5 Minute JournalClub

Key ASCO Presentations
Issue 4, 2010

Novel Three-Drug Combinations of Bortezomib, Thalidomide, Dexamethasone and Lenalidomide for Newly Diagnosed Multiple Myeloma (MM)

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and 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 patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Apply the results of new clinical research with lenalidomide/bortezomib/dexamethasone (RVD) and reduced-dose bortezomib/thalidomide/dexamethasone (vTD) to the care of patients with MM.

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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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Key ASCO Presentations
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To go directly to the slides and commentary, **click here**.

Chatting with myeloma investigators nowadays often yields extensive recounting of seemingly limitless clinical trials featuring weird acronyms and incredibly complicated results. What is also eminently apparent from these conversations is just how remarkably the face of this disease has changed with the recent introduction of two major classes of novel agents, the IMiDs® — thalidomide and lenalidomide — and the proteasome inhibitors, specifically bortezomib.

The dozens of cool papers presented at the recent ASCO meeting further affirmed the profound effects of these agents when used individually, in combination or in sequence, and here are our top picks for findings relevant to oncology practice:

1. **Triple therapy continues to impress**
   In a follow-up to a recently published paper in *Blood*, Dana-Farber's Paul Richardson once again wowed the masses as he presented unprecedented efficacy findings (100 percent response rate, 74 percent with VGPR or more) and acceptable toxicity with induction RVD (lenalidomide, bortezomib, dexamethasone). A new, huge trial will address post-transplant consolidation with this combination and also whether transplant can be delayed or avoided. In any event, our surveys of practicing oncologists and investigators show a rapid shift toward three-drug combos like RVD for patients eligible for transplant. In another impressive data set on a triple regimen, French investigators reported similar high response rates to vTD (bortezomib, thalidomide, dexamethasone), which utilized attenuated doses of both bortezomib and thalidomide that dramatically lowered the rate of peripheral neuropathy.

2. **Lenalidomide maintenance after autologous stem cell transplant is effective**
   No question this was one of the most important findings presented in any tumor type at ASCO as both the **CALGB and the French IFM** group demonstrated an impressive 50 percent reduction in disease progression among patients receiving this well-tolerated agent as maintenance therapy following transplant. Many clinical trials in both the transplant and nontransplant settings are now scrambling to add "L maintenance" to their control arms.

3. **Zoledronic acid (ZDA) may slow disease progression and extend survival**
   This MRC trial from the UK is in a sense the myeloma version of the Austrian breast cancer study presented during the ASCO plenary session two years ago. Monthly ZDA resulted in an impressive five months-plus improvement in survival compared to clodronate. Investigators are not yet jumping on the idea of treating patients without bone disease, but this might be coming in the future.

Next up on 5-Minute Journal Club: A smorgasbord of ASCO papers on breast cancer, including some interesting new data on sentinel node biopsy.

