5 Minute JournalClub

Key ASH Presentations
Issue 3, 2012

Carfilzomib with Lenalidomide and Low-Dose Dexamethasone or Single-Agent Carfilzomib for Patients with 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 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 the emerging efficacy and toxicity data with novel agents in order to inform future patients with newly diagnosed and relapsed or refractory multiple myeloma about protocol and nonprotocol options.
- Assess the clinical benefits and risks of deacetylase inhibitors in combination with proteasome inhibitors for relapsed and refractory multiple myeloma.
- Evaluate the preliminary safety profiles and response outcomes observed in studies of next-generation proteasome inhibitors for patients with relapsed or refractory and previously untreated multiple myeloma.

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


Paul G Richardson, MD

When the New England Patriots' Rob Gronkowski dived futilely for Tom Brady's final "Hail Mary" pass in Sunday night's Super Bowl, I flipped off the TV and sat down with my notes from a recent conversation with Gronk's Boston neighbor Dr Paul Richardson, a dynamic Englishman from Surrey and a profoundly knowledgeable member of Dana-Farber's powerhouse myeloma team. Dr Richardson can always be counted on to contribute a plethora of ASH papers and presentations (he had 6 orals in December), and this was part of the reason I wanted his take on the hottest new myeloma data emerging at the conference. Our recent 90-minute breathless run through the happenings was mainly focused on emerging and currently unapproved agents, and as is always the case with myeloma nowadays, there was a lot to talk about.

1. Carfilzomib

As Dr Richardson was the lead investigator on the landmark front-line Phase II trial of RVD (lenalidomide, bortezomib, dex), I was particularly interested in his perspective on Dr Andrzej Jakubowiak's second presentation of data on the so-called CRd regimen (lenalidomide, carfilzomib, low-dose dex) also in this setting. Like RVD, CRd was shown to have response rates approaching 100%, so perhaps it was to be expected that our conversation quickly led to a review of the toxicity profile of this irreversible proteasome inhibitor. While Dr Richardson noted the impressive reduced risk of peripheral neuropathy (PN), he also commented on 2 other somewhat unexpected side effects of CRd, specifically dyspnea (12% of patients) that may be cardiac related due to fluid challenge and renal impairment and hyperglycemia (76%) that may be greater than would be expected from corticosteroids alone. Regardless, Dr Richardson thinks CRd may become a critical alternative for many patients up front, but right now he, like most investigators, believes carfilzomib clearly offers an important alternative in later-line disease.

2. MLN9708

Dr R called this oral boronic acid peptide proteasome inhibitor similar to bortezomib "the myeloma news of the meeting" and labeled the related ASH data set evaluating the agent up front combined with len/dex as "a knockout...huge." This once- or twice-weekly pill causes some skin toxicity but no PN, and when combined with len/dex as an all-oral up-front regimen, responses were observed in all 15 patients. Similarly, Dr Richardson presented data in the relapsed setting where useful activity was seen "even in the ninth inning," and it seems likely that MLN9708 will soon get a catchier moniker and quickly move forward in development.

3. Pomalidomide

This third-generation IMiD already has an impressive safety and efficacy track record, and significant responses have been observed in patients with disease progressing on lenalidomide and/or thalidomide. At ASH, more encouraging data were reported that further illustrate the striking activity of this agent alone or with dex and shed light on potential dosing strategies that might be appropriate for younger patients (continuous) and older, more frail individuals (3 weeks on, 1 week off). Either way it's a therapy most investigators — including Dr R — are ready to use if approved.

4. Elotuzumab

At ASH, Dr Sagar Lonial presented an intriguing data set on this humanized monoclonal antibody targeting human CS1, a cell surface glycoprotein that is highly expressed in more than 95% of patients with myeloma. Elotuzumab acts primarily through NK cell-mediated ADCC that may be compromised because of underlying immune dysfunction in myeloma, but in vitro work suggests synergistic activity when combined with the immune modulator lenalidomide. In this Phase II study in relapsed/refractory disease the elotuzumab/lenalidomide/low-dose dex combination was well tolerated and highly active (82% response rate) and as such has now moved into Phase III testing.

