5 Minute JournalClub

POST-ASH Issue 5, 2013

Treatment of Relapsed/Refractory Multiple Myeloma with Bendamustine, Bortezomib and Dexamethasone

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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

- 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
Consultant, Division of Hematology/Oncology
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

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POST-ASH Issue 5, 2013

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 antimyeloma 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.

Neil Love, MD
Research To Practice
Miami, Florida

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Treatment of Relapsed/Refractory Multiple Myeloma with Bendamustine, Bortezomib and Dexamethasone

Presentation discussed in this issue

Ludwig H et al. **Treatment with bendamustine-bortezomib-dexamethasone in relapsed/refractory multiple myeloma shows significant activity and is well tolerated.** *Proc ASH* 2012;**Abstract 943**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Kenneth C Anderson, MD (3/29/13)

Background

- The clinical activity of bendamustine (BEN) as a single agent and in combination therapy, coupled with its potential lack of cross-resistance with several other agents, make it an attractive therapy for newly diagnosed and refractory hematologic malignancies.
- Its structural and mechanistic features differentiate it from other alkylating agents, providing increased stability and potency in DNA crosslinking and subsequent cytotoxicity.
- Several studies have suggested that bendamustine may exert synergistic activity when combined with bortezomib (BTZ) (*Proc ASH* 2007;Abstract 4851; *Proc ASCO* 2012;Abstract 8014).
- **Study objective:** To evaluate the efficacy and safety of BEN in combination with BTZ and dexamethasone (Dex) for patients with relapsed or refractory multiple myeloma (MM).

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

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Phase II Trial Design

Eligibility (n = 79)
Relapsed/refractory MM after ASCT or standard chemotherapy
From 1 to 6 prior therapy lines
Platelets: ≥100 x 10^9/L
No BEN/BTZ within previous 6 months

→

BEN + BTZ + Dex (n = 79)

BEN: 70 mg/m^2 (IV), d1, 4

BTZ: 1.3 mg/m^2 (IV), d1, 4, 8, 11

Dex: 20 mg, d1, 4, 8, 11

q4wk for up to 8 cycles

ASCT = autologous stem cell transplant

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

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

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Response Rates

Response	n = 71*
ORR	67.6%
sCR/CR/nCR	21.2%
Very good partial response (VGPR)	15.5%
Partial response (PR)	31.0%
Minimal response (MR)	16.9%
Stable disease (SD)	15.5%

CR = complete response; sCR = stringent CR; nCR = near complete response
* Eight patients who completed <2 treatment cycles were excluded from analysis.

- Of patients previously exposed to BTZ or lenalidomide (Len) and completing ≥2 cycles,
  - Those who experienced CR to PR: 28/45 (BTZ); 23/39 (Len)
  - Those who experienced CR to MR: 37/45 (BTZ); 30/39 (Len)

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

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Survival Outcomes

Intent-to-treat population	n = 79	
Median PFS	9.7 months	
Median OS	Not yet reached (NYR)	
Two-year OS	60%	
By prior lines of therapy	**1 to 2 (n = 46)**	**3 to 6 (n = 25)**
Median PFS*	12 months	7.8 months
Median OS†	NYR	20.6 months

* $p = 0.069$; † $p = 0.007$

- Median follow-up period was 13.7 months.
- No significant difference in median PFS and OS was observed when analysis was based on the time from the start of first treatment line (≤46 vs >46 months).

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

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PFS and OS According to Prior Exposure to BTZ and/or Len

Outcome	No BTZ	BTZ	*p*-value
Median PFS	12 months	7.8 months	0.187
Median OS	NYR	NYR	0.800
	No Len	**Len**	***p*-value**
Median PFS	12.8 months	8 months	0.009
Median OS	NYR	20.6 months	0.006
	No BTZ or Len	**BTZ and Len**	***p*-value**
Median PFS	12.8 months	7 months	0.001
Median OS	NYR	20.6 months	0.034

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

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PFS and OS According to Cytogenetic Risk

Outcome	Cytogenetic risk		*p*-value
	Standard	High	
Median PFS	9.7 months	9.4 months	0.662
Median OS	NYR	20.6 months	0.12

- Multivariate analysis of prognostic parameters demonstrated a significant difference in PFS when analyzed according to age (<65 versus ≥65 years), $p = 0.011$.

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

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Select Adverse Events (AEs)

AE (n = 79)	Grade 1 or 2	Grade 3	Grade 4
Anemia	—	15%	3%
Leucopenia	—	16%	1%
Thrombocytopenia	—	32%	6%
Polyneuropathy	49%	5%	1%
Infection/sepsis	43%	16%	4%
Insomnia/fatigue	40%	3%	—
Nausea/emesis	33%	1%	—
Diarrhea	22%	8%	—

- Grade 5 infection/sepsis (n = 2); Grade 4 exanthema (n = 1)
- Peripheral neuropathy (PN) increased over time from cycle 2 to 8; Grade 3 or 4 PN was highest at the end of cycle 8, observed by investigators in <10% of pts.

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

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Author Conclusions

- This study demonstrated an ORR of 67.6% and a sCR/CR of 21.2% in the evaluable patient population.
  - The rate of sCR/CR and VGPR was significantly lower for patients previously exposed to 3 or more lines of therapy (data not shown).
- In the intent-to-treat population, the median PFS was 9.7 months and the median OS has not yet been reached.
  - No significant difference was observed in PFS and OS between patients with and without high-risk cytogenetics.
  - PFS and OS were significantly shorter with BTZ and/or Len pretreatment.
- PN increased over time, and patient self-rated symptoms were significantly higher than investigator ratings.
- The BEN/BTZ/Dex treatment regimen was well tolerated.
- This regimen is a valuable choice for second- and further-line therapy.

Ludwig H et al. *Proc ASH* 2012;Abstract 943.

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Investigator Commentary: Phase II Study of Bendamustine in Combination with Bortezomib and Dexamethasone for Relapsed or Refractory MM

Ludwig and colleagues evaluated bendamustine 70 mg/m^2 on days 1 and 4, bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11 and dexamethasone 20 mg on days 1, 4, 8 and 11 every 4 weeks for a planned 8 cycles in 79 patients with relapsed or refractory MM. For 71 evaluable patients the overall response rate was approximately 67%, with 21% sCR/CR/nCR, 15.5% VGPR, 31% PR, 16.9% MR and 15.5% SD. Responses were seen in patients with heavily pretreated MM and those with adverse cytogenetics. The overall median PFS was 9.7 months. Previous exposure to lenalidomide was associated with a lower response rate and shorter time to disease progression.

This study demonstrated that the bendamustine/bortezomib/dexamethasone regimen is active in relapsed or refractory MM. Although this combination is active in patients with heavily pretreated MM, its side-effect profile may limit its repeated or chronic use. Moreover, 2 other novel agents, carfilzomib and pomalidomide, are active and are now FDA approved for the treatment of this patient population.

Interview with Kenneth C Anderson, MD, March 29, 2013