Phase II Study of Carfilzomib, Cyclophosphamide and Dexamethasone for Newly Diagnosed Multiple Myeloma
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

- Consider the benefits and risks of the investigational agent MLN9708 for patients with previously untreated multiple myeloma.
- Evaluate the efficacy and safety of carfilzomib with or without immunomodulatory drugs for newly diagnosed or relapsed/refractory multiple myeloma.
- Assess emerging clinical trial data on the novel combination of bendamustine, bortezomib and dexamethasone in relapsed/refractory multiple myeloma.
- Determine the maximum tolerated dose of pomalidomide in combination with bortezomib and low-dose dexamethasone for relapsed or relapsed/refractory multiple myeloma.
- Compare and contrast the effects of bortezomib/melphalan/prednisone/thalidomide followed by maintenance bortezomib/thalidomide to those of bortezomib/melphalan/prednisone on the overall survival of patients with relapsed/refractory multiple myeloma.

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Kenneth C Anderson, MD
Kraft Family Professor of Medicine
Harvard Medical School
Director, Jerome Lipper Multiple Myeloma Center
Director, LeBow Institute for Myeloma Therapeutics
Dana-Farber Cancer Institute
Boston, Massachusetts

Advisory Committee: Bristol-Myers Squibb Company, Celgene Corporation, Gilead Sciences Inc, Onyx Pharmaceuticals Inc, Sanofi; Other Remunerated Activities: Acetylon Pharmaceuticals Inc. A Keith Stewart, MBCHB
Dean for Research, Mayo Clinic in Arizona
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Vasek and Anna Maria Polak Professorship in Cancer Research
Scottsdale, Arizona

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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: April 2013
Expiration date: April 2014

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- Compare and contrast the effects of bortezomib/melphalan/prednisone/thalidomide followed by maintenance bortezomib/thalidomide to those of bortezomib/melphalan/prednisone on the overall survival of patients with relapsed/refractory multiple myeloma.
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Last review date: April 2013
Expiration date: April 2014
New proteasome inhibitor-based combination regimens in multiple myeloma

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

Dr Ken Anderson’s memorable Karnofsky Award presentation at ASCO 2011 provided an intriguing overview of how profoundly the clinical face of multiple myeloma (MM) has changed in the postchemotherapy era, and the recent approval of 2 new agents is additional evidence of how quickly things are moving forward. In a previous issue of this series we focused on immunomodulatory drugs, including the recently (February 8) FDA-approved pomalidomide (Pom) for relapsed/refractory disease, and in this issue we look at the other key class of agents that has revolutionized the treatment of MM, proteasome inhibitors, which were the focus of Dr Anderson’s lecture and much of his clinical and laboratory research at Dana-Farber.

In retrospect, it seems intuitive to block the mechanism by which proteins are processed and excreted in cells that are noteworthy for protein overproduction — specifically immunoglobulins — but while the translational science behind these molecules is fascinating, perhaps more important is the bottom line in terms of patient impact. In a recent JCO editorial Drs Sagar Lonial and Jonathan Kaufman make a compelling argument that in stark contrast to, for example, metastatic breast cancer, where sequential single agents are used, in MM combination regimens, although not usually curative, seem to yield better long-term outcomes. As bortezomib (BTZ) is a standard part of 2 of the most commonly used pretransplant induction regimens — RVD and CyBorD — and carfilzomib is now available for general use, it is easy to see how crucial these agents have become. Even more, at ASH we saw many interesting papers looking at various new proteasome inhibitor-based combinations that may one day soon be a part of the next generation of MM care.

1. Carfilzomib (CFZ)

This first-in-class irreversible proteasome inhibitor was approved last July for relapsed/refractory disease, but even before then there was considerable interest in testing it up front. At ASH 2011 Dr Andrzej Jakubowiak presented impressive Phase I findings with “CRd” in which the proteasome inhibitor was CFZ rather than BTZ, and this year an
NCI team added to the database by reporting a Phase II trial of 15 patients. Once again this combo was found to have a profound antomyeloma effect (14 responses) with acceptable tolerability and no reported Grade ≥3 peripheral neuropathy (PN).

