5 Minute JournalClub

Key ASH Presentations
Issue 7, 2012

Lenalidomide for Newly Diagnosed MM and the Incidence of Second Primary Cancer

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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

- Integrate emerging research information on the use of proteasome inhibitors and immunomodulatory agents to individualize induction treatment recommendations and maintenance therapeutic approaches for elderly patients with multiple myeloma.
- Compare and contrast the benefits and risks of lenalidomide- and bortezomib-based induction therapy, and consider the role of combined immunomodulatory and proteasome-inhibitor regimens for elderly patients with multiple myeloma.
- Communicate the benefits and risks of postinduction maintenance therapy with lenalidomide- and bortezomib-based therapies to elderly patients with multiple myeloma.
- Weigh the benefit of continuous therapy with lenalidomide against the risk of development of second primary cancer for patients who receive lenalidomide with alkylating agents.

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

In ancient oncology days, laboratory scientists like Drs Howard Skipper and Frank Schabel created a kinetically defined portrait of cancer that was most amenable to a "shock and awe" therapeutic strategy involving short-term chemo and indirectly led to the use of supportive transplants. This "MTD" approach has gradually given way to a new model in which more tolerable, targeted antitumor agents are utilized in doses and schedules that allow for prolonged administration. Of course the prototype for chronic anticancer treatment is imatinib in CML, but rituximab maintenance in indolent lymphoma and endocrine and anti-HER2 therapy in breast cancer are related examples, and our last email reflected on the apparent advantages to the prolonged use of bevacizumab and/or pemetrexed in nonsquamous cell lung cancer. In multiple myeloma a similar type of strategy has been increasingly discussed by investigators including Dr Antonio Palumbo, who was the first author on a related European Myeloma Network (EMN) report in the October issue of *Blood* titled "Personalized therapy in multiple myeloma according to patient age and vulnerability."

Side note: Make the experts sweat!

In less than 3 weeks (Friday, April 13th) myeloma investigators Drs Rafael Fonseca, Ravi Vij, Jeff Wolf and Jeff Zonder will join us in Miami to help create a new case-based audio program. As part of the project, we have reserved time to discuss cases and questions from the community at large. To that end, we encourage you to **visit our Facebook page** and post a case or **tweet us a question**. We will do our best to present these and follow up with the answers.

Dr Palumbo's concept — which he first presented to our audiences during an audio interview almost 2 years ago — centers on the notion that although MM is primarily a disease of older people (a third are over 75), the important improvement in survival observed in recent years from the introduction of IMiDs and proteasome inhibitors has been confined to patients under 70. As such, he has championed a new approach to treatment for older patients in which careful attention to the selection of regimen, dose, schedule and methods of administration allows for safe prolonged treatment and much better outcomes. In this issue of our program we review 5 important ASH papers, all of which directly or indirectly support this chronic disease model:

1. Continuous lenalidomide

Dr Palumbo presented a **follow-up analysis from his landmark European trial evaluating len maintenance** until and, in some cases, beyond disease progression in nontransplant-eligible patients receiving induction with either MPR or MP. The trial had previously demonstrated more than a doubling of PFS in favor of maintenance in both induction arms, and this report — which divided the results by age — found similar benefits above and below age 75. Many investigators, including Dr Sagar Lonial, believe that avoiding

disease progression and the challenge of re-treatment is particularly important in patients older than age 75.

Dr Palumbo also presented **data at ASH on second primary cancers (SPC)** in 2,459 patients from 9 trials of the EMN. Prior studies have suggested an increased incidence of SPC (particularly AML/MDS) in all patients with MM, and this post hoc analysis demonstrated a modest increased SPC risk for patients on len maintenance, particularly those who had also received melphalan-based therapy. The report concludes that the risk of SPC is much smaller than the antimyeloma benefits of maintenance len.

2. UPFRONT study: Three different induction bortezomib-based regimens

In this Phase IIIb effort, VD, VTD and VMP induction were compared and although all 3 resulted in good tumor outcomes, VTD was found to be superior but also more toxic — particularly in terms of peripheral neuropathy. These findings suggest to some that the less toxic VD regimen may be a better option for the elderly, particularly if bortezomib can be administered weekly or subcutaneously.

