5 Minute JournalClub

Key ASH Presentations
Issue 7, 2011

Carfilzomib as a Single Agent in Relapsed/Refractory Multiple Myeloma

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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 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 of single-agent carfilzomib in relapsed/refractory multiple myeloma.
- Recognize the role of off-target proteasome inhibition in the development of treatment-related peripheral neuropathy.

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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.

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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

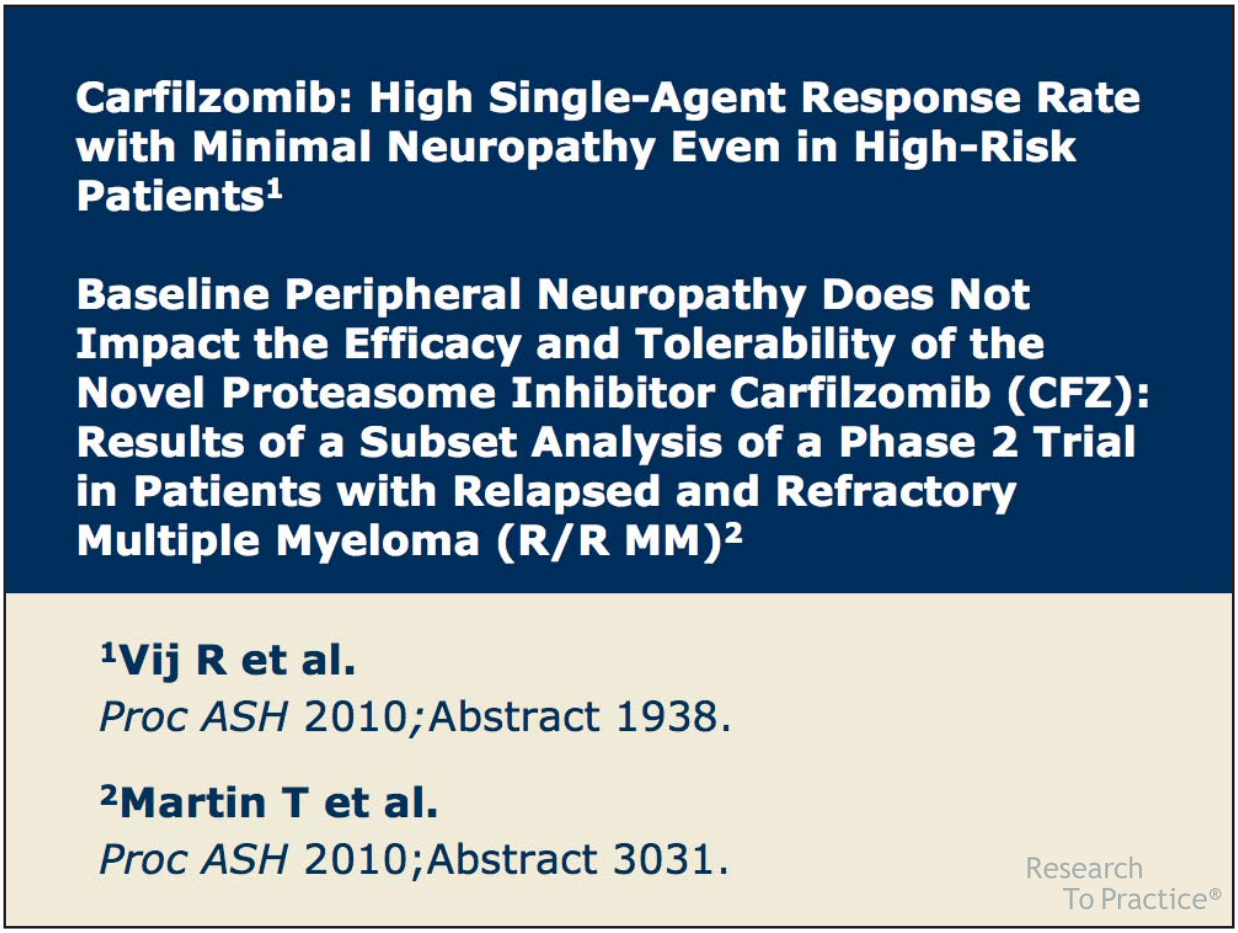
Carfilzomib as a Single Agent in Relapsed/Refractory Multiple Myeloma

Presentations discussed in this issue

Vij R et al. **Carfilzomib: High single-agent response rate with minimal neuropathy even in high-risk patients.** *Proc ASH* 2010;**Abstract 1938**.

