trial) of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 2679**.

De Vos S et al. **Multicenter randomized phase II study of weekly or twice-weekly bortezomib plus rituximab in patients with relapsed or refractory follicular or marginal zone B-cell lymphoma.** *J Clin Oncol* 2009;27(30):5023-30.

Fowler N et al. **A biologic combination of lenalidomide and rituximab for front-line therapy of indolent B-cell non-Hodgkin's lymphoma.** *Proc ASH* 2009a;**Abstract 1714**.

Fowler N et al. **Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: Encouraging activity in the phase 2 VERTICAL Study.** *Proc ASH* 2009b;**Abstract 933**.

Rummel MJ et al. **Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 405**.

Salles GA et al. **Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immuno-chemotherapy.** *Proc ASCO* 2010;**Abstract 8004**.

MANTLE-CELL LYMPHOMA (MCL)

Patients Discussed in This Program

Case 1: A 65-year-old woman initially thought to have colon cancer is diagnosed with MCL with bone marrow involvement (*from the practice of Dr Morganstein*)

Case 5: A 62-year-old woman with Stage IIA MCL receives R-CHOP induction therapy (*from the practice of Dr Deutsch*)

BR as a Front-Line Induction Option for Older Patients in MCL

DR LOVE: Bruce, would you discuss the front-line options appropriate in MCL?

DR CHESON: Currently, R-hyper-CVAD is used for younger patients or those at higher risk, and R-CHOP is used for older patients. The hyper-CVAD regimen developed at MD Anderson has been considered a standard, particularly for patients younger than age 60 or 65. Older patients cannot tolerate it well.

SWOG further investigated this regimen and was unable to reproduce the findings at MD Anderson. Therefore, whether this should be the standard is not clear. With R-CHOP, the response rate has been high — in the range of 80 to 90 percent — with many complete remissions. However, the durability of responses has been disappointing, with the median duration of response ranging from 18 to 22 months. Better therapy is clearly needed for MCL.

Other drugs effective in MCL include bortezomib, lenalidomide and bendamustine. An Intergroup study is being planned in first-line MCL. The study will randomly assign patients with MCL to BR, bendamustine/bortezomib/rituximab or BR followed by lenalidomide maintenance therapy. This study will address several important questions.

We are also interested in up-front BR for MCL because the response rate with BR in relapsed/refractory MCL is higher than 90 percent, with 50 to 60 percent of those responses being complete remissions lasting a median of about two years. Nothing else touches that in the relapsed setting. Because BR is that good in the relapsed setting, we hope it will be even more efficacious when used up front.

DR LOVE: John, how do you see BR as up-front therapy in MCL?

DR LEONARD: The study by Rummel presented at ASH comparing BR to R-CHOP had patients with MCL. Although it did not have a huge number of patients with MCL, it is one of the few randomized studies in MCL. The efficacy results showed an improved progression-free survival with BR compared to R-CHOP. In addition, the safety profile was better on the BR arm (Rummel 2009; [2.1]).

In view of this, I believe that when more intensive treatments are not being used in MCL, especially for elderly patients, using a BR-based approach as opposed to an R-CHOP-based approach may make sense. Three US cooperative groups are now collaborating on a proposal for evaluating BR-based regimens as initial therapy in MCL.

2.1 Safety Data from the Phase III Study Comparing Bendamustine/Rituximab (BR) to R-CHOP in the Front-Line Treatment of Follicular, Indolent and Mantle-Cell Lymphomas

	Grade III/IV neutropenia	Infectious complications	Peripheral neuropathy	Stomatitis	Rash	Alopecia
BR (n = 260)	10.7%	36.5%	6.9%	6.2%	16.2%	15.0%
R-CHOP (n = 253)	46.5%	47.8%	28.8%	18.6%	9.1%	62.0%
p-value	<0.0001	0.0403	<0.0001	<0.0001	0.0122	Not reported

Rummel MJ et al. *Proc ASH* 2009;**Abstract 405**.

Potential Role of Maintenance Rituximab in MCL

DR LOVE: John, could you discuss maintenance rituximab in MCL?

DR LEONARD: This is difficult to answer. Maintenance rituximab has no role in DLBCL after rituximab/chemotherapy. Data in that setting are negative — not adverse, but not positive — so it is clear in DLBCL. In FL the role of maintenance rituximab is clear and positive. In MCL it is a middle ground right now. Certain studies suggest that is does not offer much value. But one small randomized study in MCL suggested some benefit with maintenance rituximab (Forstpointner 2006; [2.2]). One could also argue that the Nordic investigators in MCL (Anderson 2009), who used an intensive approach and administered preemptive rituximab when patients experienced molecular relapses, were almost using rituximab maintenance, and that might add benefit.