3. VISTA

At ASH the final 5-year findings from this landmark Phase III trial continued to demonstrate an overall survival benefit (13.3 months) associated with the addition of bortezomib to melphalan/prednisone. With perhaps the longest follow-up reported in the era of novel agents, this study supports the concept that early treatment can profoundly affect the longer-term natural history of the disease.

4. Spanish study of maintenance with an IMiD and a proteasome inhibitor

This update presented by Dr Maria-Victoria Mateos revealed that both VT and VP maintenance after induction resulted in better outcomes with a trend favoring VT. The natural extension of this multiagent maintenance strategy is embodied in an ongoing Dana-Farber study of "RVD lite" in older patients that allows for long-term treatment by incorporating lower doses and providing flexibility in terms of bortezomib administration.

Any questions about this? **Facebook us!**

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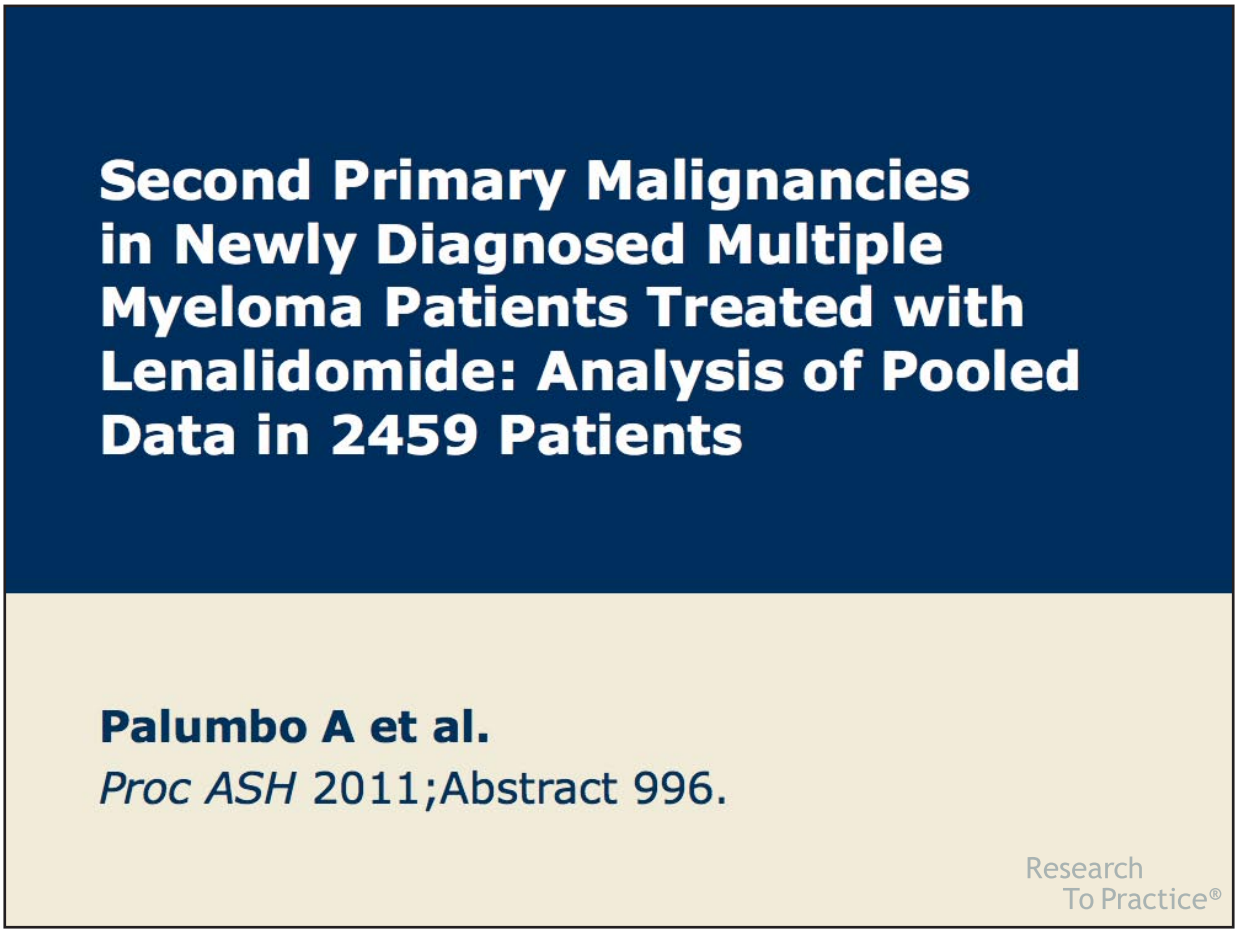
Lenalidomide for Newly Diagnosed MM and the Incidence of Second Primary Cancer