Martin T et al. **Baseline peripheral neuropathy does not impact the efficacy and tolerability of the novel proteasome inhibitor carfilzomib (CFZ): Results of a subset analysis of a phase 2 trial in patients with relapsed and refractory multiple myeloma (R/R MM).** *Proc ASH* 2010;**Abstract 3031**.

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



Carfilzomib: High Single-Agent Response Rate with Minimal Neuropathy Even in High-Risk Patients

Vij R et al.
Proc ASH 2010;Abstract 1938.

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Background

- Carfilzomib (CFZ) is a selective epoxyketone proteasome inhibitor that elicits potent and sustained proteasome inhibition.
- CFZ appears to lack some of the off-target activities associated with the proteasome inhibitor bortezomib, such as severe, dose-limiting peripheral neuropathy (PN) (*J Clin Oncol* 2009;27:3518).
- Durable single-agent activity with CFZ has been observed in patients with relapsed/refractory multiple myeloma (R/R MM) who have received multiple prior lines of therapy, as well as in patients with significant comorbidities *(Proc ASCO* 2009;Abstract 8504*)*.

Vij R et al. *Proc ASH* 2010;Abstract 1938.

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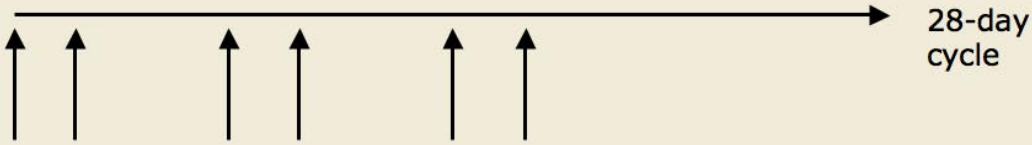
PX-171-004 Trial Schema*

Eligibility

Relapsed and/or refractory multiple myeloma, after 1-3 prior lines of therapy
Responsive (achieved minimal response or better) to standard first-line therapy



Intravenous carfilzomib on days 1, 2, 8, 9, 15, 16

Two Dose Cohorts

Cohort 1: Patients received carfilzomib 20 mg/m^2 on each administration in each cycle for up to 12 cycles

Cohort 2: Patients received carfilzomib 20 mg/m^2 on each administration in cycle 1 and at 27 mg/m^2 on each administration in subsequent cycles 2-12

*Current analysis performed on 125 patients with bortezomib-naïve disease

Vij R et al. *Proc ASH* 2010;Abstract 1938.

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Efficacy Assessment

	Cohort 1 (n = 59)	Cohort 2 (n = 64)
Overall Response (OR)	42%	53%
Clinical Benefit Rate (OR + Minimal Response)	59%	63%
Duration of Response (Median)	13.1 months	Not Reached (>13 months)

Baseline Characteristics	N	Overall Response Rate
ISS Stage I or II ISS Stage III	92 19	48% 42%
Cytogenetics/FISH: Normal/Favorable Cytogenetics/FISH: Unfavorable	88 16	50% 38%

Vij R et al. *Proc ASH* 2010;Abstract 1938.

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Author Conclusions

- Notable response rates for single-agent CFZ in bortezomib-naïve R/R MM.
  - 53% overall response in cohort 2
  - Durable responses
- Responses achieved with single-agent CFZ are durable.
  - Median DOR in Cohort 1: 13.1 months
  - Median DOR in Cohort 2: not yet reached (>13 months)
- The adverse (AE) profiles observed with both dosage regimens were similar and AEs were generally mild and clinically manageable (data not shown).
  - PN was infrequent and did not limit therapy, even in patients with active symptoms at baseline.
  - Fatigue, nausea, anemia, and dyspnea were the most commonly reported AEs.
  - There was no evidence of increased toxicity with increased CFZ dosage of 27 mg/m^2.
- CFZ is well tolerated for at least 12 cycles (~1 year), suggesting that prolonged administration is feasible.