2.2 Effect of Rituximab Maintenance on Duration of Response After Salvage R-FCM (Rituximab/Fludarabine/Cyclophosphamide/Mitoxantrone) in Patients with Recurrent/Refractory MCL

	Observation (n = 29)	Rituximab maintenance (n = 28)	*p*-value
Two-year remission rate	9%	45%	0.049

Forstpointner R et al. *Blood* 2006;108(13):4003-8.

Clinical Trials of Proteasome Inhibitors as Up-Front Therapy in MCL

DR LOVE: John, what about newer research approaches in MCL?

DR LEONARD: Incorporating new agents into initial therapy for MCL makes a lot of sense. Bortezomib, which is approved for relapsed MCL and is certainly active in that setting, is being combined with other agents in several different studies. We at Cornell did an R-CHOP with bortezomib study, which suggests some benefit to adding bortezomib, although not a dramatic effect (Ruan 2009; [2.3]). SWOG has a study administering bortezomib in combination with R-CHOP followed by bortezomib maintenance. Brad Kahl has done a study of modified R-hyper-CVAD with bortezomib (Kahl 2009; [2.4]). The CALGB has done a study of intensive induction with autotransplant followed by bortezomib as either maintenance or consolidation.

2.3 Efficacy and Safety of R-CHOP with Bortezomib at 1.0 mg/m^2 (n = 4) or 1.3 mg/m^2 (n = 32) on Days One and Four of Each Cycle for a Total of Six Cycles

N (intent to treat)	OR	CR/CRu	PFS	Two-year survival	≥Grade III peripheral neuropathy
36	81%	64%	21 months	86%	2.7%

OR = overall response; CR = complete response; CRu = unconfirmed complete response; PFS = progression-free survival

Ruan J et al. *Proc ASH* 2009;**Abstract 2682**.

2.4 Efficacy and Safety of Up-Front Bortezomib with R-Hyper-CVAD (VcR-CVAD) Followed by Maintenance Rituximab in MCL

N	OR	CR	PR	≥Grade III peripheral neuropathy
76	96%	75%	21%	0%

OR = overall response; CR = complete response; PR = partial response

Kahl BS et al. *Proc ASH* 2009;**Abstract 1661**.

I believe several single-arm studies are evaluating bortezomib as part of initial therapy.

One study is evaluating substituting bortezomib for vincristine in R-CHOP. No randomized trial in MCL has ever been conducted in the United States, so I believe interpreting single-arm Phase II studies will be a challenge. However, bortezomib is being explored as part of front-line therapy in MCL, and more data will be available in a few years.

Studies of lenalidomide maintenance therapy after rituximab/chemotherapy induction therapy and of single-agent lenalidomide in relapsed MCL are ongoing. Bendamustine is also active in MCL, and a few newer agents, including mTOR inhibitors and the PI3-kinase inhibitor, may also have activity.

Amelioration of Bortezomib-Associated Neuropathy in MCL

DR LOVE: Neil, what is your experience with bortezomib in MCL, particularly in terms of neuropathy?

DR MORGANSTEIN: Neuropathy is something you have to watch for. If you are vigilant about it and ask questions on every visit, then you can catch it early. You can then intervene earlier either by dose reduction or discontinuation. With this approach, I have been pretty lucky, and neuropathy has been manageable. Patients do develop it, but they fare well with dose reductions.

DR LOVE: Bruce, what do you think about the issue of neuropathy and bortezomib in MCL?

DR CHESON: With day one, four, eight and 11, a risk of neuropathy is present, and the neuropathy is not always reversible. In the study of bendamustine/bortezomib/rituximab, many patients had to come off study because of neuropathy. When bortezomib is used on the weekly schedule, it causes significantly less neurotoxicity. I am pushing for the weekly schedule to be included in our studies.

It is hoped that the second-generation proteasome inhibitors, such as MLN 9708, will be as effective and perhaps cause less neurotoxicity, but that remains to be seen.

Select publications

Andersen NS et al. **Pre-emptive treatment with rituximab of molecular relapse after autologous stem cell transplantation in mantle cell lymphoma.** *J Clin Oncol* 2009;27(26):4365-70.

