5 Minute JournalClub

Key ASH Presentations
Issue 1, 2011

Carfilzomib/Lenalidomide/ Dexamethasone (CRd) as Initial Therapy for Patients with Newly Diagnosed Multiple Myeloma (MM)

For more visit ResearchToPractice.com/5MJCASH2011

Research To Practice®

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 from a plethora of ongoing clinical trials 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 and other cancer clinicians in the formulation of optimal clinical management strategies for hematologic cancer.

LEARNING OBJECTIVE

- Counsel patients with MM who are being considered for proteasome inhibitor-based therapy about the safety and efficacy of carfilzomib-based therapy and the possibility of participation in ongoing clinical trials with this novel agent.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentation, read the commentary and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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:

Rafael Fonseca, MD
Consultant, Professor of Medicine
Mayo Clinic Arizona
Deputy Director, Mayo Clinic Cancer Center
Scottsdale, Arizona

Consulting Agreements: Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genzyme Corporation, Medtronic Inc, Otsuka Pharmaceutical Co Ltd; Paid Research: Celgene Corporation, Onyx Pharmaceuticals Inc.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Allos Therapeutics, Amgen Inc, AstraZeneca Pharmaceuticals LP, Aureon Laboratories Inc, Bayer HealthCare Pharmaceuticals/ Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Lilly USA LLC, Millennium Pharmaceuticals Inc, Myriad Genetics Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Sanofi-Aventis and Seattle Genetics.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This program is supported by educational grants from Allos Therapeutics, Celgene Corporation, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc and Seattle Genetics.

Last review date: January 2011
Expiration date: January 2012

5 MinuteJournalClub

Key ASH Presentations
Issue 1, 2011

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

One can make the argument that the past few years have seen more important new agents, regimens and trial reports in multiple myeloma than any other corner of oncology, including breast cancer. At last month's ASH meeting in Orlando, we once again saw a staggering array of presentations and posters that both shed light on and add complexity to the management of this fascinating disease. In this, the first of nine brief ASH "highlight reels," we capsulize a number of key papers related to up-front treatment of multiple myeloma:

1. **The new "RVD"?**
Three years after Paul Richardson's landmark presentation of unprecedented outcomes for induction with lenalidomide, bortezomib and dexamethasone (RVD), Andrzej Jakubowiak wowed the masses in Orlando with results of a Phase I/II study of the irreversible proteasome inhibitor carfilzomib in combination with len and dex. These early efficacy data look a lot like what had been previously seen with RVD (100 percent response rate, 63 percent ≥VGPR) but with essentially no peripheral neuropathy. Stay tuned.

2. **Lenalidomide maintenance continues to impress.**
In an important trend related to the benefits of more prolonged treatment, further follow-up of the IFM trial first presented at ASCO continues to demonstrate an important advantage to maintenance len after transplant. A related paper by Antonio Palumbo — in the nontransplant setting — in which len maintenance was used after induction with melphalan/lenalidomide/prednisone also showed favorable results.

3. **Longer-term bortezomib in the up-front setting appears safe and effective in older patients.**
The UPFRONT trial showed impressive efficacy and acceptable neurotoxicity when weekly maintenance bortezomib was utilized after bortezomib-based initial induction regimens. Another paper by Palumbo also reported high response rates with bortezomib/melphalan/prednisone/thalidomide (VMPT) followed by weekly maintenance bortezomib/thalidomide (VT). As has been previously reported, neurotoxicity was reduced significantly when weekly as opposed to biweekly bortezomib was utilized.

4. **More data support low-dose dex with lenalidomide induction (Rd).**
A new analysis from the landmark ECOG trial clearly demonstrates that even in younger patients, lower-dose dex results in better outcomes.

Finally, we can happily report that the increasingly complex treatment algorithms for myeloma are being successfully implemented in daily practice. A **cross-sectional case survey of patients treated in a community setting in the last two years** reported as a poster by our CME group at the ASH meeting demonstrates consistently high response rates with modest toxicities in patients older and younger than age 75.

This Friday we will welcome eight noted clinical researchers to our recording studio in Miami for our third annual NHL/CLL Think Tank, and for the next issue of this series we'll provide you with their thoughts on ASH, including perspectives on the long-awaited findings from the Intergroup trial comparing rituximab monotherapy to "watch and wait."

Neil Love, MD
Research To Practice
Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates each of the four educational activities, comprised of a slide set, for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

Carfilzomib/Lenalidomide/Dexamethasone (CRd) as Initial Therapy for Patients with Newly Diagnosed Multiple Myeloma (MM)

Presentation discussed in this issue

Jakubowiak AJ et al. **Carfilzomib, lenalidomide, and dexamethasone in newly diagnosed multiple myeloma: Initial results of Phase I/II MMRC trial.** *Proc ASH* 2010;**Abstract 862**.

