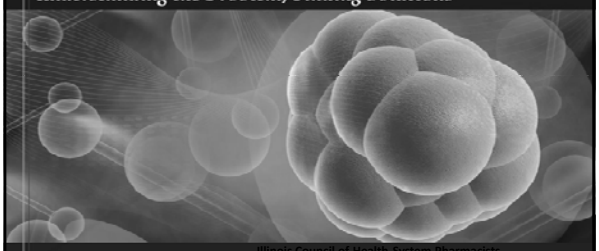
Dosing and Administration Challenges for Patients with Multiple Myeloma:

Understanding the Problem, Finding Solutions



Illinois Council of Health-System Pharmacists
Saturday, September 15, 2012 ~ 6:30am – 8:30am
Drury Lane Theater, Oakbrook Terrace, IL

Welcome & Introductions

Shawna Kraft, PharmD, BCOP
Clinical Pharmacist Hematology/Oncology
Adjunct Clinical Assistant Professor
University of Michigan Health System
Ann Arbor, MI

Kathryn Schultz, PharmD, BCOP, BCPS
Clinical Pharmacist
Hematology/Oncology and Stem-Cell Transplant
Rush University Medical Center
Chicago, IL

Agenda

6:30am – 7:00am	Breakfast & Registration
7:00am – 7:10am	Welcome & Introductions **Shawna Kraft, PharmD, BCOP**
7:10am – 7:30am	Multiple Myeloma 101 Newly-Diagnosed Patient/Multi-drug Regimen (ASCT eligible) **Kathryn Schultz, PharmD, BCPS, BCOP**
7:30am – 7:55am	Emerging Therapeutics and Administration Challenges **Shawna Kraft, PharmD, BCOP**
7:55am – 8:20am	Administration Challenges, Adverse Effect Management and Comorbidities: Personalized Medicine in Multiple Myeloma **Shawna Kraft, PharmD, BCOP**
8:20am – 8:30am	Question-and-Answer Session

Learning Objectives

- For newly diagnosed patients, identify initial dose adjustments that are required based on patient- and disease-associated factors for all drugs in the chosen regimen to ensure maximum efficacy and tolerability
- Assess the pharmacokinetics and pharmacodynamics of emerging agents when integrating these agents into treatment regimens
- Evaluate adverse event management strategies for patients with MM receiving novel therapies and multi-drug regimens

Registered Pharmacy Designation

Registered Pharmacy Designation

MLI is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. Completion of this activity provides 1.5 contact hour (0.15 CEU) of continuing education credit.

The universal activity number for this activity is 0468-9999-12-004-L01-P.

CE Information

Purpose Statement

- This program will provide health system pharmacists with reasoning tools they can employ when making dosing and administration decisions for complicated patients with MM

Target Audience

- This knowledge-based activity was developed for health system and oncology pharmacists as well as pharmacy technicians who wish to enhance their competence concerning regional/system variations in the delivery of care for patients with Multiple Myeloma

Commercial Support Acknowledgment

This activity is supported by an educational grant from Millennium: The Takeda Oncology Company

Sponsor

This activity is jointly sponsored by Medical Learning Institute, Inc. (MLI), and Center of Excellence Media, LLC (COE)

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Disclaimer

- The information provided at this CE activity is for continuing education purposes only and is not meant to substitute for the independent medical judgment of a healthcare provider relative to diagnostic and treatment options of a specific patient's medical condition.
- Recommendations for the use of particular therapeutic agents are based on the best available scientific evidence and current clinical guidelines. No bias towards or promotion for any agent discussed in this program should be inferred.

Disclosures

Before the activity, all faculty and anyone who is in a position to have control over the content of this activity and their spouse/life partner will disclose the existence of any financial interest and/or relationship(s) they might have with any commercial interest producing health care goods/services to be discussed during their presentation(s): honoraria, expenses, grants, consulting roles, speakers bureau membership, stock ownership, or other special relationships. Presenters will inform participants of any off-label discussions. All identified conflicts of interest are thoroughly vetted by MLI for fair balance, scientific objectivity of studies mentioned in the materials or used as the basis for content, and appropriateness of patient care recommendations.