Forstpointner R et al. **Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG).** *Blood* 2006;108(13):4003-8.

Gerecitano J et al. **Phase 2 study of weekly bortezomib in mantle cell and follicular lymphoma.** *Br J Haematol* 2009;146(6):652-5.

Kahl BS et al. **The VcR-CVAD regimen produces a high complete response rate in untreated mantle cell lymphoma (MCL): First analysis of E1405 — A phase II study of VcR-CVAD with maintenance rituximab for MCL.** *Proc ASH* 2009;**Abstract 1661**.

Ruan J et al. **CHOP-R + bortezomib as initial therapy for mantle cell lymphoma (MCL).** *Proc ASH* 2009;**Abstract 2682**.

Rummel MJ et al. **Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 405**.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Patients Discussed in This Program

Case 4: A 49-year-old man is cared for with "active surveillance" for Stage 0 CLL (*from the practice of Dr Deutsch*)

Case 7: A 57-year-old woman with CLL receives second-line BR after 17p deletion is diagnosed at relapse (*from the practice of Dr Morganstein*)

Case 9: A 63-year-old man with CLL/small lymphocytic lymphoma and 17p deletion attains a short-duration partial response with FR followed by observation during indolent disease progression (*from the practice of Dr Morganstein*)

Treatment Options in Front-Line CLL

DR LOVE: Bruce, what are the options for front-line treatment of CLL?

DR CHESON: The recently FDA-approved standard approach to front-line therapy for CLL is FCR — fludarabine/cyclophosphamide/rituximab — based on a large study from the German CLL Study Group and their colleagues in Europe. The study demonstrated not only a benefit in progression-free survival but also a survival advantage with the addition of rituximab to FC (Hallek 2009; [3.1]).

However, I don't use FCR. I know the country is split on this. The FR camp, the FCR camp and now the BR camp all exist. The German CLL Study Group presented Phase II data with BR as front-line therapy for CLL (Fischer 2009; [3.2]). The response rates were higher than 90 percent, with a significant proportion being complete remissions. A randomized trial of FCR versus BR is now being conducted, which, again, could change the front-line therapy for CLL.

In elderly patients the fludarabine dose has to be modified because of age-related renal insufficiency. However, with bendamustine full doses could be administered despite renal insufficiency. Therefore, BR is front-

3.1 CLL 8: A Phase III Trial Comparing Fludarabine/Cyclophosphamide/Rituximab (FCR) to FC for Patients with Previously Untreated CLL (N = 817)

	FCR	FC	*p*-value
OR	95.1%	88.4%	Not reported
CR	44.1%	21.8%	<0.001
PFS	51.8 months	32.8 months	<0.001
OS at 37.7 months	84.1%	79.0%	0.01

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

Hallek M et al. *Proc ASH* 2009;**Abstract 535**.

3.2 Phase II Multicenter Trial of BR in Advanced Untreated CLL (n = 117)

OR	CR	PR/nodular PR	SD
90.9%	32.7%	58.2%	9.1%

OR = overall response; CR = complete response; PR = partial response; SD = stable disease

Fischer K et al. *Proc ASH* 2009;**Abstract 205**.

line therapy for CLL at our institution for a patient who is not on a clinical trial. I know that this preference is not the norm, but that's what we use. Otherwise, we would use FR rather than FCR.

DR LOVE: John, what is your opinion on bendamustine or BR in CLL?

DR LEONARD: Bendamustine is an active drug and is used both in the relapsed and the up-front settings. Some Phase II studies have been evaluating it as up-front therapy, both alone and with rituximab.

We have seen some encouraging results, and Phase III studies are ongoing now. I believe it is a reasonable choice in CLL based on the data that we have.

I have not observed many people using it up front, and we generally have not been using it up front.

DR LOVE: Maggie, what is your usual approach to treatment of CLL?

DR DEUTSCH: I have not used bendamustine for these patients. I have used fludarabine in the past, although I find it to be a difficult drug to use, especially because of cytopenias. I have had several patients who developed prolonged cytopenias that don't seem to get better for weeks.

DR LOVE: Neil, what went into your initial decision to use FR as opposed to FCR for the patient in Case 7?

DR MORGANSTEIN: I have used both FR and FCR, and I believe that FCR is substantially more toxic, with more side effects.

