5 Minute JournalClub

POST-ASH Issue 1, 2013

Clarithromycin/Pomalidomide/ Dexamethasone for Relapsed/Refractory MM

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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 and new information 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, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Develop an understanding of cereblon as a mediator of immunomodulatory drug function and its correlation with the efficacy of immunomodulatory drugs in multiple myeloma.
- Compare and contrast the benefits and risks of immunomodulatory drugs in combination with other agents in the treatment of relapsed/refractory multiple myeloma.

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This activity is supported by educational grants from Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: January 2013
Expiration date: January 2014

5 MinuteJournalClub

POST-ASH Issue 1, 2013

ASH highlights: An important new IMiD is about to come on board in multiple myeloma

To go directly to slides and commentary for this issue, **click here**.

The rapid evolution of effective agents in multiple myeloma over the past few years has changed the face of the disease by tripling average overall survival rates from approximately 2-3 years to about 7-8 years. At ASH 2012 this inspiring march of progress continued most notably with the presentation of definitive data on the third-generation, orally administered immunomodulatory (IMiD) agent pomalidomide. These were accompanied by provocative findings on a new predictor of clinical benefit for this class of drugs and several other related data sets. Here's the bottom line:

1. Phase III trial of pomalidomide (POM)

Dr Meletios Dimopoulos' late-breaking presentation of a Phase III study comparing high-dose dexamethasone (HDD) to POM/low-dose dexamethasone (dex) in patients with a median of 5 prior treatments — including bortezomib and lenalidomide (len) for most — was maybe the most discussed practice changer from the meeting. Among the groundbreaking results that were unveiled, perhaps the most impressive were hazard rates for both progression-free and overall survival of about 0.5 despite the fact that 29% of patients crossed over to POM after progression on HDD.

This and prior work has shown that the drug is generally well tolerated except for some myelosuppression, and as with the other IMiDs thromboprophylaxis with at least low-dose aspirin is recommended. Even without these Phase III data many believed the FDA was poised to approve POM based on impressive Phase II results in patients with extensive prior treatment, and now it seems almost certain that in the next few weeks oncologists will have access to yet another option for patients with relapsed/refractory disease, less than a year after the approval of carfilzomib.

2. Potentially promising POM combinations

ClaPD (clarithromycin, POM, dex)

One of the more pleasant-sounding myeloma acronyms is BiRD, a regimen that was pioneered by Cornell's Dr Ruben Niesvizky that combines len and dex with a fascinating

and unusual ingredient, the macrolide antibiotic clarithromycin, which is purported to slow the hepatic clearance of dex and to possess immunomodulatory properties. Perhaps the lack of Phase III supporting data is why BiRD is not commonly used in practice today, and one has to wonder if these promising Phase II results will be enough to help this approach, which replaces len with POM, gain traction. Regardless, the findings provide even more validation of the substantial activity of POM.

PCP (POM, cyclophosphamide, prednisone)

For the past few years Dr Antonio Palumbo has been evaluating regimens that can be administered without complications for prolonged durations — particularly in elderly patients — because he believes the key to long-term success is long-term therapy. In that vein, PCP — an all-oral regimen that after 6 cycles drops the C and continues POM/prednisone until disease progression — not only produced impressive disease control (51% PR/CR with median PFS 10.4 months) but was also very well tolerated.

3. Cereblon (CRBN) as a marker for IMiD activity

A couple of years back Dr Keith Stewart noticed a **Japanese paper in *Science*** demonstrating that the clear-cut mechanism of teratogenicity for thalidomide was binding to CRBN, an adaptor protein that is part of the E3 ubiquitin ligase complex. A logical extension of this concept was the theory that this interaction was also the basis for the profound, yet somewhat obscure, antimyeloma action of IMiDs. After obtaining strong in vivo supporting evidence, Dr Stewart, his Mayo Clinic team and other sites set out to correlate CRBN levels in myeloma cells with the clinical activity of this class of agents. Two ASH papers — one in patients receiving len/dex and another in patients receiving POM/dex — moved this important initiative closer to a clinical reality by demonstrating a tripling of response and survival in individuals with higher versus lower CRBN levels. Although the ideal method to measure CRBN and the clinical applicability of these results are still being determined and debated, it seems quite plausible that in the not-too-distant future a related predictive assay will become an important part of myeloma practice.