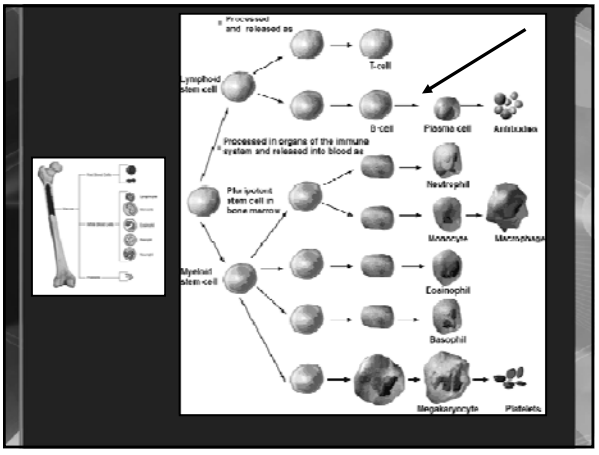
The planners and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CE activity:

Name of Planner or Manager Relationship	Company	Reported Financial Relationship
Nancy Nesser	MLI	Nothing to Disclose
Linda M Ritter, PhD	COE	Nothing to Disclose

Faculty Disclosures

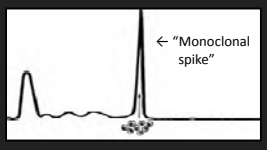
- *Shawna Kraft, PharmD, BCOP has nothing to disclose. She does not intend to discuss any non-FDA-approved or investigational use of any products/devices.*
- *Kathryn Schultz, PharmD, BCPS, BCOP has nothing to disclose. She does not intend to discuss any non-FDA-approved or investigational use of any products/devices.*

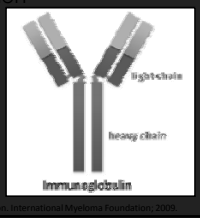
Multiple Myeloma 101



Multiple Myeloma

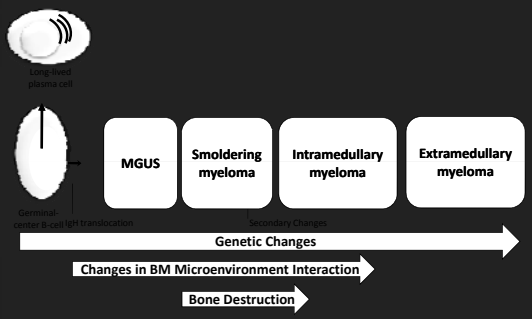
- Progressive hematologic disorder
- Accumulation of cancerous plasma cells
- Overproduction of abnormal immunoglobulins ("M proteins" or "paraproteins") in bone marrow
  - Mainly IgG or IgA
  - Excessive light chain production
  - Bence Jones proteins





Nau KC, Lewis WD. *Am Fam Physician*. 2008;78(7):853-859.
Durie BGM. Concise Review of the Disease and Treatment Options 2008/2009 Edition. International Myeloma Foundation; 2009.

Myeloma Progression



MGUS = Monoclonal gammopathy of undetermined significance

Shain et al. Multiple myeloma. In: Runge and Patterson, eds. *Molecular Medicine*. 2nd ed. Humana Press; 2006.

Multiple Myeloma
Epidemiology

- ~21,700 new cases estimated for 2012
- ~10,710 deaths estimated for 2012
- Lifetime risk is 1 in 155 (based on rates from 2006-2008)
- 5 year survival increased from 25% in 1975 to 41% in 2007

American Cancer Society. *Cancer Facts & Figures 2012*. Atlanta: American Cancer Society; 2012.
Howlander N, et al (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.

Multiple Myeloma
Survival

- The 5-year relative survival rate for MM is currently estimated at ~41%
- Survival is higher in younger people and lower in the elderly
- 5-year survival rates are based on patients diagnosed and initially treated more than 5 years ago (2001-2007)
- The recent improvements in treatment may result in a more favorable outlook for recently diagnosed patients
- Improvements in prognosis have occurred because of the introduction of newer therapies such as pulse corticosteroids, immunomodulators (thalidomide, lenalidomide), and a proteasome inhibitor (bortezomib)

Brenner H, et al. *Haematologica*. 2009; 94(2): 270–275. Howlander et al (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.

