Efficacy and Safety of Carfilzomib, Lenalidomide and Dexamethasone in MM
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 up-front and salvage therapeutic options and modalities for the evaluation of treatment response in the management of newly diagnosed and relapsed or refractory multiple myeloma (MM) 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

- Analyze recent efficacy and safety results from the Phase III ASPIRE trial evaluating carfilzomib in combination with lenalidomide and low-dose dexamethasone in the treatment of relapsed or progressive, symptomatic MM.
- Evaluate the safety and efficacy of weekly carfilzomib combined with cyclophosphamide and dexamethasone for elderly patients with newly diagnosed MM.
- Compare and contrast the benefits and risks of pomalidomide and dexamethasone with cyclophosphamide or bortezomib for patients with lenalidomide-refractory MM.
- Assess the efficacy and safety of the investigational oral proteasome inhibitors ixazomib and oprozomib as maintenance therapy and single-agent treatment, respectively, for relapsed MM.
- Examine the role of age on the efficacy of lenalidomide and low-dose dexamethasone in patients with newly diagnosed MM enrolled in the FIRST trial.
- Appraise minimal residual disease testing modalities in patients with newly diagnosed MM who received carfilzomib in combination with lenalidomide and dexamethasone.

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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 2015
Expiration date: March 2016
Last fall when I first met clinical investigator Dr Ola Landgren, aside from wanting to greet him with a very Miami--esque “Hola Ola!” I was curious to learn what prompted Memorial Sloan Kettering to lure this prominent researcher away from the cozy confines of the National Cancer Institute (NCI) to be the chief of their multiple myeloma (MM) service.

It didn’t take long to see that Dr Landgren is a passionate clinician who, like many others in the field, believes that this disease, which traditionally has been treated in a palliative mode, now seems on the verge of prolonged control for many patients. Since that first encounter, our group has worked with Dr Landgren on a number of occasions, and each time, his astute perspectives and thoughtful commentary have helped bring greater clarity to the rapidly evolving but often opaque clinical research database in this disease. For that reason, we decided to sit down with him again to get his take on the key MM presentations from the recent American Society of Hematology (ASH) meeting in San Francisco. In the first of 2 issues focused on this disease, we review research efforts attempting to maximize the treatment benefit of 2 classes of agents that have revolutionized the field, proteasome inhibitors and immunomodulatory agents (IMiDs), and in short what we learned is that the marked benefit already observed to this point may increase substantially in the future as a result of a variety of permutations of approved and emerging agents. Here’s the summary:

• **Triplet therapy for relapsed/refractory (R/R) disease:**

**The ASPIRE trial**

Many general oncologists question the concept of “using all your big guns up front,” learning long ago in another more common noncurable situation, metastatic breast cancer, that sequential single-agent chemotherapy yielded comparable long-term efficacy outcomes with better tolerability than combination approaches. In MM, although triple regimens like lenalidomide/bortezomib/dexamethasone (RVD) have been widely embraced in the induction setting, most clinicians have used a sequential “breast cancer–like” approach for R/R disease.
In San Francisco — in what Dr Landgren describes as “the number 1 myeloma message from ASH” — and soon after in the New England Journal, we saw perhaps the most convincing data available at this time suggesting a different approach. The ASPIRE trial aspired to compare carfilzomib/lenalidomide/low-dose dexamethasone (CRd) to Rd in patients who had previously received 1 to 3 systemic therapies. The study met its primary endpoint of progression-free survival (PFS), demonstrating a bump in efficacy from 17.6 to 26.3 months, and of particular interest, the complete response or better rate tripled (31.8% versus 9.3%). However, the overall survival (OS) analysis results did not cross the prespecified stopping boundary, but a trend for improvement was seen although few of the patients randomly assigned to Rd subsequently received carfilzomib. Other ongoing and future trials will hopefully further test this concept, but for now — particularly armed with these latest supportive data — many investigators (very much including Dr Landgren) are thinking about 3-drug combinations early in the R/R setting.