Neil Love, MD
Research To Practice
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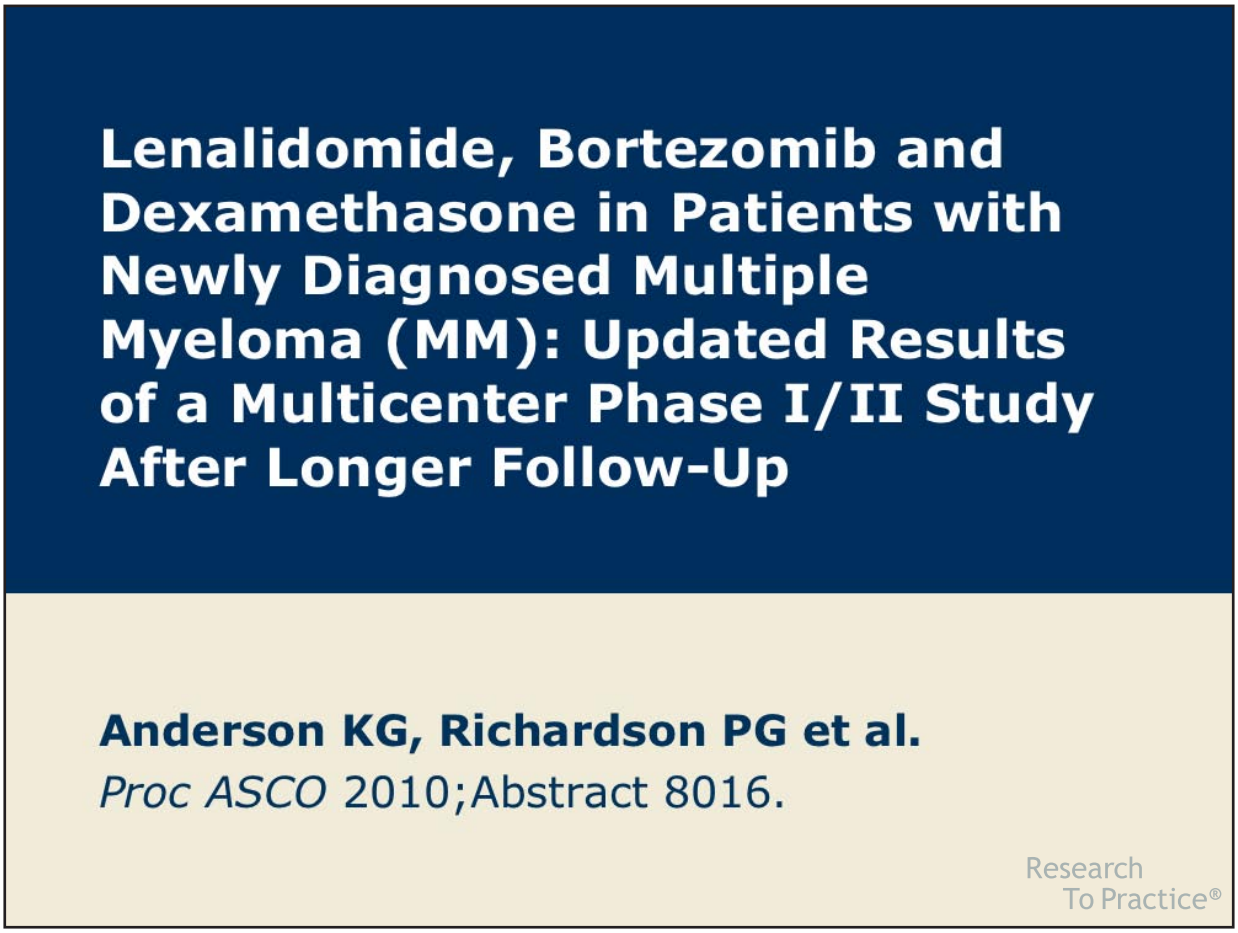
Novel Three-Drug Combinations of Bortezomib, Thalidomide, Dexamethasone and Lenalidomide for Newly Diagnosed Multiple Myeloma (MM)

Presentations discussed in this issue

Moreau P et al. **Reduced-dose bortezomib plus thalidomide plus dexamethasone (vTD) is superior to bortezomib plus dexamethasone (VD) as induction treatment prior to autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (MM): Results of IFM2007-02 prospective randomized study.** *Proc ASCO* 2010;**Abstract 8014**.

Anderson KG et al. **Lenalidomide, bortezomib and dexamethasone in patients with newly diagnosed multiple myeloma (MM): Updated results of a multicenter Phase I/II study after longer follow-up.** *Proc ASCO* 2010;**Abstract 8016**.

Slides from presentations at ASCO 2010 and transcribed comments from recent interviews with Robert Z Orlowski, MD, PhD (6/18/10) and Ravi Vij, MD (7/1/10)



Introduction

- Combinations of bortezomib (V) or lenalidomide (R) with dexamethasone (D) are highly active as front-line therapy for multiple myeloma (MM)
  - RD (*Lancet Oncol* 2010;11:29, ASCO 2008;Abstract 8521)
  - VD (*Haematologica* 2006;91:1498, ASCO 2008;Abstract 8505)
- Preclinical data suggest synergy between V and R
  - Different but overlapping mechanisms of anti-MM activity
  - Activity of D enhanced by R and V
- RVD had demonstrated excellent activity in relapsed/refractory MM
  - 69% response rate (≥PR), including 26% CR/nCR
- Preliminary results of front-line RVD indicate that it is the first regimen of its kind to result in 100% response rate (*Blood* 2010;[Epub ahead of print])
- **Current study objective:**
  - Provide updated data of front-line RVD in patients with newly diagnosed MM after a median follow-up > 27 months

Anderson KG, Richardson PG et al. *Proc ASCO* 2010;Abstract 8016.