Etiology

- Ultimately unknown
- Possible explanations
  - Hereditary linkage
  - Genetic abnormalities
  - Exposure to radiation
  - Viral infection
  - Progression of MGUS

Landgren O, Kordie N. *Oncology (Williston Park)*. 2011;25(7):589-590.

Diagnostic Criteria for Symptomatic MM

1. Monoclonal plasma cells in the bone marrow ≥10% and/or presence of a biopsy-proven plasmacytoma
2. Monoclonal protein present in the serum and/or urine
3. Myeloma-related organ dysfunction (1 or more)

Organ Dysfunction	Criteria
Calcium elevation	Serum calcium ≥11.5 mg/dL
Renal Insufficiency	Serum creatinine >2 mg/dL
Anemia	Hemoglobin <10 g/dL or >2 g/dL below LLN
Bone	Lytic lesions, severe osteopenia, or pathologic fractures

LLN=Lower limit of normal

International Myeloma Working Group. *Br J Haematol*. 2003;121:749-757.
Kyle RA, et al. *Leukemia*. 2009;23(1):3-9.

Staging

Stage	Criteria (Durie-Salmon)	Criteria (International Staging System)
I	All of the following: Hemoglobin >10 g/dL Serum Ca <12 mg/dL Normal bone structure or solitary bone lesion only Low M-component production IgG <5 g/dL IgA <3 g/dL Urine light chain M <4 g/24 h	Serum β_2-microglobulin <3.5 mcg/mL Serum albumin ≥3.5 g/dL
II	Fitting neither stage I nor III	Fitting neither stage I nor III
III	One or more of following: Hemoglobin <8.5 g/dL Serum Ca >12 mg/dL Advanced lytic bone lesions High M-component production IgG >7 g/dL IgA >5 g/dL Urine light chain M >12 g/24 h	Serum β_2-microglobulin ≥5.5 mcg/mL

Durie, Salmon. *Cancer*. 1975;36(3):842-854. Greipp et al. *J Clin Oncol*. 2005;23:3412-3420.

Newly-Diagnosed Patients and Multi-Drug Regimens

Applying Knowledge: Patient Case 1

Patient Case

- RS is a 68 year-old male who presented to ED after falling while taking down holiday lights. In the ED, x-rays confirmed he had broken his right hip. He was A&O x3 with no other signs of trauma or bleeding. Other past medical history includes HTN (for which he is on lisinopril) and Type 2 DM (controlled with diet). Labs were as follows:
  - Hemoglobin (Hgb) = 8.9 gm/dL
  - Serum creatinine (sCr) = 1.7 mg/dL
  - Calcium (Ca) = 11.9 mg/dL
  - Albumin (Alb) = 1.8 g/dL
  - β2-microglobulin (β2M) = 3.3 mcg/mL
  - Urine analysis = urine protein = M protein spike of IgA
  - Bone marrow = 19% plasma cells
  - Skeletal survey = multiple lytic lesions

Question 1

What initial therapy would you initiate for RS?

A. Melphalan/prednisone

B. Steroids alone

C. Thalidomide/dexamethasone

D. Lenalidomide/high-dose dexamethasone

E. Other

Treatment Options

- To transplant or not to transplant?
- Transplant considerations
  - Age
  - Comorbidities
  - Renal function
- No transplant?
  - Melphalan, steroid based
- Yes transplant?
  - Thalidomide/lenalidomide/steroid based

Risk Stratification

Standard Risk	Intermediate Risk	High Risk
• Hyperdiploidy • t(11;14) • t(6;14)	• t(4;14) • Deletion 13 or hypodiploidy by conventional karyotyping	• 17p deletion • t(14;16) • t(14;20) • High-risk gene expression profiling (GEP) signature • Plasma cell leukemia

Kapoor et al. *Int J Hematol.* 2011;94:310-320.
Rajkumar. *Am J Hematol.* 2012;87:79-88.

Induction Therapy for Transplant Candidates

Regimen	NCCN Category
Bortezomib/dexamethasone	1
Bortezomib/doxorubicin/dexamethasone	1
Bortezomib/thalidomide/dexamethasone	1
Lenalidomide*/dexamethasone	1
Bortezomib/cyclophosphamide/dexamethasone	2A
Bortezomib/lenalidomide*/dexamethasone	2A
Thalidomide/dexamethasone	2B
Dexamethasone	2B
Liposomal doxorubicin/vincristine/dexamethasone	2B

*Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.