Although FCR is a popular regimen, I am not completely convinced that we are providing benefit to all patients. I use it for patients who need a quick response, but I don't use it for everybody.

Role of Alemtuzumab in CLL

DR LOVE: Bruce, is anything new with alemtuzumab, and how do you use it in your practice?

DR CHESON: Alemtuzumab is an anti-CD52 monoclonal antibody that is approved for relapsed CLL. When administered intrave-

nously, it is associated with fever, rigors and other symptoms that require a great deal of premedication.

When administered subcutaneously, patients experience fewer adverse effects, but they are still there. Alemtuzumab is also immunosuppressive and knocks out both B cells and T cells. Therefore, patients are at risk for opportunistic infections and need triple prophylaxis with antifungal, antiviral and antibacterial agents. A randomized Phase II study of fludarabine/alemtuzumab versus fludarabine alone for relapsed disease was reported at ASH 2009 and showed an advantage with the combination (Engert 2009; [3.3]).

Recently, a randomized, multicenter Phase III study compared FCR to fludarabine/cyclophosphamide/alemtuzumab (FCA) in frontline CLL. The FCR arm was at least as efficacious and substantially less toxic (Lepretre 2009). Therefore, the preferred antibody in the initial treatment of CLL should remain rituximab rather than alemtuzumab.

The CALGB conducted a study with induction FR followed by consolidation alemtuzumab and sought to determine whether alemtuzumab as consolidation can improve the CR rate and eradicate minimal residual disease (MRD) in patients with previously untreated CLL.

Alemtuzumab consolidation improved the CR and MRD-negative rates after induction FR (Lin 2009; [3.4]). However, it resulted in significant toxicity, particularly a marked increase in opportunistic infections, several of which were fatal.

Those patients who became MRD-negative from the alemtuzumab consolidation therapy appear to have a longer survival, although longer follow-up is needed.

I have used alemtuzumab several times and had some impressive results with a number of patients with responses that lasted for years. However, the likelihood of reactiva-

3.3 Improved Progression-Free Survival with Alemtuzumab/Fludarabine Compared to Fludarabine Alone as Second-Line Treatment of CLL

	Fludarabine/alemtuzumab (n = 168)	**Fludarabine (n = 167)**	***p*-value**
OR	84.8%	67.9%	<0.001
CR	30.4%	16.4%	0.002
PFS	29.6 months	20.7 months	0.005

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

Engert A et al. *Proc ASH* 2009;**Abstract 537**.

3.4 Consolidation Therapy with Subcutaneous Alemtuzumab After FR Induction Therapy in Untreated CLL

	OR	**CR**	**PR**	**MRD-negative**
After induction FR (n = 102)	90%	29%	61%	15%
After consolidation alemtuzumab (n = 58)	91%	66%	26%	50%

OR = overall response; CR = complete response; PR = partial response; MRD = minimal residual disease

Lin TS et al. *Proc ASH* 2009;**Abstract 210**.

tion of cytomegalovirus is 25 to 30 percent. Alemtuzumab is active but has side effects.

DR LOVE: John, where does alemtuzumab fit in your algorithm for CLL?

DR LEONARD: Alemtuzumab is one of the agents that can be relatively more useful in patients with 17p deletion. It is better for patients with marrow and blood disease than for those with lymph node disease. The infectious issues are not trivial, and prophylaxis is necessary. However, it is a useful drug, particularly for patients with 17p deletion. The strategies that have been pursued the most with alemtuzumab in CLL have been evaluating the combinations and maintenance in patients at higher risk. As we get more experience with it, the infectious issues will be more manageable. In the context of Case 7 and the patient having deletion 17p, we discussed using maintenance alemtuzumab after BR in an attempt to maintain her remission. It is an interesting idea, though the risk-benefit profile of such an approach is currently not clear. This approach could also be reasonable for the patient in Case 9, certainly, in view of the 17p deletion.

DR LOVE: John, what kind of prophylaxis do you use with alemtuzumab?

DR LEONARD: This involves a learning curve. Antiviral prophylaxis with valganciclovir — and being mindful of cytomegalovirus if the patient is developing fevers and other related symptoms — is important. Trimethoprim/sulfamethoxazole for pneumocystis prophylaxis and fluconazole for fungal prophylaxis are often incorporated. All of these add up. However, for certain patients, alemtuzumab can be a useful agent.

Activity of Immunomodulatory Agents in CLL

DR LOVE: Bruce, what about lenalidomide in CLL?

