5 Minute JournalClub

Key ASCO Presentations
Issue 3, 2010

Complete Response Rates with Lenalidomide/Rituximab in the Front-Line Treatment of Indolent B-Cell Non-Hodgkin Lymphoma (NHL)

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Recall the Phase II efficacy and safety of lenalidomide/rituximab as front-line treatment of indolent lymphoma.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Consulting Agreements: Biogen Idec, Biotest Pharmaceuticals Corporation, Calistoga Pharmaceuticals Inc, Celgene Corporation, Cephalon Inc, CT International, Eisai Inc, EMD Serono Inc, Genentech BioOncology, GlaxoSmithKline, Gloucester Pharmaceuticals, Immunomedics Inc, Intellikine, Johnson & Johnson Pharmaceuticals, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi-Aventis, Wyeth.

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To go directly to the slides, **click here**.

Oncologists who were reared on the "shock and awe — MTD" approach to systemic anticancer therapy now understand that the chronic disease model is where the field has been headed for years, and about a decade ago, when imatinib was first being administered indefinitely in CML, Paul Goss proved that in breast cancer, fewer relapses occurred when endocrine therapy was extended beyond five years. This important development led Paul and others to compare breast cancer to follicular lymphoma (FL), with its relapsing and remitting nature and long-term requirement for treatment.

In the past six months, the breast cancer/FL analogy has become even more evident, beginning at ASH with the emergence of bendamustine/rituximab (BR), or as I see it, the "TC" of indolent lymphoma, and then at ASCO, where for the first time, we saw conclusive evidence that the duration of rituximab for FL, as in endocrine therapy for breast cancer, really matters.

A slew of imperfect answers for the question of R maintenance in FL have been reported in the past few years, but investigators were skeptical that more R after R-chemo made a difference. Oncologists in practice weren't as doubtful, and our Patterns of Care data have demonstrated that many have used this strategy for some time. The issue was somewhat laid to rest at ASCO with the **PRIMA presentation**, and Dr Richard Fisher, the paper's discussant, didn't mince words when he stated that R maintenance should now be used in patients with FL requiring treatment. However, after speaking with a number of investigators in the field, I don't see a consensus yet on the clinical and research implications of this data set, in spite of the reduction in two-year risk of disease progression from 34 percent without R maintenance to 18 percent with it. Meanwhile, the Germans, who already created BR and were kicking butt in the World Cup until they encountered Spain, continue to be ahead of the game and 14 months ago launched a randomized trial evaluating BR followed by either two or four years of R maintenance.

Also in this issue:

1. **Pretransplant R purging and post-transplant maintenance** extends progression-free survival in patients with FL.

2. **A Phase II study of the IMiD®** lenalidomide combined with rituximab for indolent lymphoma results in complete tumor responses in more than two thirds of patients.

3. In another **Phase II study for patients older than age 65 with CLL**, treatment with lenalidomide results in responses in 62 percent of patients, without Grade III/IV tumor lysis syndrome or flare.

Next up on 5-Minute Journal Club: The chronic disease model comes to multiple myeloma as two major randomized trials demonstrate benefit for lenalidomide maintenance after transplant.