Category 1 – The recommendation is based on high-level evidence and there is uniform NCCN consensus
Category 2A – The recommendation is based on lower-level evidence and there is uniform NCCN consensus
Category 2B – The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus

The NCCN Clinical Practice Guidelines in Oncology™ Multiple Myeloma (Version 1.2012). © 2011 National Comprehensive Cancer Network, Inc. Available at: NCCN.org. Accessed [March 13, 2012]. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

Newly Diagnosed Myeloma Eligible for Transplantation

High-Risk	Intermediate-Risk	Standard-Risk
VRD x 4 cycles	VCD x 4 cycles	Rd x 4 cycles
ASCT	ASCT; 2nd ASCT if not in CR or VGPR	Early ASCT / Delayed ASCT
Bortezomib-based maintenance	Bortezomib maintenance for 2 years	Lenalidomide maintenance if not in CR or VGPR following ASCT

Rajkumar SV. *Am J Hematol.* 2012;87:79-88.

Induction Therapy for Nontransplant Candidates

Regimen	NCCN Category
Melphalan/prednisone/bortezomib	1
Melphalan/prednisone/thalidomide	1
Melphalan/prednisone/lenalidomide	1
Lenalidomide/low-dose dexamethasone	1
Bortezomib/dexamethasone	2A
Melphalan/prednisone	2A
Dexamethasone	2B
Vincristine/doxorubicin/dexamethasone	2B
Thalidomide/dexamethasone	2B
Liposomal doxorubicin/vincristine/dexamethasone	2B

Category 1 – The recommendation is based on high-level evidence and there is uniform NCCN consensus
Category 2A – The recommendation is based on lower-level evidence and there is uniform NCCN consensus
Category 2B – The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus

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Newly Diagnosed Myeloma Not Eligible for Transplantation

High-Risk	Intermediate-Risk	Standard-Risk
VRD x one year	VCD x one year	Rd*
Bortezomib-based maintenance	Bortezomib maintenance for 2 years if possible	

*Dexamethasone usually discontinued after 12 months; continued long-term bortezomib or lenalidomide is an option for patients who are tolerating treatment well.

Rajkumar SV. *Am J Hematol.* 2012;87:78-88.

Maintenance Therapy

Regimen	NCCN Category
Thalidomide	1
Bortezomib	2A
Lenalidomide*	2A
Interferon	2B
Steroids	2B
Thalidomide/prednisone	2B

*There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risk of maintenance therapy vs secondary cancers should be discussed with patients.

Category 1 – The recommendation is based on high-level evidence and there is uniform NCCN consensus
Category 2A – The recommendation is based on lower-level evidence and there is uniform NCCN consensus
Category 2B – The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus

The NCCN Clinical Practice Guidelines in Oncology™ Multiple Myeloma (Version 1.2012). © 2011 National Comprehensive Cancer Network, Inc. Available at: NCCN.org. Accessed [March 13, 2012]. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

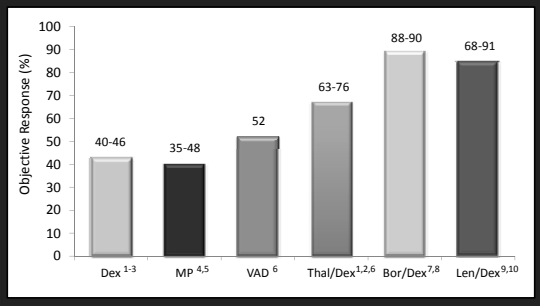
Salvage Therapy
Partial List

Regimen	NCCN Category
Bortezomib	1
Bortezomib/liposomal doxorubicin	1
Lenalidomide/dexamethasone	1
Repeat primary induction (relapse > 6 mos)	2A
Bendamustine	2A
Bortezomib/dexamethasone	2A
Bortezomib/lenalidomide/dexamethasone	2A
Cyclophosphamide/bortezomib/dexamethasone	2A
Cyclophosphamide/lenalidomide/dexamethasone	2A
Dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP)	2A
Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide (DT-PACE) ± bortezomib (VTD-PACE)	2A
High-dose cyclophosphamide	2A
Thalidomide/dexamethasone	2A