5. HDAC inhibitors

Data sets with vorinostat and panobinostat (both in combination with bortezomib) were reported at ASH, and although Dr Richardson and others believe there is a future role for this approach, the optimal doses, schedules and partner agents have yet to be defined.

Next we journey back to the solid tumor world and investigator perspectives on daily management of a common tumor that could dearly benefit from some myeloma-like progress...cancer of the pancreas.

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Carfilzomib with Lenalidomide and Low-Dose Dexamethasone or Single-Agent Carfilzomib for Patients with Multiple Myeloma

Presentations discussed in this issue

Jakubowiak AJ et al. **Final results of a frontline Phase 1/2 study of carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) in multiple myeloma (MM).** *Proc ASH* 2011;**Abstract 631**.

Vij R et al. **Final results from the bortezomib-naïve group of PX-171-004, a Phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory MM.** *Proc ASH* 2011;**Abstract 813**.

Slides from presentations at ASH 2011 and transcribed comments from a recent interview with Paul G Richardson, MD (1/24/12)

Final Results of a Frontline Phase 1/2 Study of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone (CRd) in Multiple Myeloma (MM)[1]

Final Results from the Bortezomib-Naïve Group of PX-171-004, a Phase 2 Study of Single-Agent Carfilzomib in Patients with Relapsed and/or Refractory Multiple Myeloma[2]

[1] Jakubowiak AJ et al.
Proc ASH 2011;Abstract 631.

[2] Vij R et al.
Proc ASH 2011;Abstract 813.

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Final Results of a Frontline Phase 1/2 Study of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone (CRd) in Multiple Myeloma (MM)

Jakubowiak AJ et al.
Proc ASH 2011;Abstract 631.

Background

- Carfilzomib is a next-generation proteasome inhibitor that selectively and irreversibly binds to its target, resulting in sustained inhibition in the absence of off-target effects.
- In relapsed and/or refractory MM, the combination of carfilzomib (CFZ) with lenalidomide (Len) and low-dose dexamethasone (Dex) (CRd) has shown very promising efficacy: 78% ≥PR , 40% ≥VGPR, 24% CR/nCR (Wang et al, ASCO 2011).
- In a Phase I/II study of newly diagnosed MM, the regimen was well tolerated and very active with 96% ≥PR, 70% ≥VGPR and 55% CR/nCR (Jakubowiak et al, ASH 2010).
- This study presents results after enrollment in the Phase II portion of the Phase I/II trial of CRd in MM.

Jakubowiak AJ et al. *Proc ASH* 2011;Abstract 631.

Methods

Accrual: 53 (Closed)

Eight 28-day cycles
CFZ: IV on days 1, 2, 8, 9, 15, 16
20 mg/m^2, 27 mg/m^2 (Phase I), 36 mg/m^2 (Phase I and II)
LEN: Days 1-21, 25 mg PO
Dex: Cycles 1-4/5-8, 40/20 mg PO weekly

↓

- Achieved ≥PR → stem cell collection (SCC) and autologous stem cell transplant (ASCT) after 4 cycles
- ASCT patients offered continued CRd treatment after SCC
- After 8 cycles, pts received 28-d maintenance cycles of CFZ on d1, 2, 15, 16 + LEN on d1-21 + weekly Dex at tolerable dose at end of cycle 8

Jakubowiak AJ et al. *Proc ASH* 2011;Abstract 631.

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Response to CRd by Treatment Cycles and CFZ Dose (Abstract Only)

	ORR (%)	CR/nCR (%)	≥VGPR (%)
Treatment cycles			
1+ (n = 49)	94	53	65
4+ (n = 35)	100	71	89
8+ (n = 28)	100	75	89
12+ (n = 19)	100	79	100
CFZ dose (mg/m^2)			
20 (n = 4)	100	75	100
27 (n = 13)	100	85	100
36 (n = 32)	91	38	47

Jakubowiak AJ et al. *Proc ASH* 2011;Abstract 631.