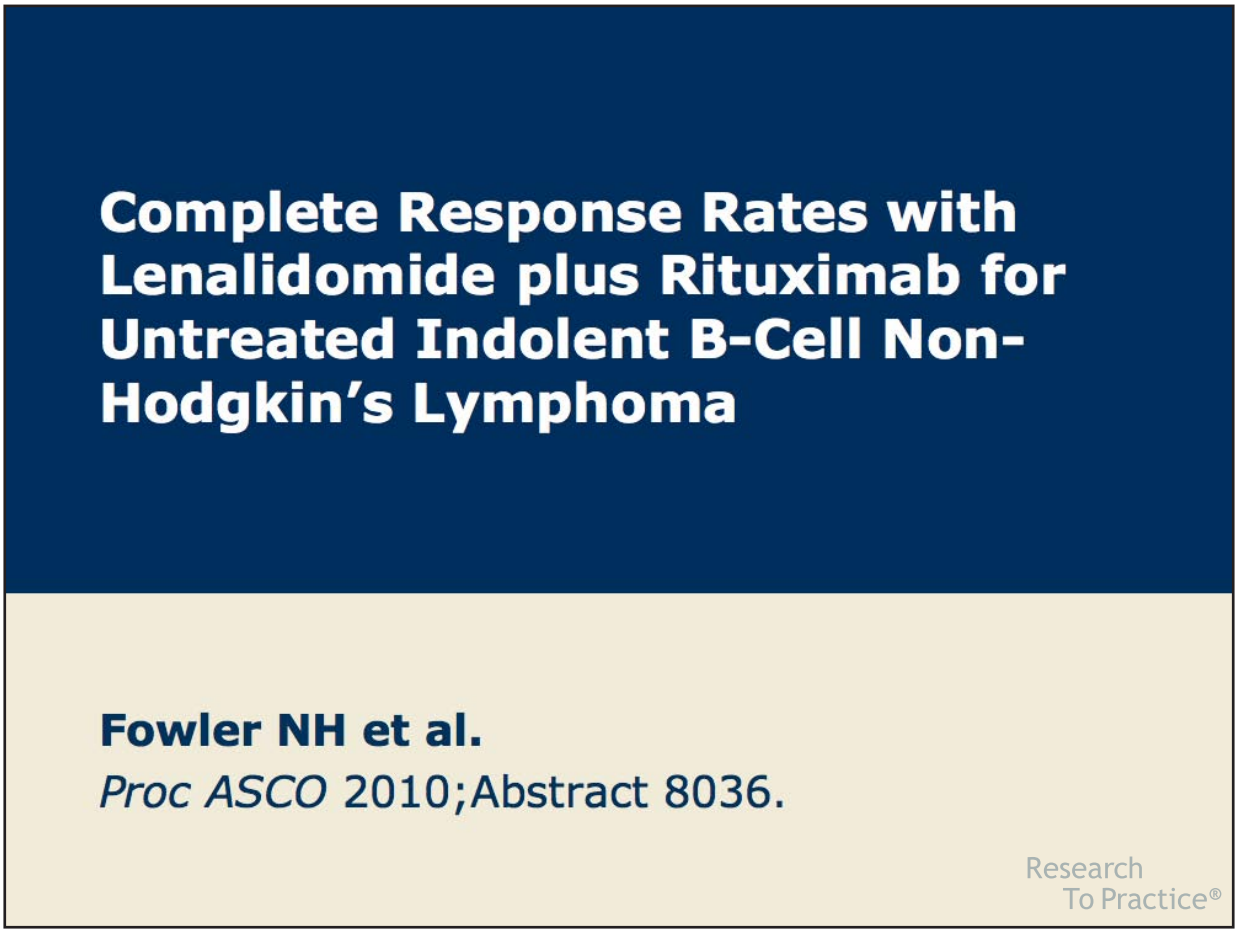
Neil Love, MD
Research To Practice
Miami, Florida

Complete Response Rates with Lenalidomide/Rituximab in the Front-Line Treatment of Indolent B-Cell Non-Hodgkin Lymphoma (NHL)

Presentation discussed in this issue

Fowler NH et al. **Complete response rates with lenalidomide plus rituximab for untreated indolent B-cell non-Hodgkin's lymphoma.** *Proc ASCO* 2010;**Abstract 8036**.

Slides from a presentation at ASCO 2010 and transcribed comments from recent interviews with Stephanie A Gregory, MD (6/18/10) and John P Leonard, MD (6/28/10)



Introduction

- The optimal treatment for newly diagnosed indolent non-Hodgkin's lymphoma (NHL) has not been established.
- Several combination chemotherapy regimens have response rates approaching 90%, but toxicity is common with genotoxic agents.
- The combination of rituximab and lenalidomide has shown responses in relapsed NHL (*Proc ASH* 2009;Abstract 2719).
- In pre-clinical models, the combination of rituximab and lenalidomide showed a higher cell kill than either agent alone (*Proc ASH* 2009;Abstract 3441, *Am J Hematol* 2009;84:553).
- **Current study objective:**
  - To evaluate the efficacy and safety of lenalidomide plus rituximab in patients with previously untreated indolent lymphoma.

Fowler NH et al. *Proc ASCO* 2010;Abstract 8036.

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Phase II Study of Lenalidomide plus Rituximab Therapy for Untreated Indolent NHL

Eligibility (N = 74)

Untreated indolent NHL (follicular lymphoma [FL], SLL/CLL, and marginal zone lymphoma)
Stage III or IV

↓

Rituximab 375 mg/m² IV d1
Lenalidomide 20 mg/d* PO d1-21
28-day cycle with delay for toxicity or cytopenia

Response assessed after cycles 3 and 6

* Lenalidomide was increased to 25 mg/d after 3 cycles if stable disease. Patients with SLL/CLL received 10 mg/d cycle 1, 15 mg/d cycle 2, 20 mg/d cycle 3.

Fowler NH et al. *Proc ASCO* 2010;Abstract 8036.

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Efficacy Results (Intent-to-Treat Population)

- Of 74 patients enrolled, 48 had completed six cycles of therapy and were included in efficacy and toxicity analyses.

Histology	Response Rates		
	CR/CRu	PR	ORR
FL (n = 30)	83%	10%	93%
SLL/CLL (n = 5)	40%	40%	80%
Marginal zone lymphoma (n = 13)	46%	16%	62%
Total (n = 48)	69%	14%	83%

CR = complete response; CRu = unconfirmed CR; PR = partial response; ORR = overall response rate

Fowler NH et al. *Proc ASCO* 2010;Abstract 8036.