Almost as important, this large Phase III study presented an ideal opportunity to again evaluate the critical issue of carfilzomib and the heart, a topic tied into the not infrequent occurrence of early-onset dyspnea. In ASPIRE there was what Dr Landgren views as a minimal increase in the risk of cardiovascular events (Grade 3 or greater heart failure 1.8% versus 3.8%). An unrelated poster also presented in San Francisco specifically evaluated this issue prospectively in 62 patients who received carfilzomib and found 5 instances of cardiac events, 3 of which were considered attributable to the drug, and only 1 of 30 patients with available echocardiogram data pre- and postcarfilzomib treatment experienced an unexplained decrease in ejection fraction. The authors noted a frequent and dramatic rise in N-terminal pro-B-type natriuretic protein, which Dr Landgren believes could have been the result of aggressive hydration, but the study did not examine this possibility. As a result of these and other findings, at this point for most patients Dr Landgren generally recommends only clinical observation and careful hydration, without the need for specific cardiac monitoring.

**Pomalidomide (P) triplets in R/R disease**

In keeping with the theme of combination versus sequential single agents, a number of studies were also unveiled at ASH examining P in concert with other agents. A randomized Phase II study evaluating Pd with or without cyclophosphamide in 70 patients demonstrated the superiority of the triplet in terms of response rate (65% versus 39%) and also revealed borderline significant improvements in PFS and OS. Similarly, a single-arm Phase II study (n = 47) evaluating the P version of RVD (PVd) demonstrated an 85% overall response rate with an impressive waterfall plot. Both of these regimens are seen by Dr Landgren as additional evidence — albeit with many fewer patients — that the “ASPIRE” principle of using triplets in the R/R setting is quite sound.
• Up-front induction regimens

More on CRd

At ASH, Dr Landgren and his former NCI colleagues updated their important Phase II trial evaluating up-front CRd. Although this specific presentation focused on the optimal assessment of minimal residual disease and showed that next-generation sequencing was more sensitive than flow cytometry, in discussing the study Dr Landgren noted that the median age of patients on the trial was 65 and that no difference was observed in benefit between younger and older individuals. In fact, the oldest trial participant was an 88-year-old man. As such, he sees no reason not to use the most effective induction regimen available, even in older patients.

Phase I-II study of the weekly carfilzomib version of “CyBorD” (weekly CCd) in patients age 65 and over

Dr Antonio Palumbo played a key role in pioneering the initial research on weekly bortezomib, and it should therefore come as no surprise that at ASH he presented findings from a study using a similar approach with carfilzomib. What he showed was that the efficacy and tolerability associated with a once-weekly carfilzomib strategy appear comparable to that of twice-weekly administration. Interestingly, as part of the study, after 9 cycles, patients were maintained on carfilzomib alone and it was noted that with time, responses became deeper. Dr Landgren believes that these results indicate that although effective, the weekly CCd regimen is slightly inferior to other combinations like CRd that include an IMiD, but he does conclude that in countries where lenalidomide is not approved as an up-front therapy, it is a reasonable consideration. Furthermore, he believes that if weekly carfilzomib becomes a reality in general, it would be an important advance for patients.

Additional data from the FIRST trial in older versus younger patients

At the ASH 2013 meeting, the landmark Phase III FIRST study grabbed headlines by revealing a marked improvement in PFS and OS in favor of indefinite Rd compared to 18 months of either Rd or melphalan/prednisone/thalidomide (MPT). One important aspect of the study is that most of the 1,623 participants were older, and although the news wasn’t as big at this year’s conference, we saw data evaluating outcomes in patients over age 75. Significantly, essentially no difference was observed in efficacy or tolerability compared to younger patients, and although Dr Landgren recognizes that patients who enter trials are generally more fit and have fewer comorbidities, he
sees these results fitting his model of providing the most effective induction antitumor regimen (currently RVD or CRd) to all fit patients regardless of age and myeloma risk status.