Similarly, Dr Antonio Palumbo presented results from a Phase II trial evaluating another CFZ combination (CFZ/cyclophosphamide/low-dose dexamethasone [dex], or CCd) as up-front therapy in 58 patients over age 65 or ineligible for transplant. Study participants received 9 cycles of CCd followed by CFZ maintenance until progression. Of note, responses were seen in all patients, including those with adverse cytogenetics, and the progression-free survival at 1 year was 88%. Again, no Grade ≥3 PN was reported.

Finally, in the relapsed/refractory setting, yet another CFZ triplet — CFZ/Pom/low-dose dex — showed encouraging activity, with 15 of 30 patients responding, including many who had received extensive prior treatment and/or had adverse cytogenetics.

2. Ixazomib

Formerly MLN9708, this boron acid-based proteasome inhibitor in clinical trial development is similar to BTZ but not only seems to cause less PN but is also orally administered, opening up the enticing possibility of an all-oral RVD-like induction regimen. At ASH we saw updated data from a Phase I/II study of ixazomib/lenalidomide/low-dose dex in 64 patients with previously untreated MM. Importantly, 92% responded and only 2 developed Grade 3 PN (3%), helping to significantly increase enthusiasm for ongoing Phase III efforts evaluating this combination versus lenalidomide/low-dose dex in previously untreated patients.

3. More on bortezomib

Bendamustine has a similar structure to alkylating agents and is thought to perhaps have synergistic activity with BTZ. For that reason, a Phase II study looked at a CyBorD-like regimen in which bendamustine was substituted for cyclophosphamide. Although significant activity was observed, including responses in 48 of 71 patients (68%), it is unclear whether this regimen will be used in US practice until further data emerge.

As usual Dr Paul Richardson was quite busy at ASH, and among his oral presentations was a Phase I study evaluating BTZ/Pom/low-dose dex in patients with relapsed/refractory MM. While data from only 15 patients were reported, the results suggest that BTZ in combination with POM is well tolerated and highly active, further justifying the ongoing Phase III clinical trial examining this strategy.
While we are all familiar with triplet regimens, many have wondered whether 4-drug combos might provide even greater benefit, and to that end, at ASH Dr Palumbo provided updated results from his Phase III study of BTZ/melphalan/prednisone/thalidomide (VMPT) with VT maintenance versus VMP alone in patients who were not transplant candidates. Previous reports showed that the quartet plus maintenance provided significantly longer disease control, and in Atlanta we came to learn that it also resulted in an overall survival advantage (HR 0.7). Of interest, patients (particularly those older than 75 years of age) in the VMPT-VT arm more commonly had to discontinue therapy or reduce the BTZ dose, suggesting that less intense therapy might be preferable, but Dr Anderson believes that subcutaneous weekly BTZ may allow more patients to be treated with this approach.

Next on this series... You’ve heard of “R squared” (lenalidomide/rituximab). How about “R squared/CHOP”? Check out our coverage of 2 major papers on this regimen in diffuse large B-cell lymphoma and other related ASH lymphoma papers.

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Miami, Florida
Phase II Study of Carfilzomib, Cyclophosphamide and Dexamethasone for Newly Diagnosed Multiple Myeloma

Presentation discussed in this issue


Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Kenneth C Anderson, MD (3/3/13)

Carfilzomib, Cyclophosphamide and Dexamethasone (CCd) for Newly Diagnosed Multiple Myeloma (MM) Patients

Palumbo A et al.
Proc ASH 2012; Abstract 730.
Background

- Carfilzomib is a novel, irreversible proteasome inhibitor that was recently FDA approved for the treatment of multiple myeloma (MM) progressing after ≥2 prior therapies.

- Even though regimens such as melphalan/prednisone/thalidomide (MPT) and bortezomib/melphalan/prednisone (VMP) are clinically effective therapies for elderly patients with MM, the toxicity profile and discontinuation rate are significantly higher than comparable regimens for younger patients (Blood 2011;118:1239; N Engl J Med 2008;359:906).

- **Study objective:** To evaluate the efficacy and safety of combination therapy with carfilzomib, cyclophosphamide and dexamethasone (CCd) patients with newly diagnosed, symptomatic MM who are ≥65 years or ineligible for autologous stem cell transplantation.