Slides from a presentation at ASH 2010 and transcribed comments from a recent interview with Rafael Fonseca, MD (12/22/10)

Introduction

- Carfilzomib (Cfz) is a novel, irreversible proteasome inhibitor that has demonstrated promising single-agent activity and a favorable toxicity profile, including very low rates of peripheral neuropathy and neutropenia in relapsed/refractory multiple myeloma (MM) (*Proc ASH* 2010;Abstract 1938).
- Additive anti-MM effects have been reported with carfilzomib in combination with lenalidomide and dexamethasone (CRd) in preclinical studies.
  - Lack of overlapping toxicity allows for the use of these agents at full doses and for extended duration of time in relapsed/refractory MM (*Proc ASH* 2009;Abstract 304).
- **Current Study Goals:** To determine the maximum tolerated dose (MTD) of CRd and to assess safety and evaluate efficacy of this combination in newly diagnosed MM.

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Research To Practice®

Methods

- **Phase I Carfilzomib Dose Escalation Trial**
- Carfilzomib (C) as only dose-escalating agent (IV on days 1, 2, 8, 9, 15, 16 in 28-day cycles)
  - Level 1: 20 mg/m^2
  - Level 2: 27 mg/m^2 (initial maximal planned dose)
  - Level -1: 15 mg/m^2 (if needed)
  - Level 3: 36 mg/m^2 (study amendment inclusion after toxicity assessment
- Lenalidomide (Len, R) administered at 25 mg PO (days 1-21) for all dose levels
- Dexamethasone (Dex, d) administered at 40/20 mg PO weekly (cycles 1-4/5-8) for all dose levels

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Research To Practice®

Methods (continued)

- **Phase I/II (Target Accrual = 36)**
- Patients achieving ≥ partial response (PR) proceed to stem cell collection (SCC) and autologous stem cell transplant (ASCT) after ≥ 4 cycles.
  - ASCT candidates offered continued CRd treatment after SCC
- After completion of 8 cycles, patients receive 28-day maintenance cycles
  - C (days 1, 2, 15, 16), R days 1-21, and d weekly at the doses tolerated at the end of 8 cycles
- 24 patients have been enrolled to date:
  - Level 1 (C, 20 mg/m^2) – 4 patients
  - Level 2 (C, 27 mg/m^2) – 14 patients
  - Level 3 (C, 36 mg/m^2) – 6 patients

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Research To Practice®

Response Rates by IMWG*

Clinical Response	CRd (n = 19)
≥Partial response (PR)	100%
≥Very good partial response	63%
Complete response (CR)/near CR	37%

* Response in evaluable patients (pts) who completed at least 1 cycle after a median of 4 (range 1-8) months of treatment

- Responses were rapid with 17 pts achieving PR after 1 cycle and improving responses with continuing therapy in all pts.
- 7 pts proceeded to SCC after a median of 4 cycles of CRd (range 4-8); all resumed CRd treatment after SCC.
- After a median of 4 months of follow-up, all evaluable pts are alive without disease progression.

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Research To Practice®

Adverse Events (AE)

Hematologic	CRd (n = 21)
Neutropenia (Grade 3 or 4)	14%
Thrombocytopenia (Grade 3 or 4)	14%
Anemia (Grade 3)	10%
Nonhematologic (Grade 3)	
Peripheral neuropathy (PN) (Grade 3 or 4)*	0%
Fatigue	5%
Mood alteration†	5%
Glucose elevations†	24%
Deep vein thrombosis (while receiving aspirin prophylaxis)	5%

* Only 2 cases of Grade 1 PN were reported, even after prolonged treatment
† AE related to dexamethasone administration

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Conclusions

- Carfilzomib plus lenalidomide/dexamethasone (CRd) is well tolerated and highly active in newly diagnosed MM.
  - ≥PR = 100%
  - ≥VGPR = 63%
  - CR/nCR = 37%
- These data represent the first report to date of treatment of front-line myeloma with carfilzomib and add support to the Phase III trial of CRd versus Rd in relapsed MM (NCT01080391).

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Research To Practice®

Investigator comment on the Phase I/II trial of carfilzomib, lenalidomide and dexamethasone in newly diagnosed multiple myeloma

This study is addressing the role of carfilzomib as an alternative to bortezomib as induction therapy for myeloma. Carfilzomib has activity in myeloma and has lesser neuropathic potential than bortezomib, and the combination presented in this paper is similar to the lenalidomide, bortezomib and dexamethasone (RVD) regimen, previously reported by Dr Richardson.

This study was received with great enthusiasm, as the response rate was essentially 100 percent with many complete responses and VGPRs. The regimen will have to be tested in larger Phase II/III trials. Examining these results, it does appear that carfilzomib, in combination with other agents, has enough antitumor activity to make it a serious contender against any regimen that is based on proteasome inhibition, and it appears to be safe for patients.

Interview with Rafael Fonseca, MD, December 22, 2010

Research
To Practice®