**Oral proteasome inhibitors: The future of maintenance therapy?**

In San Francisco we also saw more data on a critical trend that ties directly into the concept of continuous treatment. Although it could be that oral agents will provide greater efficacy either because of intrinsic antitumor activity or that patients are able to receive more consistent dosing, there can be no denying that even if equivalent, there would be a powerful impact on patient quality of life, particularly in the long-term maintenance setting.

The oral MM agent that is farthest along in development is ixazomib, which is similar to bortezomib, and at ASH we saw more encouraging data from a Phase II up-front study evaluating the agent combined with Rd in the induction setting followed by ixazomib alone as maintenance therapy.

Perhaps even more importantly, however, since ASH we have learned via press release that the pivotal Phase III TOURMALINE-MM1 trial evaluating ixazomib with Rd versus Rd in patients with R/R MM at first interim analysis achieved its primary endpoint of improving PFS. Hopefully these data will be unveiled at the upcoming ASCO meeting, but either way it seems quite plausible that this will help pave the way for widespread availability of this agent in the near future and hopefully will serve as another important step forward in terms of patient quality of life.

Of course, ixazomib is not alone, as oprozomib, an oral agent similar to carfilzomib, is also being developed. Unlike its close cousin, however, this drug has been plagued a bit by tolerability issues, particularly gastrointestinal toxicities, and at ASH we saw more data from a Phase Ib/II study of 2 dosing schedules that demonstrated good efficacy but again challenges with side effects.

**Special bonus: Serum versus urine measurement of free light chains (FLC) in light chain MM**

The inconvenience and inaccuracy of 24-hour urine measurement of FLC led to the use of serum evaluation (Freelite® kit), but little is known about how these 2 approaches directly compare. For that reason, as part of the IFM/DFCI 2009 study of RVD induction with immediate versus delayed autologous bone marrow transplant, investigators conducted both these methods of response assessment in the 16.4% of patients (n = 115) enrolled on the trial who secreted only light chains. Based on these results, it appears that serum FLC evaluation was much more accurate, and the authors (and Dr Landgren) conclude that serum FLC should replace urine measurement in these patients.

On the second MM issue of this series, we will review other recent data on new agents in this disease, including the recently approved histone deacetylase inhibitor panobinostat and several exciting monoclonal antibodies, including elotuzumab and
daratumumab, but before then we will jump into chronic lymphocytic leukemia with lots of new information relevant to clinical practice today and, very likely, tomorrow.

Neil Love, MD

Research To Practice
Miami, Florida
Efficacy and Safety of Carfilzomib, Lenalidomide and Dexamethasone in MM

Presentations discussed in this issue

Stewart AK et al. Carfilzomib, lenalidomide, and dexamethasone vs lenalidomide and dexamethasone in patients (pts) with relapsed multiple myeloma: Interim results from ASPIRE, a randomized, open-label, multicenter phase 3 study. Proc ASH 2014;Abstract 79.


Slides from presentations at ASH 2014 and transcribed comments from a recent interview with Ola Landgren, MD, PhD (2/9/15)

Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma$^{1,2}$

The Cardiovascular Impact of Carfilzomib in Multiple Myeloma$^{3}$


$^{2}$Stewart AK et al. Proc ASH 2014;Abstract 79.

$^{3}$Rosenthal AC et al. Proc ASH 2014;Abstract 4748.
Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma

Stewart AK et al.  

Stewart AK et al.  
_Proc ASH_ 2014;Abstract 79.

Background

- Phase III trials confirmed lenalidomide with high-dose dexamethasone (RD) as a reference treatment for relapsed multiple myeloma (MM).
- Lenalidomide with weekly low-dose dexamethasone (Rd) is less toxic than RD and yields similar response rates.
- Carfilzomib is an irreversible proteasome inhibitor approved as a single agent for relapsed and refractory MM.
- Carfilzomib, lenalidomide and weekly dexamethasone (CRd) was well tolerated in Phase I/II trials with encouraging clinical activity in newly diagnosed and relapsed MM (_Blood_ 2012;120:1801-9; _Blood_ 2013;122:3122-8).