4. IMiDs and monoclonal antibodies (moAbs)

It has always been a bit ironic that although moAbs have been utilized in a variety of solid tumors and hematologic cancers, none have been found useful in this disease, which is defined by abnormal antibody production. However, at ASH we saw evidence that this phenomenon may soon change based on encouraging data with elotuzumab (elo), which targets the CS1 antigen, and daratumumab, an anti-CD38 antibody.

Elo is farther along in development, and although it has minimal single-agent activity, there appears to be a true, perhaps immunologically based synergy with IMiDs. At ASH, data from a Phase II study of len/elo/dex demonstrated an encouraging overall

response rate of 84% and a PFS of more than 18 months. Ongoing Phase III studies will soon determine the future of this regimen. Importantly, myeloma is not the only place where the intuitive concept of combining an immune modulator and a monoclonal antibody is being explored, as the "R squared" combination of len/rituximab has demonstrated impressive activity in B-cell lymphoma/CLL.

And on a related note...coming up next in this series: R squared, ibrutinib, idelalisib and the provocative question posed by Dr Bruce Cheson and others — Was ASH 2012 the beginning of the end of chemotherapy in indolent lymphoma and CLL?

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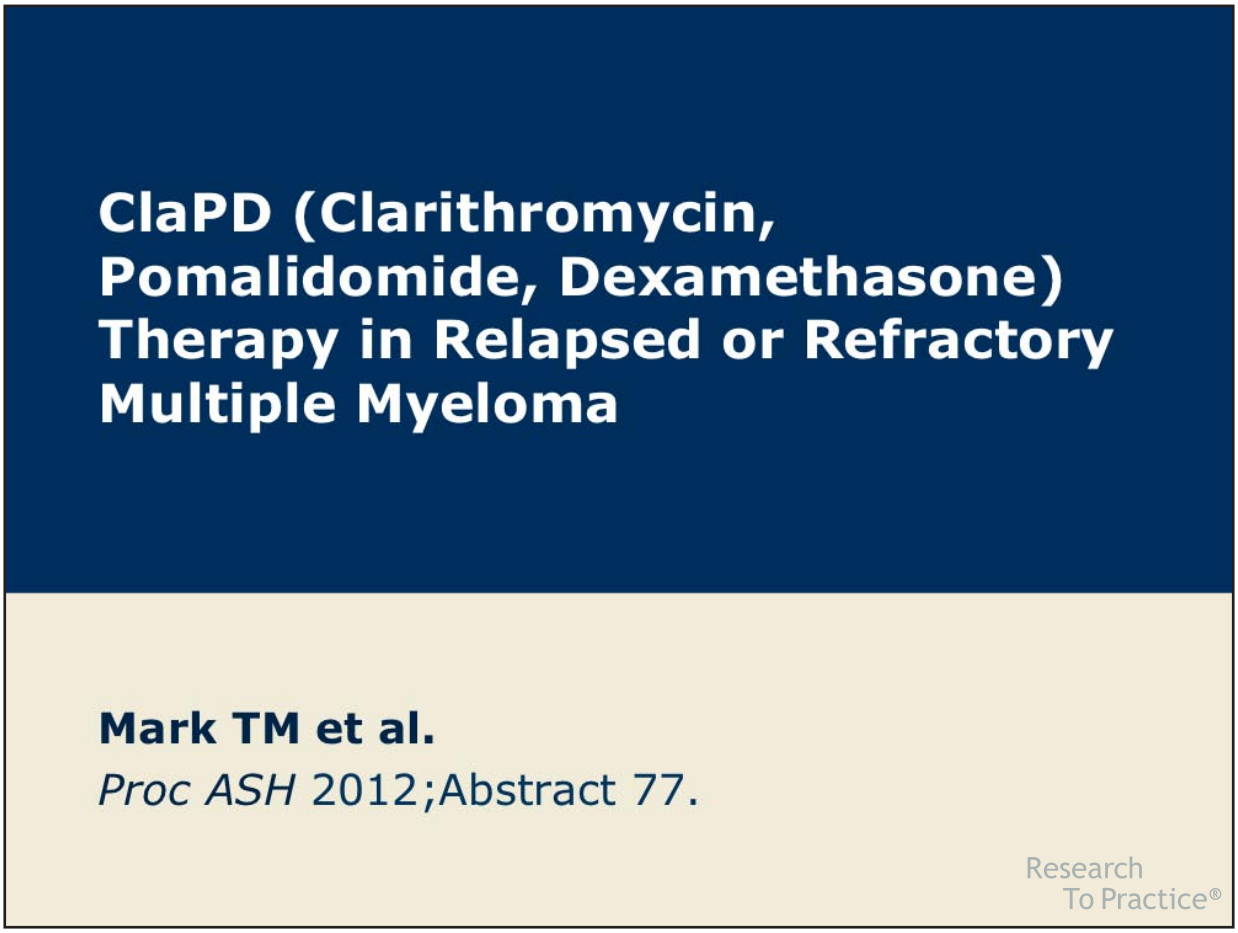
Clarithromycin/Pomalidomide/Dexamethasone for Relapsed/ Refractory MM

