5 Minute JournalClub

POST-ASH Issue 5, 2014

Carfilzomib/Lenalidomide/ Dexamethasone → Lenalidomide Extended Dosing for Newly Diagnosed MM

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on novel therapeutic options in the treatment of multiple myeloma (MM) and Waldenström's macroglobulinemia (WM) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Integrate recent clinical research findings with proteasome inhibitors and immunomodulatory agents into the development of individualized induction and maintenance treatment strategies for patients with MM.
- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens — including anti-CD38 antibodies and AKT, BTK, KSP and novel proteasome inhibitors — under evaluation for newly diagnosed and relapsed/refractory MM and WM and, where appropriate, facilitate patient access to ongoing trials of these agents.
- Appraise recent clinical research findings on the efficacy and safety of novel proteasome inhibitor- and/or BTK inhibitor-based therapeutic strategies for WM, and consider this information for the treatment of patients.

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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:

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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: March 2014
Expiration date: March 2015

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

Rafael Fonseca, MD

One might view current clinical research in multiple myeloma (MM) as being in a consolidation phase after the introduction of proteasome inhibitors, immunomodulatory drugs and bisphosphonates brought forth a huge wave of progress. This idea is reflected in many of the new MM reports presented in New Orleans, where we were treated to intriguing data attempting not only to help optimize the impact of our current tools but also to uncover novel agents that will launch a new era with even better outcomes. For this second MM issue of our ASH review series, Dr Rafael Fonseca comments on a handful of papers that help take the next step in what will hopefully be another quantum leap forward in this fascinating corner of oncology.

- **More on up-front carfilzomib/lenalidomide/dexamethasone (dex) (CRd)**

MM is only one of a number of tumor types in oncology today for which there is considerable interest in moving newly approved agents up earlier in the course of the disease. In this regard, we have already seen preliminary data from Andrzej Jakubowiak, and at ASH **the NCI presented** another major single-arm study evaluating induction CRd followed by maintenance therapy — in this case lenalidomide. As in the work presented by Dr Jakubowiak, in this study patients received long-term maintenance and transplant was optional, and with the extraordinary risk-benefit value of this regimen (near complete response [CR] or better in 73% of the 43 patients, 100% minimal residual disease negativity assessed by flow cytometry among 27 patients with near CR or stringent CR and no Grade 3 or 4 neuropathy), Dr Fonseca can foresee a time when treatment will be individualized based on depth of response, with transplant avoided in some patients and survival extended significantly. However, in terms of current practice, like most MM investigators Dr Fonseca believes that while preliminary data on this and similar regimens are very encouraging, carfilzomib should not be used up front outside of a trial setting and recommends that patients interested in this approach be referred to the major Intergroup study comparing CRd to RVD.

• Carfilzomib/cyclophosphamide/dex (CCd) up front in elderly patients

In the same vein as the previous study, another ASH data set reported on recent efforts to incorporate carfilzomib into popular and currently employed bortezomib-based up-front regimens. **This Phase II trial** looked at CCd (similar to CyBorD) induction in 55 evaluable patients aged 65 and over with newly diagnosed MM. The bottom line is that despite significant activity (47% near CR or better) and relatively good tolerability (14% of patients discontinued treatment because of toxicity, which is considerably fewer than in prior studies for elderly patients), Dr Fonseca — a major proponent of CyBorD — urges us all to hold off on CCd outside a clinical trial.

• Pomalidomide (POM)/carfilzomib/dex in relapsed/refractory (RR) disease

Combining the 2 new kids on the block, POM and carfilzomib, always seemed like a natural next step, and at ASH we saw encouraging data with this appealing regimen. **A multicenter Phase I/II effort** for patients with heavily pretreated lenalidomide-refractory MM (a median of 5 prior treatments) resulted in a 70% overall response rate among 79 evaluable patients and a manageable toxicity profile. Even more, this report demonstrates that the regimen is not only a viable option in very advanced disease but also an approach that is of great interest in up-front trials.

In a related manner, ASH also featured **2 data sets** providing updates from trials evaluating POM with low-dose dex in RR disease. Dr Fonseca's take-away from these presentations is that while patients with extensive prior treatment and adverse cytogenetic profiles often benefit from this therapy, myelosuppression in these individuals must be managed carefully with dose adjustments and growth factors.