Category 1 – The recommendation is based on high-level evidence and there is uniform NCCN consensus
Category 2A – The recommendation is based on lower-level evidence and there is uniform NCCN consensus
The NCCN Clinical Practice Guidelines in Oncology™ Multiple Myeloma (Version 1.2012). © 2011 National Comprehensive Cancer Network, Inc. Available at: NCCN.org. Accessed [March 13, 2012]. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

Emerging Therapeutics and Administration Challenges

Previously Untreated Multiple Myeloma
Response



1.Rajkumar et al. *J Clin Oncol*. 2006;24(3):431-436. 2. Rajkumar et al. *J Clin Oncol*. 2008;26(13):2171-2177. 3. Facon et al. *Blood*. 2006;107(4):1292-1298. 4. San Miguel et al. *N Engl J Med*. 2008;359(9):906-917. 5. Palumbo et al. *Lancet*. 2006;367(9513):825-831. 6. Cavo et al. *Blood*. 2005;106(1):35-39. 7. Jagannath et al. *Br J Haematol*. 2005;129(6):776-783. 8. Jagannath et al. *Br J Haematol*. 2009;146(6)619-626. 9. Rajkumar et al. *Lancet Oncol*. 2009 Oct 21 [Epub ahead of print]. 10. Rajkumar et al. *Blood*. 2005;106(13):4050-4053.

Lenalidomide/ Dexamethasone Toxicity

Grade 3/4 AEs	MM 009		MM 010	
	Len/Dex n = 177	Dex n = 175	Len/Dex n = 176	Dex n = 175
Neutropenia	41.2%	4.6%	29.5%	2.3%
Thrombocytopenia	14.7%	6.9%	11.4%	5.7%
Anemia	13.0%	5.1%	8.6%	6.9%
Febrile neutropenia	3.4%	0%	3.4%	0%
Venous thromboembolism	14.7%	3.4%	11.4%	4.6%

- Most frequently reported nonhematologic AEs
  - Fatigue, insomnia, diarrhea, constipation, muscle cramps, and infection

Weber et al. *N Engl J Med*. 2007;357:2133-2142.
Dimopoulos et al. *N Engl J Med*. 2007;357:2123-2132.

Bortezomib/Dexamethasone (Bor/Dex) vs VAD as Induction Treatment Prior to Autologous Stem Cell Transplantion (ASCT) in Newly Diagnosed Multiple Myeloma (MM): Results of the IFM 2005/01 Trial

Jean-Luc Harousseau, Michel Attal, Herve´ Avet-Loiseau, Gerald Marit, Denis Caillot, Mohamad Mohty, Pascal Lenain, Cyrille Hulin, Thierry Facon, Philippe Casassus, Mauricette Michallet, Herve´ Maisonneuve, Lotfi Benboubker, Frederic Maloisel, Marie-Odile Petillon, Iain Webb, Claire Mathiot, and Philippe Moreau

Harousseau,et al. *J Clin Oncol*. 2010;28(30):4621-4629.

IFM 2005/01 Trial
Response

Response Post-Induction	Bor/Dex* N = 214	VAD* N = 210	*P*
CR	5.8%	1.4%	.012
≥VGPR	37.7%	15.1%	< .001
≥PR	78.5%	62.8%	< .001

Response to First ASCT	Bor/Dex* n = 212	VAD* n = 213	*P*
CR	16.1%	8.7%	.016
≥VGPR	54.3%	37.2%	< .001
≥PR	80.3%	77.1%	NS

*± DCEP consolidation.

VAD= Vincristine, Adriamycin, Dexamethasone; DCEP= Dexamethasone, cyclophosphamide, etoposide and cisplatin
Harousseau, et al. *J Clin Oncol*. 2010;28(30):4621-4629.

Treatment Considerations

- Lenalidomide/Dex vs. Thalidomide/Dex
  - OS: Not reached vs. 57.2 mos. (*P*=.018)
  - Neutropenia (3/4): 14.6% vs 0.6% (*P*<.001)
  - Peripheral neuropathy: 10.4% vs 0.9% (*P*<.001)
- Lenalidomide renal dosing

Category	CrCl	Dose
Moderate Renal impairment	30-60 mL/min	10 mg Q24H
Severe renal impairment (not on dialysis)	<30 mL/min	15 mg Q48H
End stage renal disease (on dialysis)	<30 mL/min	5 mg QD (dosed after dialysis)

Gay F, et al. Blood. 2010;115(7):1343-1350. Revlimid [package insert]. Summit, NJ: Celgene Corporation; 2005-2011.