DR CHESON: Lenalidomide is an immunomodulatory drug that has clinical activity in CLL. For patients with relapsed/refractory CLL, two major single-agent trials (Chanan-Khan 2006; Ferrajoli 2008) with responses in the range of 35 to 45 percent have been conducted.

A Phase II study of lenalidomide/rituximab in relapsed/refractory CLL was published at ASH 2009 and showed response rates higher than what would be expected with either agent alone in this setting (Ferrajoli 2009; [3.5]).

This drug has interesting adverse effects, including tumor lysis syndrome and tumor flare reaction. These are important for the practicing clinician to recognize. After a week or so of administration of lenalidomide for CLL, the patients will call and say that their lymph nodes have swollen greatly and are hurting. Their white blood cell counts also increase. It is treated with aspirin, and it goes away quickly. Before we recognized tumor flare as an adverse effect of lenalidomide in CLL, these patients were being sent for a biopsy. It has been suggested that tumor flare might be predictive of a favorable outcome, although it is not known for sure.

We have a Phase I study at our institution of bendamustine with lenalidomide. We will also add rituximab as a potential new strategy for these patients. An Intergroup study of FR versus FCR versus FR followed by lenalidomide maintenance is also in progress. Lenalidomide has potential in CLL, and I believe that it can be a useful drug.

3.5 Phase II Study of Lenalidomide/Rituximab in Relapsed/Refractory CLL (n = 37)

OR	Nodular PR	PR	SD
68%	16%	51%	16%

OR = overall response; PR = partial response; SD = stable disease

Ferrajoli A et al. *Proc ASH* 2009;**Abstract 206**.

DR LOVE: Cost and reimbursement issues aside, could lenalidomide be offered outside of a protocol setting right now?

DR CHESON: We offer it outside of a protocol setting. We did not have any problems with reimbursement because we tend to use BR up front, and for our second line we have a variety of new agents in clinical trials. We tend to use lenalidomide in the third line onward, particularly for elderly patients.

Many patients in this setting cannot tolerate other options such as OFAR (oxaliplatin/fludarabine/cytarabine/rituximab), CFAR (cyclophosphamide/fludarabine/rituximab/alemtuzumab) or R-CHOP.

Select publications

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.

Engert A et al. **Improved progression-free survival (PFS) of alemtuzumab plus fludarabine versus fludarabine alone as second-line treatment of patients with B-cell chronic lymphocytic leukemia: Preliminary results from a phase III randomized trial.** *Proc ASH* 2009;**Abstract 537**.

Ferrajoli A et al. **Combination therapy with lenalidomide and rituximab in patients with relapsed chronic lymphocytic leukemia (CLL).** *Proc ASH* 2009;**Abstract 206**.

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

Fischer K et al. **Bendamustine combined with rituximab (BR) in first-line therapy of advanced CLL: A multicenter phase II trial of the German CLL Study Group.** *Proc ASH* 2009;**Abstract 205**.

Hallek M et al. **First-line treatment with fludarabine, cyclophosphamide, and rituximab (FCR) improves overall survival in previously untreated patients with advanced chronic lymphocytic leukemia (CLL): Results of a randomized phase III trial on behalf of an international group of investigators and the German CLL study group.** *Proc ASH* 2009;**Abstract 535**.

Lepretre S et al. **Immunochemotherapy with fludarabine, cyclophosphamide and rituximab (FCR) versus fludarabine, cyclophosphamide and MabCampath (FCCam) in previously untreated patients with advanced B-chronic lymphocytic leukemia (B-CLL): Experience on safety and efficacy within a randomised multicenter phase III trial of the French cooperative group on CLL and WM (FCGCLL/MW) and the "Groupe Ouest-Est d'Etudes des Leucémies Aigües et Autres Maladies du Sang" (GOELAMS): CLL2007FMP (for fit medically patients).** *Proc ASH* 2009;**Abstract 538**.

Lin TS et al. **Consolidation therapy with subcutaneous alemtuzumab after fludarabine and rituximab (FR) induction therapy improves the complete response (CR) rate in chronic lymphocytic leukemia (CLL) and eradicates minimal residual disease (MRD) but is associated with severe infectious toxicity: Final analysis of CALGB study 10101.** *Proc ASH* 2009;**Abstract 210**.