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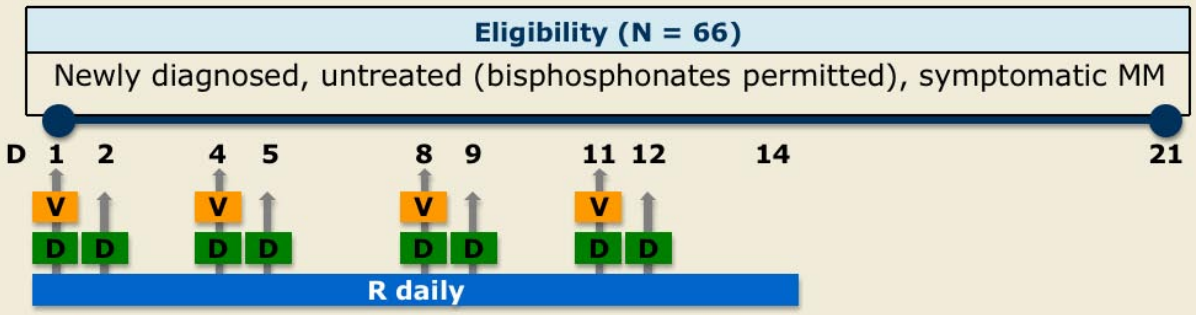
Study Design



- Up to 8 3-wk cycles at five dose levels (1-4, 4M)
- Pts with ≥PR could proceed to ASCT after ≥4 cycles
- After 8 cycles, responding pts could receive maintenance
  - 3-week cycles of R (d 1-14), and weekly V (d 1, 8), at doses tolerated at end of cycle 8, plus D 10 mg (d 1, 2, 8, 9)
- Concomitant therapy:
  - Antithrombotic therapy with daily aspirin (81 mg or 325 mg)
  - Antiviral therapy as prophylaxis against herpes zoster
  - Vitamin supplements/amino acids/emollient creams for peripheral neuropathy
  - Bisphosphonates

Anderson KG, Richardson PG et al. *Proc ASCO* 2010;Abstract 8016.

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Patient Accrual

Dose level	V dose, mg/m^2	R dose, mg	D dose, mg (cycle 1-4/5-8)	N enrolled/ treated
Phase I dose-escalation				22/21
Dose level 1	1.0	15	40/20	3/3
Dose level 2	1.3	15	40/20	3/3
Dose level 3	1.3	20	40/20	4/3
Dose level 4	1.3	25	40/20	6/6
Dose level 4M-MPD*	1.3	25	20/10	6/6
Phase I expanded cohort				11/10
Dose level 4M	1.3	25	20/10	11/10
Phase II				35/35
Dose level 4M	1.3	25	20/10	35/35

* An additional dose level 4M with reduced D dosing was included to address dose-limiting toxicity associated with higher doses of D.

Anderson KG, Richardson PG et al. *Proc ASCO* 2010;Abstract 8016.

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Best Response to RVD

Response	All patients (N = 66)	Phase II (N = 35)
Complete response (CR)	29%	37%
Near CR	11%	20%
Very good partial response (VGPR)	27%	17%
Partial response (PR)	33%	26%
CR + nCR	39%	57%
CR + nCR + VGPR	67%	74%
At least PR	**100%**	**100%**

- Response improvement seen in 42/56 patients (75%) from C4-8 and 20/38 patients (53%) beyond C8
- Median time to best overall response: 2.1 months (range: 0.6-20)

Anderson KG, Richardson PG et al. *Proc ASCO* 2010;Abstract 8016.

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Updated Outcomes

- Median follow-up: 27.3 months (range: 5.6-41.2)
- 44 patients alive and without disease progression
  - 1 patient with significant coronary artery disease died of cardiac ischemia
  - 21 patients experienced disease progression, of whom 3 died
- Patients were not censored at the time of ASCT in time-to-event analyses
  - Duration of reponse (DOR), progression-free survival (PFS) and overall survival (OS) are for RVD ± ASCT
- Median DOR not reached
  - 67% of patient are in response for > 24 months
- Median PFS and OS not reached
  - Estimated 24-month PFS: 68% (95% CI: 55, 78)
  - Estimated 24-month OS: 95% (95% CI: 86, 98)

Anderson KG, Richardson PG et al. *Proc ASCO* 2010;Abstract 8016.