• An all-oral "RVD"

For the past several years we have profiled the early development of the oral proteasome inhibitors ixazomib and oprozomib, and at ASH **Paul Richardson presented more data** from his Phase I/II study looking at ixazomib/lenalidomide/dex in previously untreated MM. This study, which evaluated twice-weekly ixazomib, revealed activity (94% response rate among 62 patients) similar to what is typically seen with RVD but slightly more peripheral neuropathy (PN) (Grade 3 in 5% of 64 patients) than has been observed in trials using weekly administration of this fascinating agent. Not surprisingly, Dr Fonseca is eagerly and optimistically awaiting the results of ongoing Phase III trials.

• Cool new compounds

For the immediate future most myeloma investigators like Dr Fonseca believe monoclonal antibodies represent the most likely path to dramatically catapult survival in this disease, and there is great hope that a rituximab-like agent may be identified. The 2 compounds we have heard the most about up to now are the anti-CD38 antibody daratumumab, which has garnered FDA breakthrough therapy status, and elotuzumab,

which is directed against human CS1 (a cell surface antigen glycoprotein that is highly expressed on MM cells) and appears to result in an R-squared-like synergy with lenalidomide.

However, for a disease diagnosed in "only" about 20,000 individuals a year in the United States, a stunning amount of active drug development is under way in MM, and at ASH we were provided with a preview of some of the agents and strategies we may be hearing a lot more about in the next few years:

– SAR650984

Similar to daratumumab, **this anti-CD38 antibody** was shown to have significant single-agent efficacy in patients with relapsed MM (31% response rate among 13 patients receiving the 10-mg/kg dose every 2 weeks) and minimal toxicity other than manageable infusion reactions. Dr Fonseca stated that "this is probably one of most important molecules for future MM therapy."

– Filanesib

A report from a **Phase II trial** of this selective inhibitor of kinesin spindle protein alone or in combination with dex demonstrated a 15% response rate among 55 evaluable patients receiving the combination and manageable toxicity. What seems most exciting about this data set is that activity was absent in patients with high serum levels of α-1 acid glycoprotein (which binds the drug, making it unavailable), potentially opening the door for a predictive biomarker.

– Afuresertib

AKT is a critical signaling node in MM, and this **single-arm Phase IB trial** evaluated the potent AKT inhibitor afuresertib in combination with dex and bortezomib in 81 patients with relapsed or refractory disease. The overall response rate was 65% and the clinical benefit rate was 73% among 37 patients in the safety expansion cohort. The results are favorable enough to justify further study, but of particular interest was the demonstration of consistent increases in the levels of the phosphorylated form of the drug target in MM cells.

• Bonus feature: Two compelling data sets in Waldenström's macroglobulinemia (WM)

WM is unusual in oncology in that investigators focused on both lymphomas and plasma cell disorders are involved in clinical research and patient care. Most importantly, borrowing from progress in both of these fields, the outlook for the 1,500 US patients diagnosed annually continues to improve as reflected in the following data sets:

– Carfilzomib

The lack of PN with carfilzomib, even in indirect comparison to weekly subcutaneous bortezomib, is particularly appealing in WM, in which PN is part of the disease biology. As such, this agent was **evaluated in a Phase II study** combining it with rituximab and dex for 31 patients with symptomatic WM. As reported at ASH, this combination resulted in a best overall response rate of 81% and significant IgM declines along with improved marrow profiles and hemoglobin levels. Even more important, PN of Grade 2 or higher was not reported, leading the authors to conclude that the regimen represents a "neuropathy-sparing approach" for the treatment of WM. In relation to these findings, Dr Fonseca verbalized his concern that the rarity of this disease has led to a dearth of FDA-approved therapies, making it a considerable challenge to obtain reimbursement for novel agents with proven patient benefit.

– Ibrutinib

Now approved for mantle-cell lymphoma and chronic lymphocytic leukemia, perhaps it should not be that big of a surprise that ibrutinib is effective in WM, especially since a somatic mutation (MYD88 L265P) that appears to support malignant growth through Bruton tyrosine kinase is present in more than 90% of these patients. Indeed, in this **exciting Phase II study** 51 of 63 patients (81%) had best overall responses — which were usually rapid, often with rising hematocrit and reductions in serum IgM — strongly suggesting that this agent is destined to have a critical role in the care of these patients.

Next up, we focus on papers in Hodgkin lymphoma and the rapidly emerging role of the antibody-drug conjugate brentuximab vedotin.