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

Patients Discussed in This Program

Case 2: A 48-year-old man with large liver masses is diagnosed with DLBCL and treated with R-CHOP-14 and intrathecal methotrexate (*from the practice of Dr Morganstein*)

Case 11: A 46-year-old man with B-cell lymphoma diagnosed on a needle biopsy of a paraspinal mass receives R-CHOP (*from the practice of Dr Deutsch*)

Dose-Dense Chemotherapy in DLBCL

DR LOVE: John, would you comment on R-CHOP-14 versus R-CHOP-21 in DLBCL?

DR LEONARD: The German group considered CHOP-14 versus CHOP-21, particularly for older patients with large-cell lymphoma, and suggested a benefit to the 14-day schedule of CHOP in older patients. When rituximab came along, the Germans stuck with the 14-day schedule, R-CHOP-14, whereas most in the US switched from CHOP-21 to R-CHOP-21. The question remained whether the 14-day versus 21-day schedule makes a difference when rituximab is administered with CHOP.

So far, two studies examining this issue have been preliminarily reported. A randomized Phase III study reported similar response rates and similar safety (Cunningham 2009; [4.1]). The similar safety is likely a result of uniform growth factor use — that is, pegfilgrastim — on the 14-day schedule and less routine use in the 21-day schedule.

The other study focused on older patients, and an interim analysis was presented at ASH 2009. The efficacy was similar with both schedules and perhaps a little bit better with the 21-day schedule (Delarue 2009; [4.2]). However, growth factors were not used uniformly in the 14-day schedule. Therefore, the dose intensity of the 14-day schedule was less than what one might expect. So it was not dose-dense therapy in the truest form, and I believe this is an imperfect study.

I use the 21-day schedule. I know that many people use the 14-day schedule, which is reasonable. R-CHOP-14 is not unreasonable to use for sicker patients, in whom a more rapid response is needed, or among patients with whom you simply want to move things forward a little faster. However, the 21-day schedule is probably, for most patients, the standard approach. We eagerly await the final results of these ongoing studies.

4.1 R-CHOP-14 versus R-CHOP-21 in Newly Diagnosed DLBCL (N = 1,080)

	R-CHOP-14	R-CHOP-21
Complete response/unconfirmed complete response	47%	47%
Grade III/IV neutropenia	31%	57%
Grade III/IV thrombocytopenia	9%	5%
Grade III/IV infection	17%	22%

Cunningham D et al. *Proc ASCO* 2009;**Abstract 8506**.

4.2 R-CHOP-14 versus R-CHOP-21 for Elderly Patients with DLBCL

	R-CHOP-14 (n = 103)	R-CHOP-21 (n = 98)	*p*-value
Complete response/unconfirmed complete response	67%	75%	Not significant
Two-year event-free survival	48%	61%	Not significant
Two-year overall survival	67%	70%	Not significant

Delarue R et al. *Proc ASH* 2009;**Abstract 406**.

Proteasome Inhibition as a Potential Strategy in the Nongerminal Center Subtype of DLBCL

DR LOVE: John, what about studies evaluating molecular profiling in DLBCL?

DR LEONARD: A study that I believe is of interest is evaluating R-CHOP versus R-CHOP in combination with bortezomib in previously untreated nongerminal center or activated B-cell DLBCL. Patients are immediately classified centrally as having activated B-cell subtype disease and then randomly assigned to R-CHOP or R-CHOP with bortezomib.

The activated B-cell or nongerminal center subtype seems to have activation of NF-kappa-B, which is associated with a less favorable prognosis. The question is whether inhibition of NF-kappa-B with bortezomib may overcome the less favorable prognosis of this subtype of DLBCL.

Also, lenalidomide has activity in large-cell lymphoma as a single agent, with responses of approximately 25 percent in the relapsed setting. A Phase I/II study of R-CHOP/lenalidomide was presented at ASH 2009, which suggested that the addition of lenalidomide to R-CHOP did not affect hematological recovery and did not result in treatment delays (Nowakowski 2009).

Another ongoing major clinical trial in DLBCL, which aims to prospectively assess molecular profiling, is the Intergroup trial led by the CALGB.

That study involves a comparison between standard R-CHOP and the infusional dose-adjusted R-EPOCH regimen developed by the National Cancer Institute investigators for previously untreated DLBCL.

The study is trying to identify whether molecular signatures such as germinal-center type DLBCL or activated B-cell type DLBCL may be correlated with outcome after either dose-adjusted R-EPOCH or standard R-CHOP-21 therapy.