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Response to CRd (Abstract Only)

Clinical parameter (n = 49)*	ORR (%)	CR/nCR (%)	≥VGPR (%)
Cytogenetics			
Normal/favorable (n = 33)	91	52	61
Unfavorable (n = 16)	100	56	75
ISS stage			
I (n = 20)	90	50	65
II (n = 16)	94	44	56
III (n = 13)	100	69	77

* Response by IMWG criteria

Jakubowiak AJ et al. *Proc ASH* 2011;Abstract 631.

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Adverse Events (Abstract Only)

Event	n = 51*
Hematologic (Grade 3/4)	
Anemia	18%
Neutropenia	12%
Thrombocytopenia	10%
Nonhematologic (Grade 3/4 in ≥10%)	
Hyperglycemia	24%
Dyspnea	12%
Deep vein thrombosis/pulmonary embolism while on ASA prophylaxis	10%
Nonhematologic (all grades)	
Hyperglycemia	76%
Hypophosphatemia	61%
Infection	53%
Peripheral neuropathy (Grade 1 or 2)	24%

* As of June 30, 2011

Jakubowiak AJ et al. *Proc ASH* 2011;Abstract 631.

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Author Conclusions

- CRd is highly active and well tolerated, allowing the use of full doses for an extended time in patients with newly diagnosed MM with limited need for dose modification.
- Responses are rapid and improve over time, reaching 100% ≥VGPR, and early time-to-event data are encouraging.
- These results compare favorably to the best front-line regimens in MM.

Jakubowiak AJ et al. *Proc ASH* 2011;Abstract 631.

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Investigator Commentary: Front-Line Carfilzomib, Lenalidomide and Low-Dose Dexamethasone in MM

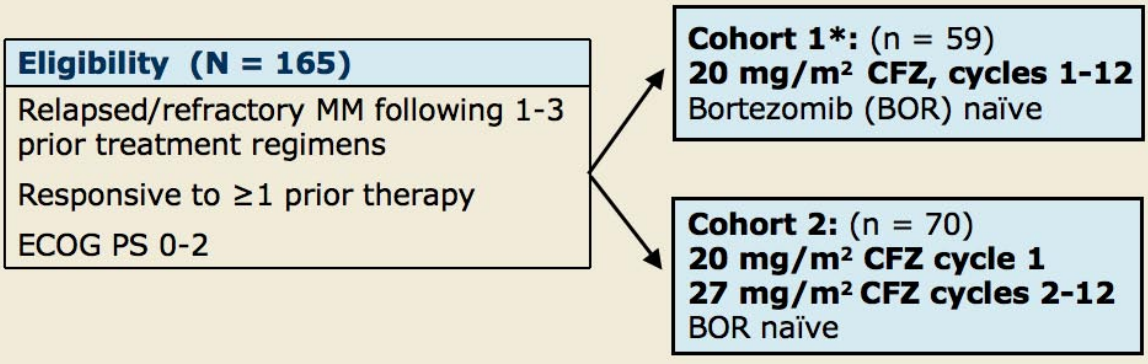
The overall response rate in the study presented by Dr Jakubowiak and his team was 94% partial response or better, which is a response rate similar to that seen with lenalidomide combined with bortezomib and dexamethasone (RVD), with which a rate of partial response or better of 100% was reported. It is also exciting that such high-quality results were seen early in the course of this study because the quality of responses may improve with longer follow-up. Importantly, the side effects appear very manageable, with a relative lack of neurotoxicity and an approximately 25% rate of treatment-emergent peripheral neuropathy overall, which is significantly less than with RVD. Conversely, the 53% incidence of infection was not unexpected in this setting, as upper respiratory infections in patients with newly diagnosed (ND) MM are common, but the 76% incidence of significant hyperglycemia is more difficult to explain. Another important side effect seen with CFZ and Rd, which was not reported with RVD, was shortness of breath at the time of drug administration or shortly thereafter. At the ASH meeting, Dr Jakubowiak suggested that this could have been due to the aggressiveness of the fluid challenge that was administered with CFZ, and this may indeed be true but the rate of approximately 12% is significant, and possibly attributable toxicity warrants some caution. Overall, however, I believe that CFZ and Rd is an outstanding combination based on current data and is very promising as we go forward in developing novel up-front 3- and 4-drug regimens for ND MM.