Palumbo A et al. *Proc ASH* 2012;Abstract 730.

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Phase II Trial Design

**CCd Induction**

Cycles 1-9

- **Response Assessments**

<table>
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<th>Cycle day</th>
<th>1</th>
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<th>8</th>
<th>9</th>
<th>15</th>
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Dosing

- **Cycle 1**
- **Cycle 2**
- **Cycle 3**

**C Maintenance**

Until progression

- Cyclophosphamide 300 mg/m² orally
- Dexamethasone 40 mg orally

**Primary objectives:**

- Safety: Grade 4 neutropenia (>3 d), Grade 4 thrombocytopenia (>7 d), Grade ≥3 nonhematologic toxicity
- Efficacy: Partial response (PR)

Palumbo A et al. *Proc ASH* 2012;Abstract 730.
Response Rates by Treatment Duration (n = 58)

CR = complete response; sCR = stringent CR; nCR = near CR; VGPR = very good PR

Time to Response (n = 58)

Median treatment duration, cycles (range): 5 (1-9)

With permission from Palumbo A et al. Proc ASH 2012;Abstract 730.
Subgroup Analysis of Best Response Rates

By ISS Staging (n = 58)

By Cytogenetic Risk (n = 51)

* Defined as presence of t(4;14), t(14;16) or del(17p)

With permission from Palumbo A et al. Proc ASH 2012;Abstract 730.

Progression-Free Survival (PFS) and Overall Survival (OS)

PFS

OS

With permission from Palumbo A et al. Proc ASH 2012;Abstract 730.
Adverse Events (AEs) of All Grades (n = 58)

Hematologic

Nonhematologic*

* No difference between patients younger or older than 75 years
  - Grade 3 cardiac AEs: Acute MI, atrial fibrillation; Grade 3 infections: Pneumonia and bronchitis; Grade 4 GI AEs: Ileum perforation

With permission from Palumbo A et al. Proc ASH 2012;Abstract 730.

Author Conclusions

- In comparison to other regimens, CCd showed encouraging activity in elderly patients with newly diagnosed MM.
  - ≥VGPR: CCd (77%), MPT (36%), VMP (41%)
  - nCR/CR/sCR: CCd (53%), MPT (27%), VMP (30%)
  - sCR: CCd (23%), MPT (not reported), VMP (not reported)
- The CCd combination was well tolerated.
  - Platelets: CCd (5%), MPT (3%), VMP (37%)
  - Peripheral neuropathy: CCd (0%), MPT (6%), VMP (14%)
  - Venous thromboembolism: CCd (0%), MPT (9%), VMP (1%)
  - Discontinuation: CCd (12%), MPT (35%), VMP (33%)

Investigator Commentary: CCd for Elderly Patients with Newly Diagnosed MM

For elderly patients with newly diagnosed MM, melphalan and prednisone have been combined with novel therapies like lenalidomide or bortezomib. These combinations have prolonged PFS and OS compared to melphalan/prednisone alone in randomized trials. Palumbo and colleagues similarly combined carfilzomib, a novel proteasome inhibitor, with cyclophosphamide and dexamethasone, followed by carfilzomib maintenance. The response rate increased to ≥PR of 100%, ≥VGPR of 77% and CR/sCR/nCR of 53% with sCR of 23% after 9 cycles of therapy. Although the follow-up period was short, 1-year PFS and OS were 88% and 87%, respectively. These data suggest that, like bortezomib, the incorporation of carfilzomib into the initial treatment of elderly patients with newly diagnosed MM can achieve high rates and extent of response, with a favorable side-effect profile. Also, it was possible to escalate the carfilzomib dose to 36 mg/m² while maintaining a favorable therapeutic index. It is exciting that the CCd regimen was effective even in patients with high-risk cytogenetics, although follow-up was short and early relapses may still occur. This study suggests that carfilzomib in combination with melphalan/prednisone may have utility as first-line therapy for elderly patients with MM and warrants further testing. This is one of the first studies to examine the efficacy and tolerability of carfilzomib maintenance in this setting.

Interview with Kenneth C Anderson, MD, March 3, 2013