Select publications

Cunningham D et al. **A phase III trial comparing R-CHOP-14 and R-CHOP-21 for the treatment of patients with newly diagnosed diffuse large B-cell non-Hodgkin's lymphoma.** *Proc ASCO* 2009;**Abstract 8506**.

Delarue R et al. **R-CHOP-14 compared to R-CHOP-21 in elderly patients with diffuse large B-cell lymphoma: Results of the interim analysis of the LNH03-6B GELA study.** *Proc ASH* 2009;**Abstract 406**.

Nowakowski GS et al. **A Phase I/II trial of lenalidomide and RCHOP (R2CHOP) in patients with newly diagnosed diffuse large B-cell (DLBCL) and follicular grade 3 lymphoma.** *Proc ASH* 2009;**Abstract 1669**.

T-CELL LYMPHOMAS

Patients Discussed in This Program

Case 8: A 65-year-old man with massive ascites, cytopenia and diffuse adenopathy is diagnosed with T-cell angioimmunoblastic lymphoma with t(2;5) translocation (*from the practice of Dr Morganstein*)

Case 10: A 27-year-old woman is found to have atypical lymphoid cell population on an excisional biopsy of a localized cutaneous right axillary mass (*from the practice of Dr Deutsch*)

Newly Approved Agents Pralatrexate and Romidepsin in T-Cell Lymphomas

DR LOVE: John, what are some of the new agents for T-cell lymphomas that may be relevant in Case 8?

DR LEONARD: We have a couple of new drugs available for T-cell lymphomas, and in some of these studies patients with angioimmunoblastic disease have been included. One that may be most relevant to this patient (Case 8) is pralatrexate, a novel antifolate agent. It has an approximately 30 percent response rate in recurrent peripheral T-cell lymphomas, and it is administered weekly on an outpatient basis. The primary side effects are nausea and cytopenias. Patients also experience mucositis, so it's important to supplement treatment with vitamin B12 and folate as supportive care. Histone deacetylase inhibitors such as vorinostat and romidepsin are also active in T-cell lymphomas.

DR LOVE: Bruce, what's your perspective on these newer drugs for T-cell lymphomas?

DR CHESON: Pralatrexate was recently approved on the basis of the PROPEL trial, which is an international Phase II study evaluating pralatrexate for patients with relapsed/refractory peripheral T-cell lymphoma. The response rate in the study was 27 percent (O'Connor 2009).

The other drug, romidepsin, is a histone deacetylase inhibitor. It has activity in cutaneous T-cell lymphoma and has a 25 to 30 percent or higher response rate in peripheral T-cell lymphomas.

Alemtuzumab in T-Cell Lymphomas

DR CHESON: Alemtuzumab is another drug that has activity in T-cell lymphoma. A study of CHOP/alemtuzumab in patients with peripheral T-cell lymphoma was recently presented (5.1). The results were interesting, but it was a relatively small trial with short follow-up. However, at this time it should not be used outside of a clinical trial because of the predilection for infections with alemtuzumab, which may enhance the already increased risk in patients with T-cell lymphomas.

5.1 Phase II Study of CHOP/Alemtuzumab as Front-Line Therapy in Peripheral T-Cell Lymphomas (N = 24)

OR	CR	PR	One-year overall survival
75%	70.8%	4.2%	70%

OR = overall response; CR = complete response; PR = partial response

Gallamini A et al. *Blood* 2007;110:2316-23.

Select publications

Gallamini A et al. **Alemtuzumab (Campath-1H) and CHOP chemotherapy as front-line treatment of peripheral T-cell lymphoma: Results of a GITIL multicenter trial.** *Blood* 2007;110(7):2316-23.

O'Connor O et al. **PROPEL: Results of the pivotal, multicenter, phase II study of pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).** *Proc ASCO* 2009;**Abstract 8561**.

Piekarz R et al. **Final results of a phase 2 NCI multicenter study of romidepsin in patients with relapsed peripheral T-cell lymphoma (PTCL).** *Proc ASH* 2009;**Abstract 1657**.