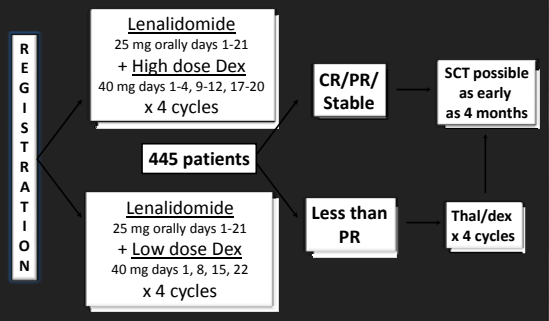
Lenalidomide plus high-dose Dexamethasone (LD) vs. Lenalidomide Plus Low-dose Dexamethasone (Ld) as Initial Therapy for Newly Diagnosed Multiple Myeloma: An Open-label Randomised Controlled Trial

S. Vincent Rajkumar, Susanna Jacobus, Natalie Callander, Rafael Fonseca, David Vesole, Michael Williams, Rafat Abonour, David Siegel, Michael Katz, and Philip Greipp; Eastern Cooperative Oncology Group

Mayo Clinic, Rochester, MN, USA; Dana Farber Cancer Institute, Boston, MA, USA; University of Wisconsin, Madison, WI, USA; Mayo Clinic, Scottsdale, AZ, USA; St. Vincents Comprehensive Cancer Center, New York, NY, USA; University of Virginia, Charlottesville, VA, USA; Indiana University Medical Center, Indianapolis, IN, USA; Hackensack University Medical Center, Hackensack, NJ, USA; International Myeloma Foundation, North Hollywood, CA, USA

Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37.

ECOG E4A03: Study Design



Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37.

ECOG E4A03
Adverse Events

	Lenalidomide High-Dose Dex	Lenalidomide Low-Dose Dex	*P*
≥Grade 3 thromboembolic event –after addition of aspirin	26% 16%	12% 8%	< .0003
Grade 3 infection/pneumonia	16%	9%	.04
Any nonhematological toxicity ≥ grade 4	21%	14%	.0002

Rajkumar SV, et al. *Blood.* 2007;110. Abstract 74.
Rajkumar SV, et al. *J Clin Oncol.* 2008;26(15S). Abstract 8504.
Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37.

ECOG E4A03
Lenalidomide + Low- or High-Dose Dexamethasone

Response	Lenalidomide High-Dose Dex N = 214	Lenalidomide Low-Dose Dex N = 208	*P*
≥PR within 4 cycles	79%	68%	.008
≥VGPR within 4 cycles	42%	24%	<.0001
Toxicity			
Any grade ≥3 non-heme toxicity (<4 months)	52%	35%	.0001
Early deaths (<4 months)	5%	<1%	.003

Rajkumar SV, et al. *Blood.* 2007;110. Abstract 74.
Rajkumar SV, et al. *J Clin Oncol.* 2008;26(15S). Abstract 8504.
Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37.

Lenalidomide + Low- or High-Dose Dex ECOG E4A03
*Overall Survival (OS)**

	Lenalidomide High-Dose Dex N = 223	Lenalidomide Low-Dose Dex N = 221	*P*
1-year OS	87%	96%	.01
2-year OS	75%	87%	.007

**Although OS was not a protocol-specified endpoint, the study was stopped on recommendations of the independent data monitoring committee at a median follow-up of 12.5 months because OS was significantly higher with low dose than with high dose dexamethasone.*

Jacobus SJ, et al. *Blood.* 2008;112. Abstract 1740.
Rajkumar SV, et al. *Blood.* 2007;110. Abstract 74.
Rajkumar SV, et al. *J Clin Oncol.* 2008;26(15S). Abstract 8504.
Rajkumar SV. Clinical oncology update: studies from the 2008 ASCO Annual Meeting. Presented at the ASH/ASCO Joint Symposium. December 7, 2008; San Francisco, CA.
Rajkumar SV, et al. *Lancet Oncol.* 2010;11(1):29-37.