Presentation discussed in this issue

Palumbo A et al. **Second primary malignancies in newly diagnosed multiple myeloma patients treated with lenalidomide: Analysis of pooled data in 2459 patients.** *Proc ASH* 2011;**Abstract 996**.

Slides from a presentation at ASH 2011 and transcribed comments from a recent interview with Paul G Richardson, MD (1/24/12)



Background

The observation of an 8-fold increased incidence of AML/MDS in MGUS (monoclonal gammopathy of undetermined significance) compared to that of the general population supports a role of nontreatment-related factors in the development of AML/MDS in plasma cell dyscrasias (*Blood* 2011:118, 4086).

- In patients with multiple myeloma (MM), the risk of second primary malignancy (SPM) is influenced by age and the use of alkylating agents.
- **Current study objective:**
  - Post hoc analysis to assess the risk of development of SPMs in patients with newly diagnosed MM who were enrolled in 9 studies of the European Myeloma Network

Palumbo A et al. *Proc ASH* 2011;Abstract 996.

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Study Method

- SPM incidence rates per 100 person-years were examined from 9 trials: RVMM EMN01; RVMMEMN 441; RVMM PI 026; RVMM PI 302; RVMM PI 209; GIMEMA MM 03 05, GIMEMA MM 04 05, GISMM 2001; HOVON 87.
- Treatment received in the examined trials:
  - Cyclophosphamide-lenalidomide-corticosteroids (CRC), n = 326
  - Melphalan-prednisone-lenalidomide (MPR), n = 668
  - Autologous stem cell transplant followed by lenalidomide maintenance (ASCT-R), n = 484
  - Melphalan-prednisone (MP), n = 164
  - MP-thalidomide (MPT), n = 384
  - MP-bortezomib (VMP), n = 257
  - MPV-thalidomide (VMPT), n = 254
  - Lenalidomide-low-dose dexamethasone (Rd), n = 147

Palumbo A et al. *Proc ASH* 2011;Abstract 996.

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Incidence of SPMs per 100 per year*

Treatment received	Median follow-up (mo)	Incidence (%)
All patients (n = 2,283)	29.1	0.87
Dex/cyclo-lenalidomide (n = 351)	17.1	0.4
Melphalan-lenalidomide (n = 972)	30.0	0.95
Melphalan-thalidomide (n = 539)	35.9	1.05
Melphalan no IMiDs (n = 421)	40.6	0.42

Dex = dexamethasone; Cyclo = cyclophosphamide

* Post hoc analysis was restricted to pooled data from 2,283 patients with at least 1 year of follow-up.

Palumbo A et al. *Proc ASH* 2011;Abstract 996.

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SPM Cases

Treatment received	SPMs (%)		
	Total	Solid tumors	Hematologic cancer
All patients (n = 2,283)	2.1	1.7	0.4
Dex/cyclo-lenalidomide (n = 351)	0.6	0.6	0.0
Melphalan-lenalidomide (n = 972)	2.4	2.2	0.2
Melphalan-thalidomide (n = 539)	3.1	1.8	1.3
Melphalan no IMiDs (n = 421)	1.4	1.2	0.2

Dex = dexamethasone; Cyclo = cyclophosphamide

Post hoc analysis was restricted to pooled data from 2,283 patients with at least 1 year of follow-up.

Palumbo A et al. *Proc ASH* 2011;Abstract 996.