Savage KJ et al. **Pralatrexate induces responses in patients with highly refractory peripheral T-cell lymphoma (PTCL).** *Proc ASH* 2009;**Abstract 1678**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **What is the median progression-free survival for patients on the BR arm in the German trial comparing BR to R-CHOP in the up-front treatment of FL, indolent lymphomas and MCL?**
   a. 24.8 months
   b. 34.8 months
   c. 54.8 months

2. **What is the complete response rate for patients on the BR arm in the German trial comparing BR to R-CHOP in the up-front treatment of FL, indolent lymphomas and MCL?**
   a. 20.1 percent
   b. 40 percent
   c. 60.1 percent

3. **The overall response rate reported by Fowler and colleagues at ASH 2009 with lenalidomide/rituximab in the up-front treatment of FL was _____.**
   a. 34 percent
   b. 54 percent
   c. 84 percent

4. **What is the incidence of Grade III or higher peripheral neuropathy with bortezomib/bendamustine/rituximab in the VERTICAL trial in relapsed/refractory FL?**
   a. Six percent
   b. 20 percent
   c. 40 percent

5. **Which of the following has been achieved in FL with maintenance rituximab after initial induction with rituximab/chemotherapy?**
   a. Improvement in progression-free survival
   b. Improvement in overall survival
   c. Both a and b
   d. Neither a nor b

6. **What is the incidence of Grade III or higher peripheral neuropathy, as reported by Ruan and colleagues at ASH 2009, with the combination of bortezomib and R-CHOP as up-front therapy in MCL?**
   a. 2.7 percent
   b. 18.7 percent
   c. 38.7 percent

7. **A trial of alemtuzumab/fludarabine versus fludarabine alone in second-line CLL demonstrated an improvement in _____ with the combination.**
   a. Complete response
   b. Overall response
   c. Progression-free survival
   d. All of above

8. **Which of the following is true regarding R-CHOP-14 versus R-CHOP-21 in DLBCL?**
   a. R-CHOP-14 has better efficacy than R-CHOP-21
   b. R-CHOP-14 has better safety than R-CHOP-21
   c. Neither a nor b

9. **Proteasome inhibition is being investigated as a potential therapeutic strategy in the _____ subtype of DLBCL.**
   a. Germinal center
   b. Nongerminal center

10. **What is the overall response rate reported by Fischer and colleagues at ASH 2009 with BR in the initial treatment of CLL?**
    a. 90.9 percent
    b. 60.9 percent
    c. 40.9 percent

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

Educational Assessment and Credit Form
Visiting Professors Hematologic Oncology, Issue 1, 2010

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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
Utility of BR in the treatment of CLL and MCL	4 3 2 1	4 3 2 1
Clinical trials of bortezomib as part of first-line therapy in MCL	4 3 2 1	4 3 2 1
Interim PET scans in the management of DLBCL	4 3 2 1	4 3 2 1
Clinical trial results with lenalidomide/rituximab in FL	4 3 2 1	4 3 2 1
Maintenance rituximab in different subtypes of NHL	4 3 2 1	4 3 2 1
Efficacy and safety of alemtuzumab in CLL	4 3 2 1	4 3 2 1

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

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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:

- Use case-based learning, innovative communication strategies and shared clinical insight to provide comprehensive and compassionate oncology care. . . . . 4 3 2 1 N/M N/A
- Refine current treatment approaches through appraisal of therapeutic advances in NHL and CLL. . . . . 4 3 2 1 N/M N/A
- Communicate the existing and emerging therapeutic roles of proteasome inhibitors and IMiDs to patients with NHL. . . . . 4 3 2 1 N/M N/A
- Summarize the clinical results of combinations including novel alkylating agents such as bendamustine in the up-front treatment of mantle-cell lymphoma. . . . . 4 3 2 1 N/M N/A
- Recall the rationale for and design of clinical trials investigating proteasome inhibitors as part of initial therapy in diffuse large B-cell lymphoma. . . . . 4 3 2 1 N/M N/A
- Use prognostic and predictive clinical and molecular markers to aid in treatment decision-making for NHL and CLL. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trial participation. . . . . 4 3 2 1 N/M N/A

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 editor for this educational activity

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

Faculty	Knowledge of subject matter				Effectiveness as an educator			
John P Leonard, MD	4	3	2	1	4	3	2	1
Bruce D Cheson, MD	4	3	2	1	4	3	2	1
Neil Morganstein, MD	4	3	2	1	4	3	2	1
Margaret A Deutsch, MD	4	3	2	1	4	3	2	1
Editor	**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 editor for this activity:

. . . . . .

REQUEST FOR CREDIT — Please print clearly

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Professional Designation:

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Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

Signature: . . . . . Date: . . . . . .

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at **CME.ResearchToPractice.com**.

VPNHL10

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