Interview with Paul G Richardson, MD, January 24, 2012

Final Results from the Bortezomib-Naïve Group of PX-171-004, a Phase 2 Study of Single-Agent Carfilzomib in Patients with Relapsed and/or Refractory Multiple Myeloma

Vij R et al.
Proc ASH 2011;Abstract 813.

Study Design



CFZ = carfilzomib IV qd x 2, 3 wks (28-d cycle)

* Results in BOR-treated (n = 35) group have been previously reported

Sixty-six percent of patients in cohort 1 and 64% patients in cohort 2 were refractory to most recent therapy.

Vij R et al. *Proc ASH* 2011;Abstract 813.

Efficacy Outcomes

Outcome	Cohort 1	Cohort 2*
Overall response rate (n = 59, 67)	42%	52%
Clinical benefit rate (n = 59, 67)	59%	64%
Median duration of response (n = 25, 35)	13.1 mo	NR
Median duration of clinical benefit response (CBR) (n = 35, 43)	11.5 mo	NR
Median time to progression (n = 59, 67)	8.3 mo	NR
Median time to response (n = 25, 35)	1.0 mo	1.9 mo
Median time to CBR (n = 35, 43)	0.5 mo	0.5 mo
Median progression-free survival (n = 59, 67)	8.2 mo	NR
Median overall survival (n = 59, 67)	NR	NR
Median follow-up (n = 59, 67)	23.2 mo	13.8 mo

* Three patients not evaluable for response
NR = not reached

Vij R et al. *Proc ASH* 2011;Abstract 813.

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Grade 3/4 Adverse Events

Event (≥5% patients)	Cohort 1 (n = 59)	Cohort 2 (n = 70)
Hematologic		
Lymphopenia	14%	19%
Anemia	12%	17%
Thrombocytopenia	15%	11%
Neutropenia	12%	14%
Nonhematologic		
Pneumonia	14%	11%
Fatigue	12%	1%
Dyspnea	5%	6%
Treatment-emergent neuropathy	2%	0%

Vij R et al. *Proc ASH* 2011;Abstract 813.

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Author Conclusions

- Carfilzomib showed robust and durable single-agent activity in bortezomib-naïve patients with relapsed/refractory MM.
- ORR of 42%–52% and a CBR of 59%–64% were observed in 2 separate dose cohorts. These data are suggestive of a dose–response relationship and are being further evaluated in the exploratory Phase Ib/II study PX-171-007.
- The most common adverse events included fatigue, nausea, anemia, dyspnea, cough and pyrexia, and the majority of AEs were Grade 1 or 2.
- Carfilzomib was associated with minimal peripheral neuropathy.

Vij R et al. *Proc ASH* 2011;Abstract 813.

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Investigator Commentary: Single-Agent Carfilzomib in Relapsed and/or Refractory MM

The PX-171-004 Phase II study by Dr Vij and colleagues showed an overall response rate of 42% in cohort 1 and 52% to CFZ in cohort 2 for patients with bortezomib-naïve relapsed MM. This is really quite encouraging because it suggests that CFZ is similar to bortezomib in terms of efficacy as monotherapy, albeit with low-dose dexamethasone administered as a premedication at the time of CFZ administration. Importantly, there was a markedly lower incidence of peripheral neuropathy and, in the context of an equivalent response rate, this is an obvious advantage. For comparison, the Phase III APEX trial recorded a similar overall response rate of 43% to bortezomib as a single agent, with the more recent Phase III study of SC bortezomib (led by Dr Moreau and colleagues) showing a rate closer to 50%, but half as much neuropathy, with the SC route of bortezomib administration having this as a clear benefit to its use.

Interview with Paul G Richardson, MD, January 24, 2012

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