5 Minute JournalClub

Key ASH Presentations

Issue 1, 2011

Lenalidomide with Low- or High-Dose Dexamethasone for Patients with Newly Diagnosed Multiple Myeloma (MM)

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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 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

- In patients for whom up-front lenalidomide/dexamethasone is being considered, use a lower dose of dexamethasone, which has equivalent efficacy but improved safety compared to higher-dose dexamethasone, regardless of patient age.

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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
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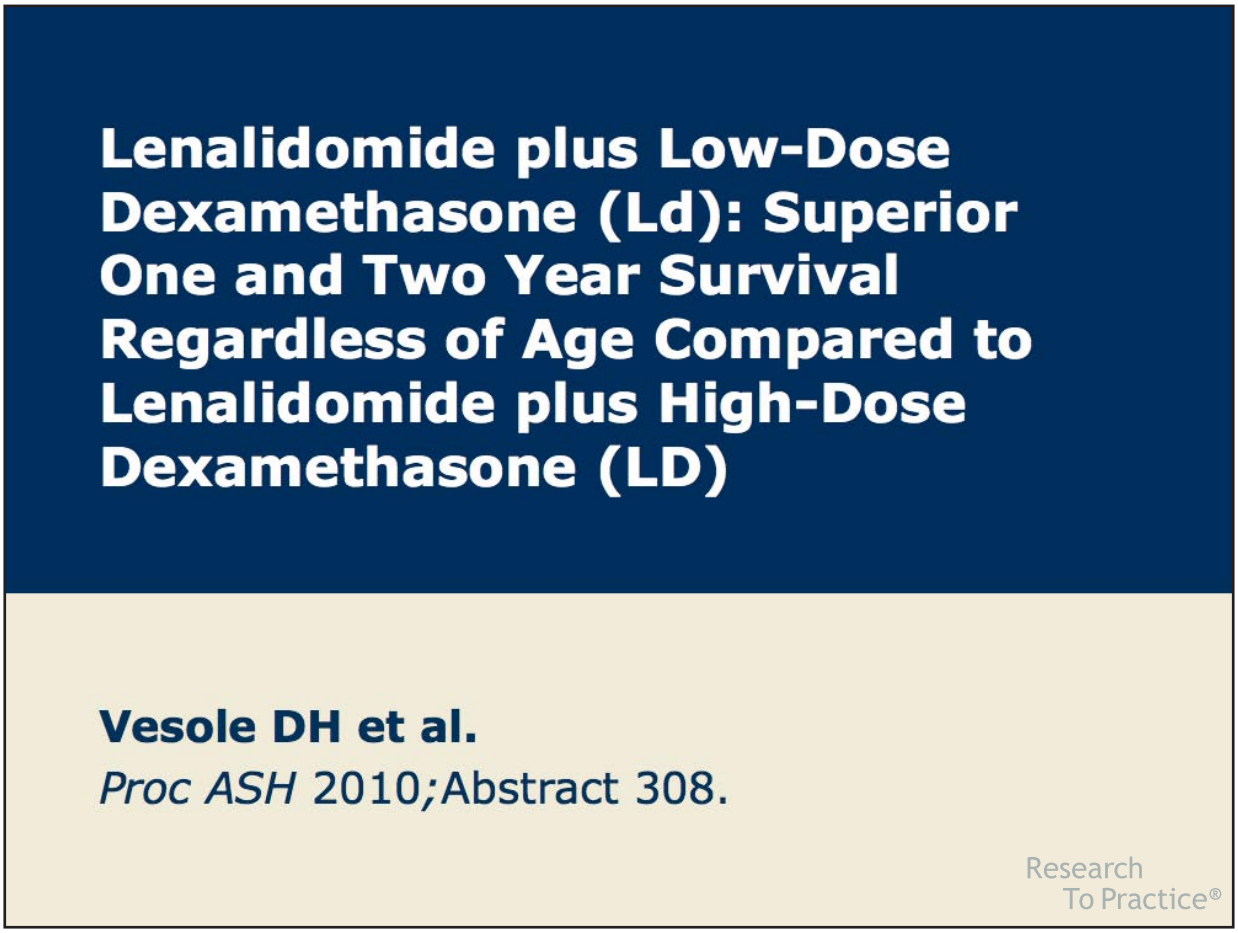
Lenalidomide with Low- or High-Dose Dexamethasone for Patients with Newly Diagnosed Multiple Myeloma (MM)

