5 Minute JournalClub

Key ASH Presentations
Issue 3, 2012

Phase II Trial of Elotuzumab with Lenalidomide and Low-Dose Dexamethasone for Patients with 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 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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Phase II Trial of Elotuzumab with Lenalidomide and Low-Dose Dexamethasone for Patients with Relapsed/Refractory Multiple Myeloma

Presentation discussed in this issue

Lonial S et al. **A Phase 2 study of elotuzumab in combination with lenalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma.** *Proc ASH* 2011;**Abstract 303**.

Slides from a presentation at ASH 2011 and transcribed comments from a recent interview with Sagar Lonial, MD (1/25/12)

Background

- Elotuzumab is a humanized IgG1 mAb targeting human CS1, a cell surface glycoprotein (*Clin Cancer Res* 2008;14:2775; *Blood* 2008;112:1329).
- CS1 is highly expressed on >95% of MM cells (*Blood* 2008;112:1329; *Mol Cancer Ther* 2009;8:2616).
- The mechanism of action of elotuzumab is primarily through NK cell-mediated ADCC against myeloma cells (*Clin Cancer Res* 2008;14:2775; *Blood* 2008;112:1329).
- In an MM xenograft mouse model, the combination of elotuzumab and lenalidomide significantly reduced tumor volume compared to either agent alone (*Mol Cancer Ther* 2009;8:2616).

Lonial S et al. *Proc ASH* 2011;Abstract 303.

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Study Schema

Eligibility (N = 73)

Relapsed/refractory MM with 1-3 prior therapies

Measurable disease by M protein

Creatinine clearance ≥50 mL/min

No prior treatment with LEN

No thalidomide, bortezomib or corticosteroids within 2 wks of first elotuzumab dose

R

Elotuzumab 10 mg/kg IV + LEN + LoDEX (n = 36)

Elotuzumab 20 mg/kg IV + LEN + LoDEX (n = 37)

LEN = lenalidomide 25 mg; LoDEX = low-dose dexamethasone 40 mg

A premedication regimen of methylprednisolone/dexamethasone, diphenhydramine, ranitidine and acetaminophen was administered 30-60 min prior to each elotuzumab infusion.

Lonial S et al. *Proc ASH* 2011;Abstract 303.

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Best Response (IMWG Criteria)

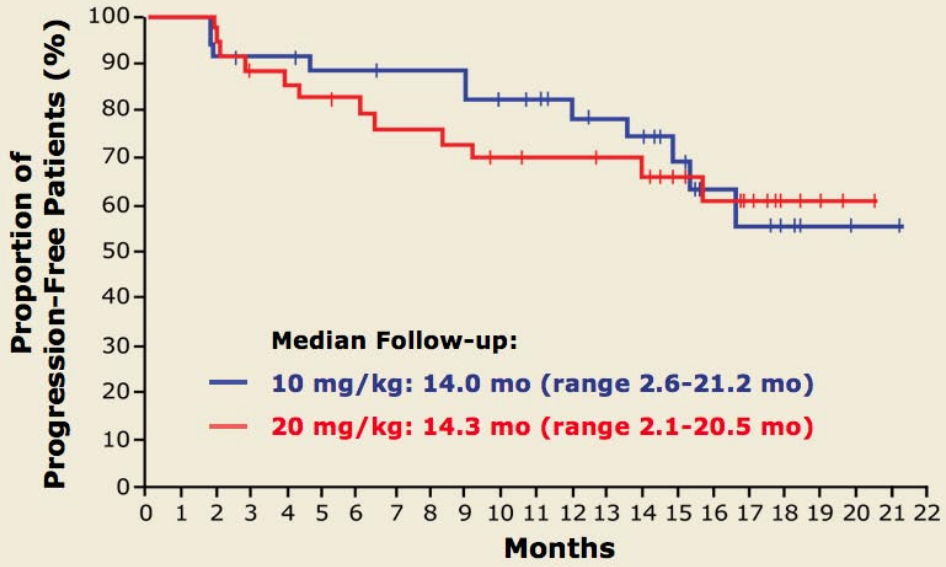
Clinical parameter	Elotuzumab 10 mg/kg (n = 36)	Elotuzumab 20 mg/kg (n = 37)	Total (N = 73)
ORR (≥PR)	92%	73%	82%
CR/stringent CR	14%	11%	12%
VGPR	39%	32%	36%
PR	39%	30%	34%
<PR	8%	27%	18%
ORR with # prior therapies	**(n = 16)**	**(n = 17)**	**Total (n = 23)**
One prior therapy	100%	82%	91%
Two prior therapies	85%	65%	75%

ORR = objective response rate; PR = partial response; CR = complete response; VGPR = very good partial response

Median time to response = 1 mo (range, 0.7-5.8); median time to best response = 2.2 mo (range, 0.7-17.5)

Lonial S et al. *Proc ASH* 2011;Abstract 303.

Progression-Free Survival



At a median follow-up of 14.1 months, the median PFS was not reached.
PFS rate was 75% (elotuzumab 10 mg/kg) and 65% (elotuzumab 20 mg/kg).

With permission from Lonial S et al. *Proc ASH* 2011;Abstract 303.

Select Treatment-Emergent Adverse Events (AEs)

Event	Elotuzumab 10 mg/kg (n = 36)	Elotuzumab 20 mg/kg (n = 37)	Total, Gr 3/4 only (N = 73)
Muscle spasms	53%	57%	3%
Diarrhea	56%	51%	5%
Fatigue	53%	43%	7%
Anemia	36%	27%	11%
Neutropenia	31%	22%	16%
Thrombocytopenia	31%	19%	16%
Lymphopenia	28%	19%	16%

One patient had Grade 5 pneumonia complicated by cellulitis and sepsis leading to multiorgan failure.

Peri-infusion AEs (all grades) reported in 67% of patients.

Lonial S et al. *Proc ASH* 2011;Abstract 303.

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Author Conclusions

- Elotuzumab plus LEN and LoDEX has a high ORR in relapsed and relapsed/refractory MM (all patients = 82%, elotuzumab 10 mg/kg = 92% and elotuzumab 20 mg/kg = 73%).
- At a median follow-up of 14.1 months, the median PFS was not reached (elotuzumab, 10 mg/kg = 65% and 20 mg/kg = 75%).
- The combination was generally well tolerated:
  - Most common Grade 3/4 treatment-emergent AEs were neutropenia (16%), thrombocytopenia (16%) and lymphopenia (16%).
  - The premedication regimen decreased the incidence and mitigated severity of infusion reactions.
- Two Phase III trials of elotuzumab 10 mg/kg plus LEN and LoDEX for previously untreated and relapsed/refractory MM are ongoing (NCT01335399, NCT01239797).

Lonial S et al. *Proc ASH* 2011;Abstract 303.

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Investigator Commentary: Novel Humanized Monoclonal Antibody Elotuzumab for Relapsed and/or Refractory MM

I was the principal investigator of this study, but I believe this agent represents a completely new approach for us in myeloma. Treatment with monoclonal antibodies has permeated all of oncology fairly well. The problem in myeloma has been that even when a good target exists, the immune function may be limiting the ability of an antibody to be effective in treatment. The target can be ligated with an antibody, but if the natural killer cells and others are not available to induce antibody-dependent, cell-mediated cytotoxicity, an antibody-coded cancer cell can continue to act.

I believe that the administration of LEN both enhances the immune function and improves the efficacy of the monoclonal antibody.

Interview with Sagar Lonial, MD, January 25, 2012

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