**Study objective:** To evaluate the safety and efficacy of CRd compared to Rd for patients with relapsed MM.

Phase III ASPIRE Trial Design

Eligibility (n = 792)

- Relapsed or progressive symptomatic MM
- Measurable disease
- 1-3 prior therapies
- Partial response or better to at least 1 prior Tx

CRd, 28-day cycles (n = 396)

Rd, 28-day cycles (n = 396)

Patients were stratified by β2-microglobulin, prior bortezomib or prior lenalidomide.

- **Primary endpoint**: Progression-free survival (PFS)
- **Secondary endpoints** included overall survival (OS), overall response rate (ORR), duration of response, safety


Survival

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CRd (n = 396)</th>
<th>Rd (n = 396)</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>26.3 mo</td>
<td>17.6 mo</td>
<td>0.69</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median OS</td>
<td>NE</td>
<td>NE</td>
<td>0.79</td>
<td>0.04</td>
</tr>
</tbody>
</table>

NE = not estimable

- PFS benefit in the CRd arm was observed across all prespecified subgroups
- Median OS: Trend in favor of the CRd arm, but results did not cross the prespecified stopping boundary for OS at the interim analysis
- Two-year OS rates: 73.3% (CRd) versus 65.0% (Rd)

## Response

<table>
<thead>
<tr>
<th>Best response</th>
<th>CRd (n = 396)</th>
<th>Rd (n = 396)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>87.1%</td>
<td>66.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥CR</td>
<td>31.8%</td>
<td>9.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>69.9%</td>
<td>40.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical benefit rate</td>
<td>90.9%</td>
<td>76.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CR = complete response; VGPR = very good partial response

- Stringent CR: 14.1% (CRd) versus 4.3% (Rd)
- Median duration of response: 28.6 mo (CRd) versus 21.2 mo (Rd)

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## Select Adverse Events (AEs)

<table>
<thead>
<tr>
<th>Event</th>
<th>CRd (n = 392)</th>
<th>Rd (n = 389)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19.4%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14.3%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>8.4%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>6.4%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>5.9%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

- Median treatment duration: 88.0 wk (CRd) versus 57.0 wk (Rd)
- Discontinuation due to AEs: 15.3% (CRd) versus 17.7% (Rd)

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Author Conclusions

- CRd led to a significant improvement in PFS compared to Rd for patients with relapsed MM.
- Interim OS analysis showed a trend in favor of the CRd arm.
- The ORR was higher with CRd, and a significantly higher number of patients achieved CR or better with CRd versus Rd.
- In the CRd group, adverse events led to fewer discontinuations, and patients remained on study treatment longer.
  - Cardiac- and renal-event rates were consistent with those in prior studies of single-agent carfilzomib.
- CRd consistently improved health-related quality of life compared to Rd (data not shown).


Investigator Commentary: The Phase III ASPIRE Study of CRd versus Rd for Relapsed MM

This large Phase III trial is an important study that randomly assigned 792 patients in 20 countries to CRd or Rd. One of the key findings was the depth of responses observed with CRd. A high response rate with deep responses was observed with CRd despite the fact that patients had relapsed disease and had received 1 to 3 prior lines of therapy. The rate of CR or better was 31.8% with CRd, which is unprecedented. Do the depth and duration of response matter? I definitely believe so. The median PFS was 26.3 months with CRd versus 17.6 months with Rd, showing that patients who receive this 3-drug combination can remain progression free for an additional 8 to 9 months. That is an impressive finding. Although in the interim analysis OS did not cross the prespecified stopping boundary, the risk of death was approximately 20% lower with CRd than with Rd.