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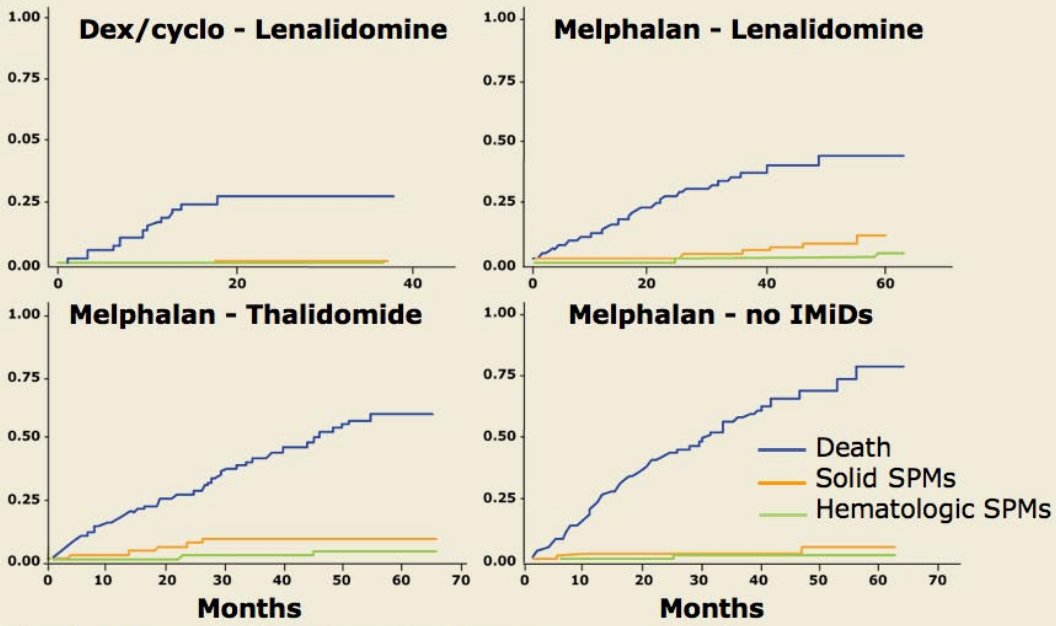
Incidence of SPMs per 100 per Year Subgroup Analysis According to Therapy

	All patients	Dex/Cyclo Lenalidomide	Melphalan Lenalidomide	Melphalan Thalidomide	Melphalan no IMiDs
Hematologic SPMs	0.18	0	0.08	0.43	0.07
Solid SPMs	0.69	0.4	0.86	0.62	0.35

SPMs = second primary malignancies; Dex = dexamethasone; Cyclo = cyclophosphamide

With permission, Palumbo A et al. *Proc ASH* 2011;Abstract 996.

SPMs and Risk of Death



Risk of death is greater than the risk of SPMs

With permission, Palumbo A et al. *Proc ASH* 2011;Abstract 996.

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Author Conclusions

- With a short follow-up time as a study limitation, the data currently support a role for nontreatment-related factors as causes of SPMs.
- SPM incidence was lower than expected in all treatment groups, and the observed and expected rates of SPMs were similar (data not shown).
- The benefits of continuous therapy with lenalidomide outweigh the potential risk of SPMs:
  - The risk of death is greater than the risk of SPM.
- Longer follow-up is needed to assess the risks of SPMs in patients receiving lenalidomide with alkylating agents.

Palumbo A et al. *Proc ASH* 2011;Abstract 996.

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Investigator Commentary: Assessment of SPM Risk in MM

This study from the European Myeloma Network clearly noted no reported cases of SPM in patients receiving cyclophosphamide and lenalidomide as a combination therapy. By contrast, melphalan, which is more genotoxic than cyclophosphamide, is associated with a small but observable rate of increased acute leukemia/MDS in particular. I am aware from my own practice, and from historical data with melphalan, that there is a real signal in terms of secondary leukemia from treatment with melphalan.

In a number of trials in the relapsed setting, in which patients have been receiving lenalidomide-based therapy for prolonged periods of time — either lenalidomide alone or lenalidomide with dexamethasone — the signals for a secondary malignancy related to lenalidomide use have been minimal.

Based on the data from the IFM 2005-02 trial, I would say that the risk of SPM from maintenance lenalidomide after transplant is low, but if patients have not received much genotoxic therapy, they are much less likely to develop SPMs. Given the survival benefit now seen in the CALGB trial with the use of lenalidomide maintenance after SCT, these data must be kept very much in perspective, and certainly in our group the enthusiasm for continued therapy with lenalidomide in the appropriate clinical context remains high.

Interview with Paul G Richardson, MD, January 24, 2012