5 Minute JournalClub

Key ASH Presentations
Issue 7, 2011

Pomalidomide/Dexamethasone Combination in Relapsed/ Refractory Multiple Myeloma

For more visit ResearchToPractice.com/5MJCASH2011

Research To Practice®

CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including 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 hematologic cancer.

LEARNING OBJECTIVES

- Recall the efficacy and safety outcomes with the pomalidomide/dexamethasone combination in patients with multiple myeloma refractory to both bortezomib and lenalidomide.
- Identify the two dosing schedules of pomalidomide currently under investigation in refractory multiple myeloma.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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:

Rafael Fonseca, MD
Consultant, Professor of Medicine
Mayo Clinic Arizona
Deputy Director, Mayo Clinic Cancer Center
Scottsdale, Arizona

Consulting Agreements: Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genzyme Corporation, Medtronic Inc, Otsuka Pharmaceutical Co Ltd; Paid Research: Celgene Corporation, Onyx Pharmaceuticals Inc.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Allos Therapeutics, Amgen Inc, AstraZeneca Pharmaceuticals LP, Aureon Laboratories Inc, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Lilly USA LLC, Millennium — The Takeda Oncology Company, Mundipharma International Limited, Myriad Genetics Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Sanofi-Aventis and Seattle Genetics.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This program is supported by educational grants from Allos Therapeutics, Celgene Corporation, Millennium — The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc and Seattle Genetics.

Last review date: March 2011
Expiration date: March 2012

5 MinuteJournalClub

Key ASH Presentations
Issue 7, 2011

Click here for papers on proteasome inhibitors and IMiDs in multiple myeloma

In the last issue of our San Antonio-focused edition of this series, we opined about the lack of recent research progress in breast cancer and looked to a tumor occurring at one tenth the frequency for inspiration and hope. Multiple myeloma affects approximately 20,000 new patients in the US annually and for a long time was a disease stuck for new therapeutic options. However, fairly recently two classes of treatments have stormed onto the scene — immunomodulatory agents (IMiDs) and proteasome inhibitors — making myeloma perhaps the fastest moving and most dynamic area in oncology.

It's difficult to figure out exactly what led to this encouraging state of affairs, but those in the middle of it all claim that an effective partnership between academia, industry and unusually active advocacy groups made it happen. One might also consider that perhaps there was a unique and fortunate tumor biopharmacology at work here. Regardless of the source of this important progress, currently, lenalidomide, bortezomib and to a lesser extent thalidomide are helping patients with myeloma live longer and feel better. Perhaps even more importantly, two exciting but not yet approved agents — carfilzomib and pomalidomide — seem poised to further transform the classic paradigms of this enigmatic disease. Several related ASH data sets provide a glimpse of what the future may hold for these unique classes of agents:

1. **Subcutaneous bortezomib**

A large (n = 222) international Phase III study demonstrated similar efficacy but markedly less neurotoxicity when SC bortezomib was compared to IV administration in the refractory setting. These intriguing findings suggest that higher peak drug levels occurring with IV treatment may correlate with neuronal damage and that the SC approach may offer obvious patient care advantages. Investigators are very quickly attempting to further validate this interesting concept. Another important clinical research avenue with bortezomib as presented by Antonio Palumbo and others is weekly dosing of the agent, which seems to be equally efficacious and much less neurotoxic

2. **Pomalidomide**

Two more Phase II studies of this fascinating and well-tolerated IMiD combined with dexamethasone demonstrated substantial antitumor effect in almost half of the trial participants, all of whom were considered refractory to both bortezomib and lenalidomide. Clinicians seem ready to use this drug now.

3. **Carfilzomib**

Again, significant activity was seen in later-line treatment in two separate Phase II studies, with minimal neurotoxicity, including a lack of worsening of this challenging adverse effect in patients with baseline peripheral neuropathy. A current compelling Phase III study is randomly assigning patients to either CRD or Rd in the search for the "R-CHOP" of myeloma. As with pomalidomide, oncologists again seem ready and interested in utilizing this agent.

Next up on our final ASH *5-Minute Journal Club*: Papers on MDS, AML and my personal favorite current topic in oncology, AP.

Neil Love, MD
Research To Practice
Miami, Florida

Pomalidomide/Dexamethasone Combination in Relapsed/ Refractory Multiple Myeloma

Presentations discussed in this issue

Lacy MQ et al. **Pomalidomide plus low dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: Comparison of two dosing strategies in dual-refractory disease.** *Proc ASH* 2010;**Abstract 863**.

Leleu X et al. **Phase 2 study of 2 modalities of pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. IFM 2009-02.** *Proc ASH* 2010;**Abstract 859**.