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Conclusions

- RVD is highly effective for previously untreated MM
  - First regimen to result in a 100% response rate (≥PR) without ASCT
  - Remarkably high rates of CR/nCR and ≥VGPR
- Outcomes data with RVD ± ASCT are promising
  - Estimated 24-month PFS: 68%
  - Estimated 24-month OS: 95%
- Very good tolerability over a lengthy treatment period (data not shown)
  - Manageable toxicities
  - Grade 3 sensory peripheral neuropathy: 2%
  - Deep vein thrombosis: 6%
  - No treatment-related mortality

Anderson KG, Richardson PG et al. *Proc ASCO* 2010;Abstract 8016.

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Investigator comment on RVD therapy for patients with newly diagnosed myeloma

With this regimen, the rate of very good partial response or better was 74 percent, and 57 percent of patients had complete or near-complete responses. These are better rates than were seen, for example, in the study of VTD induction followed by stem cell transplant. So with RVD, you now are achieving similar response rates without the need for stem cell transplant.

Some issues arose with RVD and stem cell harvesting and, more importantly, with engraftment. Typically these issues would not be clinically relevant, but they should be considered in cases in which there is concern that there may be some difficulty collecting stem cells.

Progression-free survival in this study has been quite good, and data on the impact of cytogenetic abnormalities suggest that even in patients with high-risk features, the RVD combination is effective. For patients who are transplant eligible, we've been predominantly using this regimen. Many people feel that RVD is now the standard regimen, and many places, including the MD Anderson Cancer Center, are building on RVD by adding drugs.

Interview with Robert Z Orlowski, MD, PhD, June 18, 2010

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Investigator comment on RVD therapy for patients with newly diagnosed myeloma

The RVD regimen is now becoming one standard against which other regimens are being compared. Trials are in progress, also adding a fourth agent to the combination to learn whether we can ultimately achieve a CHOP or an R-CHOP for myeloma that would potentially lead to some cures. RVD is moving into the transplant arena in trials, both as induction therapy and as consolidation.

So the fact is that while you cannot be faulted right now, in the absence of survival data, for using a two-drug combination, more and more people are adopting three-drug regimens because the majority of the data in the front-line setting, especially with transplant-eligible patients, suggest that patients who have complete responses have better overall survival. So we can either wait several years for the data to emerge, or we can make the change now and hope that we are doing good for our patients.

Interview with Ravi Vij, MD, July 1, 2010

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Reduced-Dose Bortezomib plus Thalidomide plus Dexamethasone (vTD) is Superior to Bortezomib plus Dexamethasone (VD) as Induction Treatment Prior to Autologous Stem Cell Transplantation (ASCT) in Newly Diagnosed Multiple Myeloma (MM): Results of IFM2007-02 Prospective Randomized Study

Moreau P et al.

Proc ASCO 2010;Abstract 8014.

Introduction

- VD is superior to vincristine/doxorubicin/dexamethasone (VAD) for patients with newly diagnosed MM.
  - Improved progression-free survival and response rates[1] ([1] *Proc ASH* 2009;Abstract 353)
- VTD (bortezomib/thalidomide/dexamethasone) is superior to TD in patients with newly diagnosed MM.
  - Superior progression-free survival and response rates[2] ([2] *Proc ASH* 2009;Abstract 351)
- VD and VTD are associated with significant toxicity:
  - Grade 3/4 neuropathy rates
    - 7% in VD arm[1]; 9% in VTD arm[2]
- **Current study objective:**
  - Compare response and safety with vTD versus VD prior to and following ASCT in patients with newly diagnosed MM.

Moreau P et al. *Proc ASCO* 2010;Abstract 8014.

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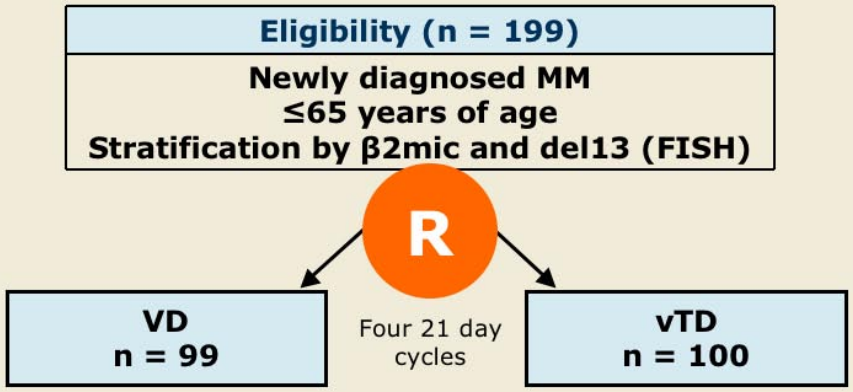
IFM 2007-02 Study Design