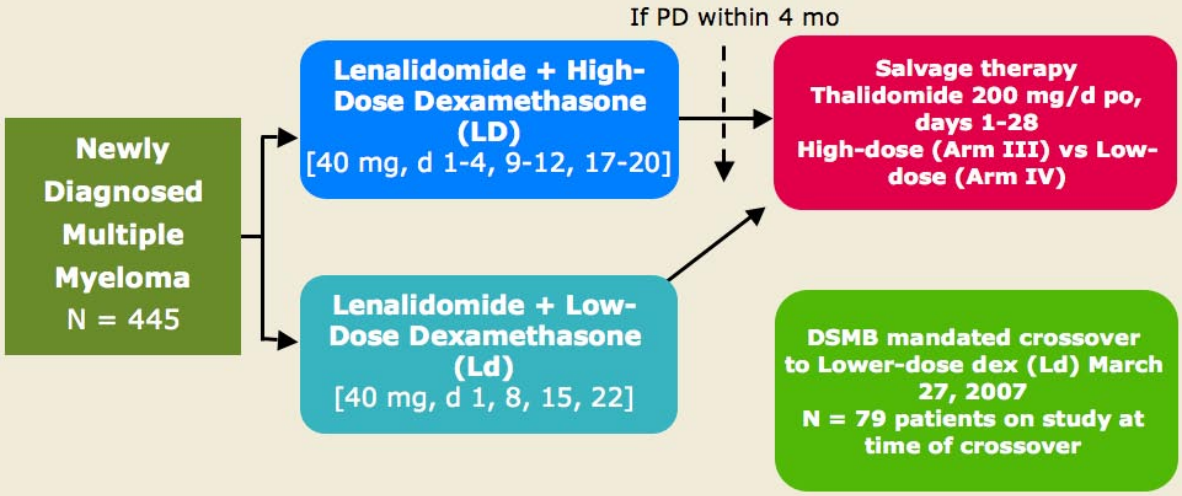
Presentation discussed in this issue

Vesole DH et al. **Lenalidomide plus low-dose dexamethasone (Ld): Superior one and two year survival regardless of age compared to lenalidomide plus high-dose dexamethasone (LD).** *Proc ASH* 2010;**Abstract 308**.

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



ECOG-E4A03 Study Schema



Lenalidomide: 25 mg daily, days 1-21 of a 28-day cycle; High-dose Dex: total 480 mg/28-day cycle; Low-dose Dex: total 160 mg/28-day cycle

Vesole DH et al. *Proc ASH* 2010;Abstract 308.

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Best Response: ≥PR

	LD (n)	Ld (n)	Odds ratio	*p*-value
Overall	81.3% (214)	70.2% (208)	1.85	0.009
<65	85.4% (103)	66.0% (103)	3.02	0.002
≥65	77.5% (111)	74.3% (105)	1.19	0.634
≥70	74.6% (71)	73.8% (65)	1.04	1.000
≥75	77.8% (36)	70.4% (27)	1.47	0.566

Vesole DH et al. *Proc ASH* 2010;Abstract 308.

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Overall Survival Probability

Intent-to-Treat Analysis				
	1-year OS		2-year OS	
Age	Ld	LD	Ld	LD
< 65 (n = 108; 104)	0.96	0.92	0.92	0.86
> 65 (n = 114; 119)	0.95	0.84	0.85	0.72
> 70 (n = 71; 76)	0.96	0.78	0.89	0.67
> 75 (n = 30; 38)	0.90	0.76	0.76	0.60
4-Month Landmark Analysis				
	1-year OS		2-year OS	
Age	Ld	LD	Ld	LD
< 65 (n = 106; 103)	0.98	0.93	0.93	0.86
> 65 (n = 113; 109)	0.96	0.92	0.86	0.79
> 70 (n = 70; 67)	0.97	0.88	0.90	0.76
> 75 (n = 29; 34)	0.93	0.85	0.79	0.67

Vesole DH et al. *Proc ASH* 2010;Abstract 308.

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Adverse Events

	≥Grade 3 or 4 nonhematologic toxicity		All Grade 5 toxicity	
	Ld	LD	Ld	LD
Overall	50.5%	61.4%	2.3%	5.8%
Age < 65	45.8%	52.9%	1.0%	1.9%
Age > 65	54.9%	68.9%	3.5%	9.2%
Age ≥ 70	60.6%	68.4%	4.2%	13.2%
Age ≥ 75	66.7%	71.1%	10.0%	13.2%

Vesole DH et al. *Proc ASH* 2010;Abstract 308.

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Conclusions

- OS was not superior with LD compared to Ld in any age group despite a higher response rate with LD in patients < 65.
  - Response rate was not significantly improved in any other age group
  - Confirmed in the landmark analysis to eliminate the 5% early deaths seen in the first 4 months of treatment.
- OS benefit with Ld accrues as age increases.
- No age group shows a superior outcome with LD, yet toxicities are higher in all age groups.
- Lenalidomide plus low-dose dexamethasone (Ld) is the treatment of choice for ALL age groups.
- It is unknown if extrapolation of Ld data in up-front setting can be applied to the treatment of relapsed MM.

Vesole DH et al. *Proc ASH* 2010;Abstract 308.

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Investigator comment on lenalidomide-based induction and maintenance for patients with myeloma

I was a participant in the study by Dr Vesole. When this study showed globally that Ld was superior to LD, an immediate criticism arose that this would be true for the elderly, but certain individuals, such as younger patients, might be better served by LD.

This presentation basically states that there is no age category in which LD is superior to Ld. However, I would agree that the question is still valid whether certain clinical settings exist in which treatment with high doses of dexamethasone may be considered. One clinical situation in which the high-dose dexamethasone approach might be relevant is in the setting of acute renal failure, with which there is a definite need to control the myeloma as soon as possible. The level of toxicity is clearly higher with higher doses of dexamethasone, and the bulk of the evidence suggests that there is no advantage with its use.

Interview with Rafael Fonseca, MD, December 22, 2010

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