Slides from presentations at ASH 2010 and transcribed comments from a recent interview with Rafael Fonseca, MD (12/22/10)

Pomalidomide plus Low-Dose Dexamethasone in Myeloma Refractory to Both Bortezomib and Lenalidomide: Comparison of Two Dosing Strategies in Dual-Refractory Disease[1]

Phase 2 Randomised Open Label Study of 2 Modalities of Pomalidomide plus Low-Dose Dexamethasone in Patients with Multiple Myeloma, Refractory to Both Lenalidomide and Bortezomib. IFM 2009-02[2]

[1]Lacy MQ et al.
Proc ASH 2010;Abstract 863.

[2]Leleu X et al.
Proc ASH 2010;Abstract 859.

Research To Practice®

Pomalidomide plus Low-Dose Dexamethasone in Myeloma Refractory to Both Bortezomib and Lenalidomide: Comparison of Two Dosing Strategies in Dual-Refractory Disease

Lacy MQ et al.

Proc ASH 2010;Abstract 863.

Background

- Pomalidomide/dexamethasone (pom/dex) regimen using a pom dose of 2 mg/day has demonstrated response rates of:
  - 63% in relapsed multiple myeloma (*JCO* 2009;27:5008)
  - 32% in a lenalidomide-refractory cohort (*Leukemia* 2010;24:1934)
- The maximum tolerated dose of pomalidomide has been determined to be 4 mg/day for 21 of 28 days (*Proc ASH* 2009;Abstract 301).
- Two sequential phase II trials were opened to evaluate the efficacy of a pom/dex regimen using different doses of pom in patients with multiple myeloma refractory to both lenalidomide and bortezomib.

Lacy MQ et al. *Proc ASH* 2010;Abstract 863.

Study Methods and Objectives

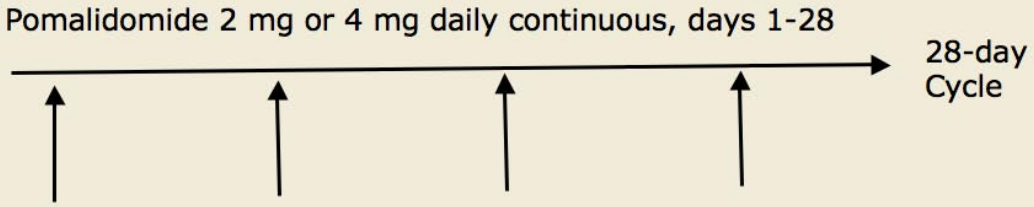
- **Methods**
  - Two sequential Phase II trials opened with 35 patients each
    - May 2009 - Nov 2009: Cohort A (2 mg/day pom)
    - Nov 2009 - Apr 2010: Cohort B (4 mg/day pom)
  - Responses were assessed according to IMWG response criteria
- **Study Objectives**
  - Assess response rate and duration of remission in dual-refractory multiple myeloma
  - Assess toxicity in this patient population

Lacy MQ et al. *Proc ASH* 2010;Abstract 863.

Research To Practice®

Treatment Schema

Eligibility
Previously treated multiple myeloma
Resistant/refractory to both lenalidomide and bortezomib
≥1 prior regimen; no upper limit on number of previous regimens



Dexamethasone 40 mg days 1, 8, 15, 22
Aspirin 325 mg daily

If no response after 2 cycles, or if progression, then pomalidomide dose could be increased to 4 mg/day in the 2 mg cohort.

Lacy MQ et al. *Proc ASH* 2010;Abstract 863.

Research To Practice®

Efficacy Assessment

	Pomalidomide 2 mg (n = 35)	Pomalidomide 4 mg (n = 35)
Confirmed Response (≥PR)	26%	26%
≥Minimal Response	49%	40%
Time to Response (Median)	1 month	1.7 months
Duration of Response	12 months	Not attained
Survival Rate at 6 Months	78%	69%

≥MR in patients from both subgroups (N = 62) considered to be at high risk was 33%.

Lacy MQ et al. *Proc ASH* 2010;Abstract 863.

Research To Practice®

Select Adverse Events

	Pomalidomide 2 mg (n = 35)	Pomalidomide 4 mg (n = 35)
Grade 3/4 Neutropenia	49%	66%
All Grades Neuropathy (Possibly attributed to pomalidomide)	20%	29%
Grade 3/4 Neuropathy (Possibly attributed to pomalidomide)	0%	3%
Thromboembolic Events	9%	6%

Lacy MQ et al. *Proc ASH* 2010;Abstract 863.

Research To Practice®

Author Conclusions

- Pomalidomide/dexamethasone has significant activity in heavily pretreated myeloma refractory to lenalidomide and bortezomib.
- Responses are rapid with median time to response within 2 months.
- Toxicity is manageable at both dose levels and consists primarily of neutropenia, but rate is higher at the 4-mg continuous dose.
- No evidence for dose response; responses appear similar with both dose levels.
- Effective in patients at high risk.
- Studies ongoing to assess whether pom starting dose of 4 mg for 21 of 28 days is equally efficacious while producing less toxicity.