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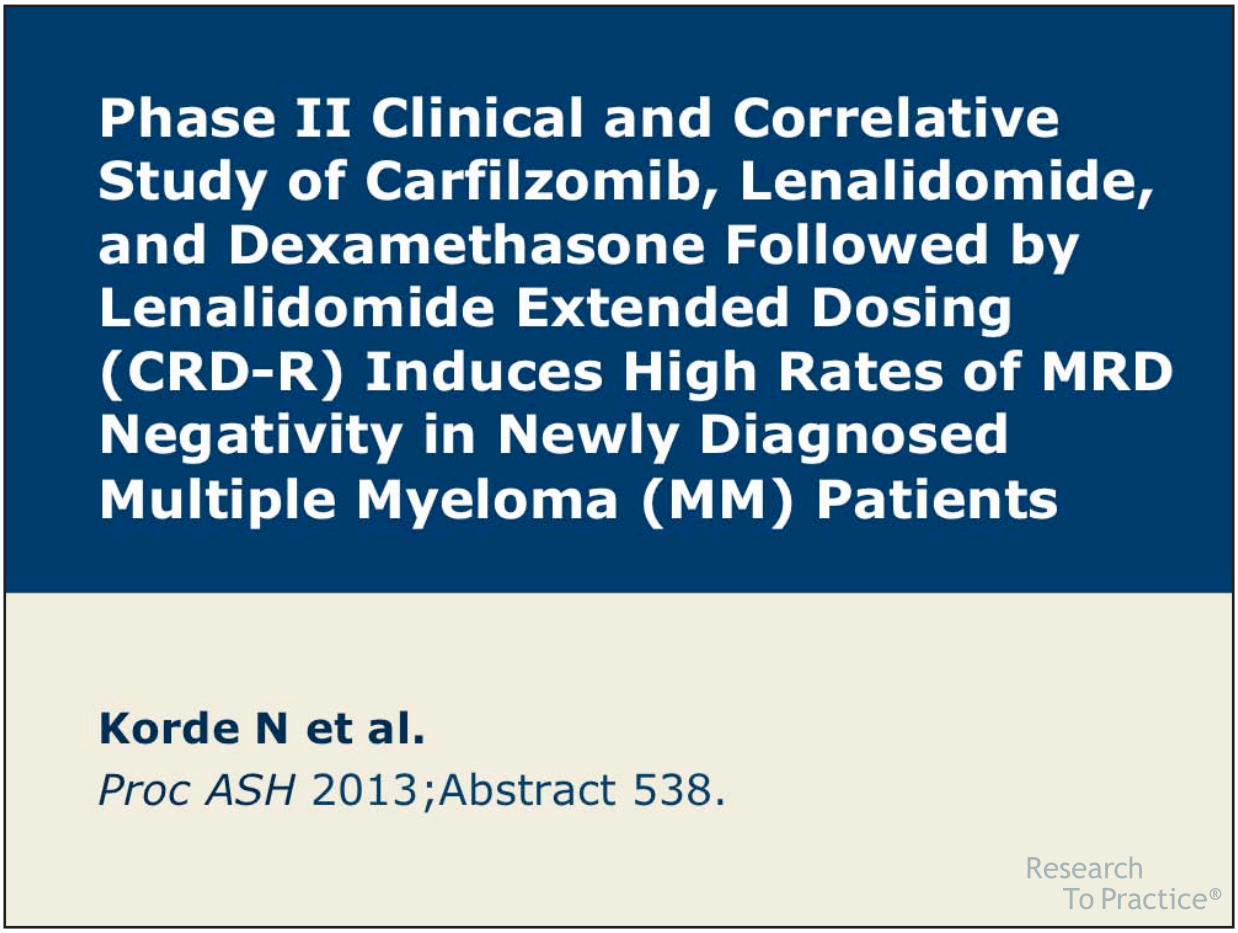
Carfilzomib/Lenalidomide/Dexamethasone → Lenalidomide Extended Dosing for Newly Diagnosed MM

Presentation discussed in this issue

Korde N et al. **Phase II clinical and correlative study of carfilzomib, lenalidomide, and dexamethasone followed by lenalidomide extended dosing (CRD-R) induces high rates of MRD negativity in newly diagnosed multiple myeloma (MM) patients.** *Proc ASH* 2013;**Abstract 538**.

Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with Rafael Fonseca, MD (2/14/14)



Background

- Recent emerging evidence indicates a potential role for flow cytometry, functional imaging and PCR-based assays as possible methods to detect residual disease.
  - As therapies improve, there are increasing needs for characterization of deep responses with more sensitive technology and of long-term disease remissions.
- Carfilzomib (Cfz) is an irreversible proteasome inhibitor with potent anti-multiple myeloma (MM) effects resulting in deep clinical responses and durable remissions as well as decreased peripheral neuropathy compared to bortezomib.
- **Study objective:** To determine the incidence of Grade ≥3 neuropathy and the efficacy of Cfz, lenalidomide (Ln) and dexamethasone (CRd) → 2 years of Ln maintenance in patients with newly diagnosed MM.

Korde N et al. *Proc ASH* 2013;Abstract 538.

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CRd in Newly Diagnosed MM

	Jakubowiak et al study* (Phase I/II, n = 53)	Current study (Phase II, n = 45)
Combination therapy	CRd (Phase II Cfz 20/36 mg/m^2) 8 cycles	CRd (Cfz 20/36 mg/m^2) 8 cycles
Extended dosing	CRd (Cfz every other week) 16 cycles, off-protocol Ln at last tolerated dose d1-21 after 16 cycles	Ln 10 mg d1-21, 24 cycles
Transplant	≥PR stem cell collection, HDM optional	Stem cell collection
Correlatives	Flow cytometry — MRD	Flow cytometry — MRD, PET-CT, proteasome assays, GEP, whole-genome sequencing

* Jakubowiak A et al. *Blood* 2012;120(9):1801-8.

GEP = gene expression profiling

Korde N et al. *Proc ASH* 2013;Abstract 538.

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Study Objectives and Enrollment

- **Primary study objective:**
  - Incidence of Grade ≥3 neuropathy
- **Secondary study objectives:**
  - Correlatives: GEP, biomarkers, proteasomes, flow cytometry, PCR, FDG PET-CT
  - Clinical: Response rate, progression-free survival (PFS), overall survival and duration of response
- **Target enrollment (n = 45):**
  - Phase II study, 2-stage design:
    - Stage I: Patients 1-20 — If 4 or more develop Grade ≥3 neuropathy, then study stops
    - Stage II: Patients 21-45

Korde N et al. *Proc ASH* 2013;Abstract 538.

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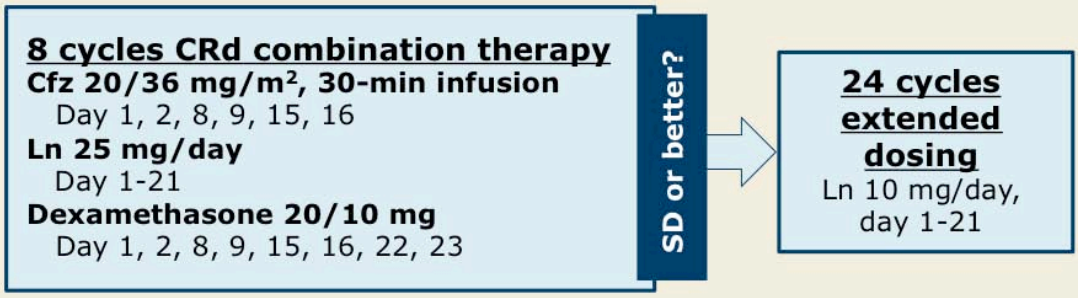
Phase II Study Design



- Each cycle is 28 days
- Stem cell harvest after ≥4 cycles of CRd for patients <75 years of age
- Cycle 1, day 1, 2: Cfz dose is 20 mg/m²
- Cycles 1-4: Dexamethasone dose is 20 mg; cycles 5-8: Dexamethasone dose is 10 mg

SD = stable disease

Korde N et al. *Proc ASH* 2013;Abstract 538.

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Patient Characteristics

Variable	
Patients enrolled	45
Patients completed 2 cycles (evaluable)	43
Median age, y (range)	60 (40-88)
Male sex, n (%)	26/43 (60)
Isotype, n (%) IgG IgA Kappa Lambda	 28 (65) 10 (23) 4 (9) 1 (2)
Median cycles of CRd → Ln received (range)	12 cycles (2-25)
Median follow-up in months (range)	12 months (2-26)
Patients completed 8 cycles of CRd	29

Korde N et al. *Proc ASH* 2013;Abstract 538.