Vij R et al. *Proc ASH* 2010;Abstract 1938.

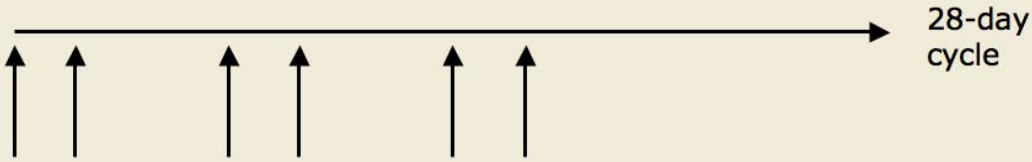
Baseline Peripheral Neuropathy Does Not Impact the Efficacy and Tolerability of the Novel Proteasome Inhibitor Carfilzomib (CFZ): Results of a Subset Analysis of a Phase 2 Trial in Patients with Relapsed and Refractory Multiple Myeloma (R/R MM)

Martin T et al.

Proc ASH 2010;Abstract 3031.

PX-171-003-A1 Trial Schema

Eligibility (N = 266)
Relapsed/refractory multiple myeloma



Intravenous carfilzomib: 20 mg/m^2 on days 1, 2, 8, 9, 15, 16 in cycle 1 and thereafter 27 mg/m^2 for up to cycle 12 on days 1, 2, 8, 9, 15, 16 of the respective cycles

Patients completing 12 cycles were eligible for an extension study

Subset analysis performed on patients with baseline Grade 1-2 peripheral neuropathy [PN] (206/266; 77%)

Martin T et al. *Proc ASH* 2010;Abstract 3031.

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Efficacy Assessment (from Abstract)

Response Category (n = 202)*	CFZ
Overall Response Rate	24%
Clinical Benefit Rate (≥Minimal Response)	36%

***Responses in the subset of patients with baseline PN were nearly identical to those seen in the full study population**

	Overall Cohort (n = 266)	Baseline PN Cohort (n = 202)
Duration of Response (Median)	7.4 months	7.4 months
Duration of Minor Response (Median)	6.3 months	6.3 months

Martin T et al. *Proc ASH* 2010;Abstract 3031.

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Select Safety Events (from Abstract)

Grade 3/4 Neutropenia	9%
All Grades New Onset PN	15%
Grade 3/4 New Onset PN	0.4%

Martin T et al. *Proc ASH* 2010;Abstract 3031.

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Author Conclusions

- Analysis of the subset of patients (77%) with active Grade 1-2 peripheral neuropathy demonstrates that baseline PN has no impact on depth or durability of responses or on the tolerability of carfilzomib in heavily pretreated patients with relapsed refractory MM.
- New or worsening PN is very uncommon.
- Paresthesias and dysesthesia were generally infrequent and mild (data not shown).
- Carfilzomib can be administered to patients with baseline PN with little risk of exacerbation.
- Prolonged therapy is possible in this patient population.

Martin T et al. *Proc ASH* 2010;Abstract 3031.

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Investigator Commentary: Carfilzomib for Patients with Relapsed or Refractory Multiple Myeloma

Both of these presentations show that the rate of peripheral neuropathy in patients treated with carfilzomib is quite low, and in fact there appears to be a lack of worsening in patients with pre-existing neuropathy. One more theme emerging here is the possibility that carfilzomib, like bortezomib, may be particularly important for patients who have unfavorable cytogenetic findings.

Although these studies are somewhat limited by the sample size, it is quite possible that carfilzomib will have a high activity as a proteasome inhibitor, with particular potential benefit for patients with high-risk disease. The presentations confirm the safety of carfilzomib in this patient population.

Interview with Rafael Fonseca, MD, December 22, 2010

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