Presentation discussed in this issue

Mark TM et al. **ClaPD (clarithromycin, pomalidomide, dexamethasone) therapy in relapsed or refractory multiple myeloma.** *Proc ASH* 2012;**Abstract 77**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with A Keith Stewart, MBChB (1/9/13)



Background

- The addition of clarithromycin was previously reported to enhance antimyeloma activity of lenalidomide/dexamethasone in the up-front treatment of multiple myeloma (MM) (*Blood* 2008;111(3):1101).
- Pomalidomide is an immunomodulatory agent with a significant response rate in combination with dexamethasone for patients with relapsed/refractory MM (*J Clin Oncol* 2009;27(30):5008).
- Initial results suggested that clarithromycin may enhance pomalidomide/dexamethasone activity in relapsed or lenalidomide-refractory MM (*Proc ASCO* 2012;Abstract 8036).
- **Study objective**: To examine the efficacy and tolerability of ClaPD in relapsed/refractory MM.

Mark TM et al. *Proc ASH* 2012;Abstract 77.

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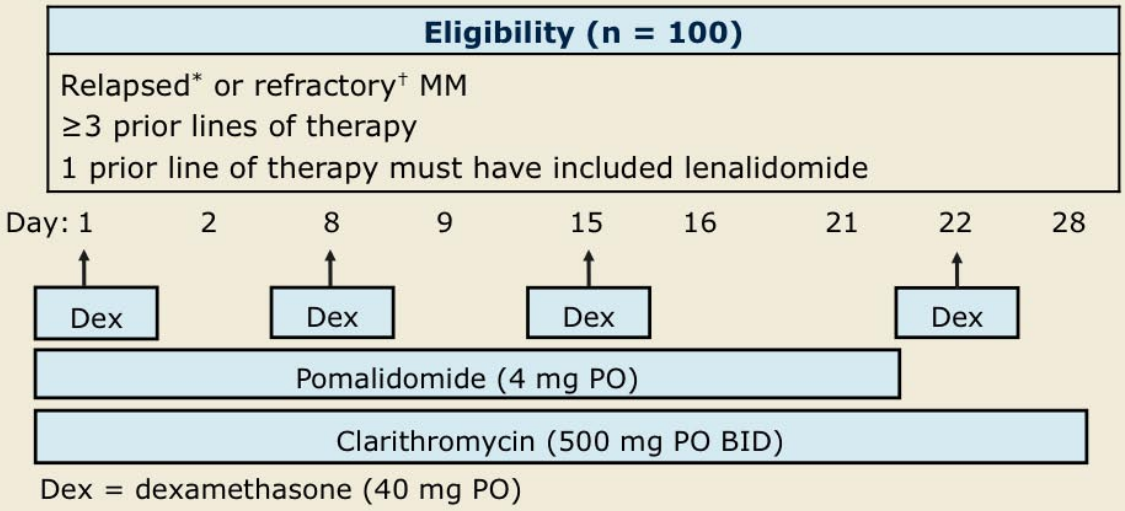
Phase II Trial Design



Dex = dexamethasone (40 mg PO)

* Relapsed: Previously treated myeloma that progresses and requires initiation of salvage therapy but does not meet the definition of refractory MM

† Refractory: Disease that is nonresponsive on therapy or progresses within 60 d of last therapy

Mark TM et al. *Proc ASH* 2012;Abstract 77.