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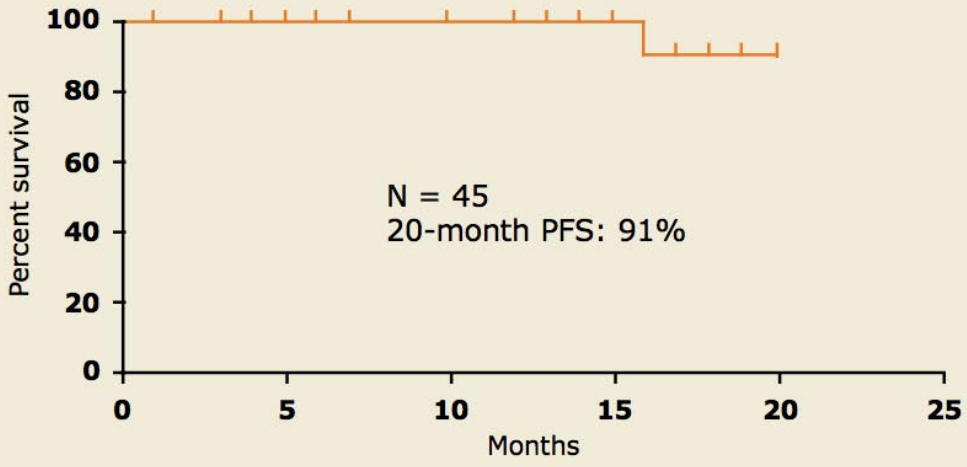
Progression-Free Survival (Median Follow-Up 12 Months)

- Progression-free survival (PFS): at a median of 12 months (range, 3-20) 1 patient (FL) has progressed



With permission from Fowler NH et al. *Proc ASCO* 2010;Abstract 8036.

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Molecular Response

- Bone marrow and peripheral blood were analyzed in 29 patients by PCR at baseline and after cycles 3 and 6.
- Nearly all patients were PCR negative by cycle 6.

PCR Result	Baseline n	Post-Cycle 3 n (%)	Post-Cycle 6 n (%)
BCL-2 positive	11	3	1
BCL-2 negative	18	26	28
Total % conversion	—	8/11 (73%)	10/11 (91%)

Fowler NH et al. *Proc ASCO* 2010;Abstract 8036.

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Adverse Events

Adverse Event*	Grade 3/4 (n = 48)
Neutropenia	21%
Thrombocytopenia	13%
Rash	13%
Thrombosis	4%
Fatigue	2%
Infection	2%
Neuropathy	2%

* Rash (all grades) was seen in 22 (46%) patients. The most common Grade 1/2 events were fatigue and myalgia. No patient developed tumor lysis syndrome.

Fowler NH et al. *Proc ASCO* 2010;Abstract 8036.

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Conclusions

- The combination of rituximab and lenalidomide produces excellent overall and complete response rates in patients with untreated indolent NHL.
- Toxicity profile of rituximab-lenalidomide combination is mild with manageable hematologic side effects.
- Future randomized trials are planned.

Fowler NH et al. *Proc ASCO* 2010;Abstract 8036.

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Investigator comments on a Phase II study of lenalidomide and rituximab for untreated indolent NHL

We've observed activity with lenalidomide in recurrent lymphomas of all types, and now we're starting to see combinations with rituximab.

In fact, we have a Phase II CALGB study going on right now in recurrent indolent lymphoma, in which patients are randomly assigned to lenalidomide alone or lenalidomide with rituximab, to determine what rituximab adds to lenalidomide. It makes sense to start evaluating this agent in combination with rituximab and other agents, and as we move away from the relapse setting, it makes sense to evaluate it in the up-front setting as well.

The findings from this study suggest that this combination might be a building block for other nonchemotherapy-containing regimens, which would be a nice alternative to chemotherapy for many patients. In the CALGB, we've been developing this sort of concept for a while with biologic doublets, and we're getting ready to open a trial of lenalidomide with rituximab as initial therapy for follicular lymphoma, which is similar to this MD Anderson study.

Interview with John P Leonard, MD, June 28, 2010

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Investigator comments on a Phase II study of lenalidomide and rituximab for untreated indolent NHL

This was an impressive paper. Laboratory data suggest synergy with the combination of lenalidomide and rituximab, and here they resulted in an overall response rate of 93 percent and a complete response rate of 83 percent. This is interesting and it looks as if the combination might be best used in patients with indolent lymphoma and low tumor burdens for whom many doctors are using rituximab alone.

Interview with Stephanie A Gregory, MD, June 18, 2010

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