A Prospective Head-to-Head Assessment of Cell-Based, Molecular and Molecular-Imaging Modalities of Testing Minimal Residual Disease 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 hemato-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
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To go directly to slides and commentary for this issue, click here.

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.

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Research To Practice
Miami, Florida
A Prospective Head-to-Head Assessment of Cell-Based, Molecular and Molecular-Imaging Modalities of Testing Minimal Residual Disease in MM

Presentation discussed in this issue


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

**Minimal Residual Disease (MRD) Testing in Newly Diagnosed Multiple Myeloma (MM) Patients: A Prospective Head-to-Head Assessment of Cell-Based, Molecular, and Molecular-Imaging Modalities**

*Korde N et al.*

*Proc ASH 2014; Abstract 2105.*
Background

● Recent studies show that patients with newly diagnosed MM (NDMM) who achieve MRD negativity have better progression-free (PFS) and overall survival outcomes (Blood 2014;123:3073; JCO 2013;31:2540).

● Measurement of MRD in these studies was carried out by either multicolor flow cytometry (MFC) or next-generation sequencing (NGS).

● Heterogeneity in MRD testing techniques may hinder interpretation of results.

● Study objective: To prospectively conduct comprehensive assessment of MRD testing modalities in a patient cohort uniformly treated with carfilzomib/lenalidomide/dexamethasone (CRd) followed by lenalidomide maintenance.


Study Methods

● 45 patients with NDMM who received 8 cycles of CRd followed by 2 years of maintenance lenalidomide (ASH 2013;Abstract 538) were evaluated.

● At baseline, NGS was used to amplify IgH, IgK and joining gene segments (VDJ rearrangement analysis) from DNA obtained from CD138+ bone marrow (BM) lysate or cell-free BM aspirate.

● MM clonotype was defined as a VDJ rearrangement identified by NGS at a frequency of ≥5%.

● MRD assessment was repeated by NGS, MFC and positron emission tomography (PET) when patients achieved complete response (CR) or completed 8 cycles of therapy.

● NGS was performed in peripheral blood (plasma) at baseline and after 2 cycles of treatment in a subset of patients.

Korde N et al. Proc ASH 2014;Abstract 2105 (Abstract only).
MRD Assessments

- MRD assessments by NGS:
  - At least 1 clonal rearrangement was detected in BM CD138+ cell samples in 31/34 patients (91%).
  - Overall, clonal rearrangement was detected in 37/45 (82%) BM aspirates at baseline.
  - 18/32 patients (56%) who had achieved CR or completed 8 cycles of therapy had MRD as assessed in cell-free BM aspirates.
- Among 31 patients assessed by NGS and MFC, 23 samples were concordant (9 positive, 14 negative).
  - Among 8 discordant cases, all were positive by NGS and negative by MFC ($p = 0.0078$).
- Assessment by PET scan for patients who achieved CR or completed 8 cycles of therapy:
  - 19/43 (44%) had positive/partial PET scans.
  - 24/43 (56%) had negative/declined PET scans.

Korde N et al. Proc ASH 2014;Abstract 2105 (Abstract only).

MRD and PFS Estimates

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Korde N et al. Proc ASH 2014;Abstract 2105 (Abstract only).
**MM Clonotype**

- NGS was performed in peripheral blood samples collected at baseline from 14 patients.
- 13/14 patients had at least 1 MM clonotype detected in their baseline BM that was also detected in their plasma samples.
- The number of myeloma-specific molecules per million diploid genomes in the plasma was 3-log-fold lower than in the BM:
  - Median 252 vs 730,950 MM-specific clonal molecules per million diploid genomes
- After 2 cycles of treatment, 12/13 patients were still positive by serum electrophoresis and/or immunofixation.
  - Only 1 patient had detectable myeloma clonotypes in the plasma.

Korde N et al. Proc ASH 2014;Abstract 2105 (Abstract only).

**Author Conclusions**

- Detection of myeloma-specific clonotypes by NGS of the immunoglobulin VDJ segments in the BM is feasible for the majority of patients with NDMM.
- MRD detection by NGS compares favorably to detection by MFC because all patients with residual disease by MFC were MRD-positive by NGS.
  - An additional 8 patients who were MRD-negative by MFC were MRD-positive by NGS.
- MRD negativity by MFC or NGS are both associated with significantly better PFS.

Korde N et al. Proc ASH 2014;Abstract 2105 (Abstract only).
Author Conclusions (continued)

- Tumor load in the peripheral blood plasma is >2,000-fold lower than in the BM. Therefore, using standard volumes of plasma the levels of myeloma-specific clonotypes were too low to be quantified after 2 cycles of therapy.
  - This was true despite the presence of positive serum electrophoresis and/or immunofixation.
- Additional studies to understand the dynamics of the myeloma clonotype level in peripheral blood plasma are necessary in order to determine the optimal MRD testing regimen.

Korde N et al. *Proc ASH* 2014;Abstract 2105 (Abstract only).

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Investigator Commentary: MRD Assessments in NDMM

MRD testing has come to stay in MM. We now have effective therapies that are not intense, and using the established response criteria it’s apparent that in the NDMM setting the vast majority of patients reach the highest level of responses.

Studies conducted for patients who have achieved a CR by standard criteria have been able to show, by sensitive techniques such as MFC and NGS, that detectable disease is left behind in these patients. It is important to know that for patients in the CR category, detectable disease is associated with a PFS and overall survival difference. This affects patient outcome. This study suggests that NGS is a more sensitive method of detecting MRD than MFC because some patients with negative results by MFC received positive results by NGS. Peripheral blood is unfortunately not reliable for defining MRD because of the low concentrations of tumor DNA in comparison to that in the bone marrow.

We are almost at a turning point. In my practice I am starting to implement MRD testing for our patients because we are now able to administer effective therapies that take many patients into CR, and we need to see if disease is left behind. That will affect how we care for patients beyond that point.

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