I'm not a proponent of risk-adapted therapy. I believe that for patients with relapsed MM in addition to those with newly diagnosed disease, we should administer the best therapy based on the data. The best therapy should be administered up front. Reducing the disease burden will translate into the best outcome.

*Interview with Ola Landgren, MD, PhD, February 9, 2015*
The Cardiovascular Impact of Carfilzomib in Multiple Myeloma

Rosenthal AC et al. 
*Proc ASH 2014;Abstract 4748.*

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**Study Rationale and Design**

- In Phase II trials, carfilzomib (Cfz) was associated with dyspnea (34%), hypertension (14%), renal insufficiency (24%), and peripheral edema (24%), with cardiac events reported in 7% of patients.

- **Study objective:** To better understand these toxicities, 62 patients with MM who received Cfz between August 2011 and May 2014 were evaluated.

- **Design**
  - The study recorded Cfz dose, concurrent chemotherapy, hydration, blood pressure, creatinine level on days 1 and 2, troponin and N-terminal pro-B-type natriuretic protein (NT-proBNP), baseline and cycle 4 echocardiograms with ejection fraction, strain and compliance.
  - Notable cardiac events were examined for attribution.

Patient Characteristics

- Median patient age was 65 years, and 60% of the patients were male.
- 20 patients had received no prior therapies, and 42 had relapsed disease (mean: 4 prior therapies).
- 20 patients received induction chemotherapy (Cfz, dexamethasone, thalidomide, cyclophosphamide).
- At relapse, Cfz was administered alone to 21 patients, with cyclophosphamide to 10 patients and with an IMiD to 10 patients.
- Cfz dose was 20 mg/m² on days 1 and 2 and ranged from 27 to 45 mg/m² on subsequent treatment days.
- Dexamethasone was administered at 20 to 40 mg/week to 77% of the patients.
- Hydration (250 to 500 mL) was delivered in 89% of patients before and 63% after treatment.

Rosenthal AC et al. Proc ASH 2014;Abstract 4748 (Abstract only).

Author Conclusions

- Patients with MM frequently have baseline elevated cardiac peptides (59%) and abnormal cardiac strain (15% at new diagnosis and 36% at relapse).
- A frequent and sometimes dramatic rise in NT-proBNP occurs immediately after Cfz-based chemotherapy.
- Acute structural cardiac events were uncommon (3%) in the absence of confounding illness.
  - 5 of 62 (8%) patients had serious cardiac events that were probably attributable to Cfz in 3 cases (5%).
- Prospective controlled studies with longer follow-up and bortezomib-treated controls are necessary to accurately document the cardiovascular effects of Cfz and the role of proteasome inhibition.

Rosenthal AC et al. Proc ASH 2014;Abstract 4748 (Abstract only).
Investigator Commentary: Cardiovascular Effects of Carfilzomib

The study used different approaches to evaluate the effect of CFz on the cardiovascular system. The investigators used the blood test for proBNP, which cardiologists use to measure cardiac failure. The study reported that proBNP levels rise after administration of Cfz, and I have observed that in my practice. Cfz is administered with fluid, and that could increase the likelihood of raising the proBNP level. That possibility was not evaluated in this study.

Five of 62 patients in this study experienced a cardiac event, and for 3 of these patients the event was thought to be attributable to Cfz. I believe that this suggests a cardiovascular signal from the drug, which is what other groups have found. However, in the ASPIRE trial analysis of cardiovascular events after the addition of Cfz to Rd, no major difference in cardiovascular adverse outcomes was reported. Dr Stewart reported at ASH that no data from the ASPIRE trial support a significant association between cardiovascular adverse effects and Cfz. It is not clear why a cardiovascular signal was observed in this smaller study. It could be because of a sampling error. It is difficult to determine whether the adverse cardiac outcomes reported in this study are due to Cfz or due to the disease.

Interview with Ola Landgren, MD, PhD, February 9, 2015