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Best Response Rates (Median Follow-Up: 9.6 Months)

	n = 98*
Overall response rate (≥PR)	57%
Stringent CR (sCR)	6%
Very good PR (VGPR)	17%
Partial response (PR)	34%
Minimal response (MR)	9%
Clinical benefit rate (≥MR)	66%

* Patients who completed ≥1 cycle of ClaPD

- Median time to PR = 1 cycle; median time to best response = 2 cycles

Mark TM et al. *Proc ASH* 2012;Abstract 77.

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Best Response by Treatment History

	R refractory (n = 83)	V refractory (n = 82)	RV refractory (n = 72)
ORR (≥PR)	63%	56%	54%
sCR	7%	6%	7%
VGPR	16%	16%	13%
PR	34%	34%	35%
MR	10%	10%	11%
CBR (≥MR)	67%	65%	65%

R = lenalidomide; V = bortezomib; CBR = clinical benefit rate

Mark TM et al. *Proc ASH* 2012;Abstract 77.

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PFS by Cytogenetic Risk and Prior Treatment History

- Median PFS for all patients (n = 100): 8.67 mo

PFS by subset analysis	HR	*p*-value
Standard (n = 41) vs high risk (n = 55)	1.23	0.448
R-relapsed (n=15) vs R-refractory (n=85)	1.00	0.995
V-relapsed (n = 16) vs V-refractory (n = 84)	1.09	0.806
RV-nonrefractory (n = 26) vs RV-refractory (n = 74)	1.35	0.307

HR = hazard ratio; RV-nonrefractory = not refractory to both lenalidomide and bortezomib

Mark TM et al. *Proc ASH* 2012;Abstract 77.

Adverse Events*

Occurring in ≥10% of patients	Grade 3	Grade 4
Anemia	21%	4%
Thrombocytopenia	17%	16%
Neutropenia	33%	14%
Lymphopenia	31%	6%
Febrile neutropenia	2%	1%
Pulmonary embolism	1%	—
Deep vein thrombosis	4%	—

* Three patients withdrew due to Grade 3 fatigue (n = 1), Grade 4 muscular weakness (n = 1) and Grade 4 neutropenic sepsis (n = 1).

No treatment-related mortality observed.

Mark TM et al. *Proc ASH* 2012;Abstract 77.

Author Conclusions

- ClaPD is an effective regimen for patients with heavily pretreated relapsed or refractory MM.
- ClaPD demonstrated clinical activity in patients with advanced MM treated with multiple lines of therapies, including those with R- and V-refractory disease.
- Following treatment with ClaPD, PFS was sustained for >8 months for the majority of patients on the study and was not influenced by high-risk cytogenetics nor a history of R-, V- or RV-refractory disease.
- Overall survival was not significantly affected by high-risk cytogenetics, but a trend toward shorter survival was observed for patients with double-refractory disease (data not shown).

Mark TM et al. *Proc ASH* 2012;Abstract 77.

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Investigator Commentary: A Phase II Trial of ClaPD in Heavily Pretreated Relapsed or Refractory MM

Clarithromycin is an interesting antibiotic that Dr Niesvizky and colleagues in New York have been promoting for many years as a drug with the ability to increase response rates for patients receiving immunomodulatory drugs in combination with steroids. It appears to accentuate steroid potency, but by itself it is not particularly active. I have seen some impressive results, including this presentation, demonstrating higher response rates than one would predict without clarithromycin.

I wouldn't say that it's currently being widely used, but some of my colleagues certainly administer it frequently now. It is a well-known antibiotic that is fairly innocuous and easy to combine with other agents. So, in the absence of any Phase III testing, it seems like a reasonable addition to therapy. However, it may exacerbate steroid side effects and one needs to watch out for this. I think it is beginning to increase in popularity, is unlikely to have deleterious effects and may be beneficial.

Interview with A Keith Stewart, MBChB, January 9, 2013

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