Lacy MQ et al. *Proc ASH* 2010;Abstract 863.

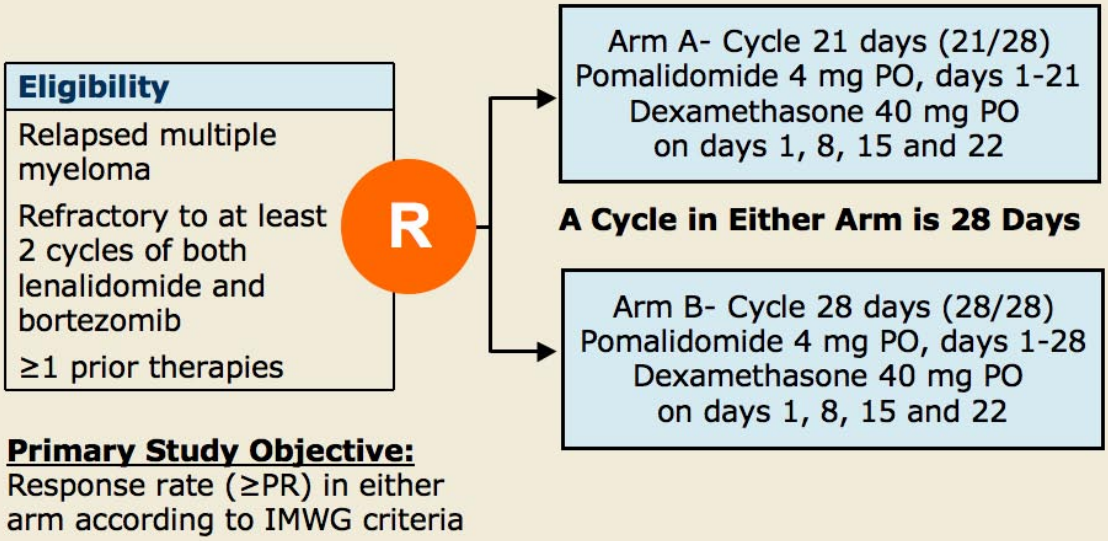
Phase 2 Randomised Open Label Study of 2 Modalities of Pomalidomide plus Low-Dose Dexamethasone in Patients with Multiple Myeloma, Refractory to Both Lenalidomide and Bortezomib. IFM 2009-02

Leleu X et al.

Proc ASH 2010;Abstract 859.

Research
To Practice®

IFM 2009-02 Phase II Study Schema



Primary Study Objective:
Response rate (≥PR) in either arm according to IMWG criteria

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Research To Practice®

Efficacy Assessment

	Arm A (21/28) (n = 43)	Arm B (28/28) (n = 41)
Overall Response Rate (≥PR)	42%	39%
Stable Disease	46.5%	51%
Time to Best Response	2 months	1.7 months
Time to Progression, Median*	7 months	9.7 months

* Median follow-up was 6.5 months for Arm A and 7 months for Arm B.

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Research To Practice®

Select Adverse Events

	Arm A (21/28) (n = 43)	Arm B (28/28) (n = 41)
≥Grade 3 Events	23.5%	26.5%
Percentage Hematologic Events of All ≥Grade 3 Events	66%	76%
Neuropathy	0	0
Deep Vein Thrombosis (with prophylactic treatment)	0	0

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Author Conclusions

- Pomalidomide and dexamethasone combination provides responses in patients with advanced myeloma refractory to bortezomib and lenalidomide.
- Pomalidomide 4 mg per day is well tolerated.
- Pomalidomide 4 mg per day 21 days out of 28-day cycle does not appear inferior to pomalidomide 4 mg per day continuous on 28-day cycle.

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Research To Practice®

Investigator comment on pomalidomide/dexamethasone combination for multiple myeloma refractory to both lenalidomide and bortezomib

The presentation by Lacy was from a series of Phase II trials conducted at my institution. The study essentially showed that significant activity with the pomalidomide/dexamethasone combination is observed in patients who are truly refractory to both bortezomib and lenalidomide. The minor responses were as high as 49 percent, and thus support that once approved, this combination could be an alternative for patients with refractory disease.

The study by Leleu also showed that in this patient population with heavily pretreated disease, there is a significant likelihood of patients achieving responses. Regarding the specific issues of the two dosing cycles of 21/28 or 28/28, I believe it is hard to compare them right now, so I would not like to make a statement that either therapy was better. My take from this study is that even being the third IMiD® and being similar to both thalidomide and lenalidomide, pomalidomide has a different efficacy and safety profile, and in my opinion, it will soon be part of the standard armamentarium against myeloma.

Interview with Rafael Fonseca, MD, December 22, 2010