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Response Rates

Response	2 cycles	8 cycles	Best response*
ORR (≥PR)	98%	97%	98%
≥VGPR	51%	91%	88%
nCR/CR/sCR	16%	73%	67%
CR/sCR	7%	42%	51%
VGPR	35%	18%	21%
PR	47%	6%	9%
SD	2%	3%	2%

ORR = overall response rate; PR = partial response; VGPR = very good PR; nCR = near complete response; sCR = stringent CR

* Median 12 cycles of CRd → Ln maintenance

Korde N et al. *Proc ASH* 2013;Abstract 538.

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Time to CR/sCR and PFS

Time to CR/sCR	
CR/sCR, n/N (%)	22/43 (51%)
Patients reaching CR/sCR with ≥8 cycles of CRd, n/N (%)	5/22 (23%)
Median time to CR/sCR, months (range)	5 (2-18)
PFS at 12 months	**97%**

- 4 patients have come off study treatment, 3 due to progression and 1 due to personal reasons. All other patients remain on study treatment.

Korde N et al. *Proc ASH* 2013;Abstract 538.

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Select Grade 3/4 Adverse Events (AEs)

Nonhematologic AEs	(n = 43)
Electrolyte disturbances	21%
LFT elevation	12%
Skin (rash, pruritus, eye)	12%
Constitutional (fatigue, presyncope, dehydration, adrenal insufficiency)	12%
Lung (dyspnea, respiratory failure)	9%
Cardiac (hypertension, heart failure)	9%
Infection (pneumonia, enterocolitis, febrile neutropenia)	9%
VTE	7%

- None of the 43 evaluable patients developed Grade ≥3 neuropathy

Korde N et al. *Proc ASH* 2013;Abstract 538.

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Select Grade 3/4 AEs (Continued)

Hematologic AEs	(n = 43)
Lymphopenia	65%
Anemia	28%
Neutropenia	21%
Thrombocytopenia	19%

- **Dose reductions**:
  - 4 decreased Cfz (dyspnea, renal injury)
  - 11 decreased dexamethasone (fatigue, anxiety, dyspnea)
  - 12 decreased Ln (rash, fatigue, renal adjustment, cytopenias and LFT increase)

Korde N et al. *Proc ASH* 2013;Abstract 538.

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Author Conclusions

- Treatment with CRd → Ln maintenance did not result in any incidence of Grade 3/4 neuropathy in patients with newly diagnosed MM.
  - Limited severe toxicities
- Treatment resulted in high response rates as well as deep and rapid responses.
  - ORR (PR or better) = 98%
  - nCR/CR/sCR = 67%
  - Median time to sCR = 5 months (range: 2-18)
- PFS rate at 12 months is 97%.
- CRd → Ln maintenance is an effective and tolerable therapy for older patients (data not shown).
- Among 27 patients with nCR/sCR assessed by flow cytometry, all were MRD negative (data not shown).

Korde N et al. *Proc ASH* 2013;Abstract 538.

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Investigator Commentary: Phase II Clinical and Correlative Study of CRd → Lenalidomide — Extended Dosing Induces High Rates of MRD Negativity in Newly Diagnosed MM

In addition to the quality of the data, the correlative science associated with this elegant study taught us more than would a standard Phase II clinical trial. Consistent with what was reported in a recent paper from Andrzej Jakubowiak (*Blood* 2012;120(9):1801), this was a highly active regimen. The current study attempted to focus predominantly on particularly deep responses. Patients who were able to go through 8 cycles of therapy and were assessed for response at that point achieved a nCR, CR or sCR rate of 73%, which is impressive. These results help set the stage for what the majority of people in the field are considering: As your first intention, getting a deep response with induction therapy seems to be an important goal.

(Continued)

This potentially sets the patient up for even better outcomes after transplant. I say "potentially" because this study has raised the question, is there a future in which transplant is not part of treatment for myeloma? The majority of patients on this study who achieved nCR/sCR also had MRD-negative disease. That certainly provides a context in which to ask this question as we move into the future. The treatment of myeloma must still be based on clinical parameters, but perhaps it's time that we incorporate some of these biomarkers earlier on to better gauge what kind of progress we're making as we treat the disease.

Interview with Rafael Fonseca, MD, February 14, 2014

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