V, 1.3 mg/m² d1, 4, 8, 11
D, 40 mg d1-4, 9-12 for cycles 1 and 2
d1-4 for cycles 3 and 4

v, 1.0 mg/m² d1, 4, 8, 11*
T, 100 mg/d*
D, 40 mg d1-4, 9-12 for cycles 1 and 2
d1-4 for cycles 3 and 4

* Doses increased to 1.3 mg/m² (v) and 200 mg/d (T) if response < PR after 2 cycles

Moreau P et al. *Proc ASCO* 2010;Abstract 8014.

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Response Status at Cycles 2 and 4: Intent-to-Treat

Response after 2 cycles	vTD n = 100	VD n = 99	*p*-value
≥Partial response (PR)	**90%**	**78%**	**0.008**
≥Very good PR (VGPR)	22%	20%	0.77
Complete response (CR) + near CR	15%	16%	0.95
CR	4%	6%	0.71
Response after 4 cycles	**vTD**	**VD**	***p*-value**
≥PR	90%	81%	0.079
≥VGPR	**51%**	**35%**	**0.037**
CR + nCR	32%	22%	0.104
CR	13%	12%	0.74

Moreau P et al. *Proc ASCO* 2010;Abstract 8014.

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Response Status After ASCT: Intent-to-Treat

	vTD n = 100	VD n = 99	*p*-value
≥Partial response (PR)	90%	84%	0.23
≥Very good PR (VGPR)	**73%**	**59%**	**0.037**
Complete response (CR) + near CR	61%	54%	0.35
CR	30%	33%	0.65

Moreau P et al. *Proc ASCO* 2010;Abstract 8014.

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Peripheral Neuropathy

	vTD	VD	*p*-value
All grades	55%	63%	0.24
Grade ≥2	15%	28%	0.03
Grade ≥3	3%	6%	0.34
Serious adverse event leading to treatment discontinuation	0%	4%	0.12

Moreau P et al. *Proc ASCO* 2010;Abstract 8014.

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Conclusions

- Response rates significantly improved with vTD in comparison to VD
  - Primary objective: CR rate after induction is similar
  - CR/VGPR rate superior both after induction and after ASCT
- Decreasing the doses of bortezomib and thalidomide does not impair efficacy.
- The addition of cyclophosphamide to GCSF is required for stem cell harvest on the vTD combination (data not shown).
- Incidence of Grade III/IV adverse events was low (data not shown).
- Incidence of Grade II/III peripheral neuropathy was significantly reduced with the vTD combination.
- vTD combination is superior to VD with a good efficacy/toxicity ratio.

Moreau P et al. *Proc ASCO* 2010;Abstract 8014.

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Investigator comment on the results of the IFM2007-02 study

After four cycles, a trend was apparent toward a better complete plus near complete response rate with vTD. There was also an improvement in the rate of very good partial response or better after vTD compared to VD, with a *p*-value that reached statistical significance.

People who received vTD induction did on average need more sessions of apheresis to collect stem cells. They also on average had a higher risk of needing the addition of cyclophosphamide to GCSF to mobilize enough stem cells, and fewer CD34-positive stem cells were collected in this group. So that may be a concern, especially for patients who may have some baseline difficulty with stem cell collection.

Importantly, even though vTD combines two drugs that can induce neuropathy — bortezomib and thalidomide — its use resulted in a trend toward less neuropathy because of the lower doses of bortezomib and thalidomide, supporting the concept that using bortezomib at a reduced dose twice weekly can result in less neuropathy.

Interview with Robert Z Orlowski, MD, PhD, June 18, 2010

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Investigator comment on ameliorating bortezomib-associated neurotoxicity

The amelioration of bortezomib neurotoxicity is something people are pursuing with various strategies. In this IFM study by Moreau, the bortezomib neurotoxicity was ameliorated by dose reduction. In a recent Italian trial, once-weekly bortezomib led to similar outcomes as a twice-weekly schedule with less neurotoxicity. Both the Italian and the current important French trial have reduced the toxicity of bortezomib, either by less frequent administration or by dose reduction, respectively, without compromising efficacy outcomes.

Interview with Ravi Vij, MD, July 1, 2010

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