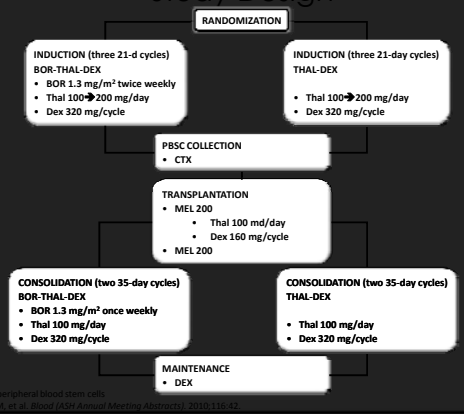
Bortezomib-Thalidomide-Dexamethasone Compared with Thalidomide-Dexamethasone as Induction and Consolidation Therapy Before and After Double Autologous Transplantation In Newly Diagnosed Multiple Myeloma: Results From a Randomized Phase 3 Study

Michele Cavo, Giulia Perrone, Silvia Buttignol, Elisabetta Calabrese, Monica Galli, Sara Bringhen, Tonino Spadano, Luca Baldini, Tommaso Caravita, Chiara Nozzoli, Annamaria Brioli, Luciano Masini, Anna Furlan, Lucia Pantani, Daniele Derudas, Stelvio Ballanti, Francesco Pisani, Valerio De Stefano, Gioacchino Catania, Luca Castagna, Felicetto Ferrara, Vincenzo Callea, Pellegrino Musto, Elena Zamagni, and Michele Baccarani

Seragnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; Department of Hematology/Oncology, University of Bologna, Bologna, Italy; 3GIMEMA Italian Myeloma Network, Italy

Cavo M, et al. *Blood (ASH Annual Meeting Abstracts)*. 2010;116:42.

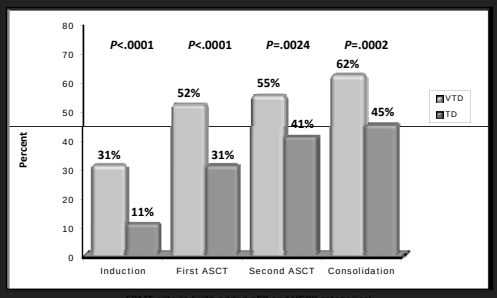
Study Design



PBSC=peripheral blood stem cells

Cavo M, et al. *Blood (ASH Annual Meeting Abstracts)*. 2010;116:42.

Increased CR-nCR Rates with VTD Compared to TD



EBMT criteria (with added nCR and VGPR categories)

VTD=bortezomib-thalidomide-dexamethasone; TD=thalidomide–dexamethasone

Cavo M, et al. *Blood (ASH Annual Meeting Abstracts)*. 2010;116:42.

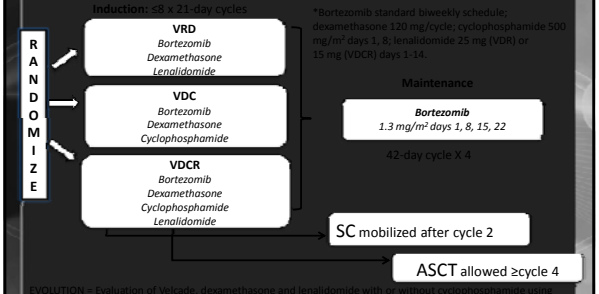
Phase 1/2
3- and 4-Drug Combinations

Efficacy	Len/Cyc/Dex[1] N = 53	Len/Btz/[a]Dex[2] N = 63	Btz/Dex/Cyc/Len[3] N = 25	Btz/Cyc/Dex → Btz/Thal/Dex[4] N = 44
Best Response				
ORR	**55 (85%)**	**62 (98%)[b]**	**25 (100%)**	**42 (95%)**
≥ nCR	**NR**	**23 (36%)**	**8 (32%)**	**15 (34%)**
≥ VGPR	**17 (32%)**	**45 (71%)[b]**	**17 (68%)**	**24 (55%)**
Median OS		**NR at 8 months**		**86% 12-month estimate**

[a]Dexamethasone, 20 mg Days 1–2, 4–5, 8–9, 11–12.
[b]Independent of ISS and high-risk cytogenetics
Len = lenolidomide; Btz = bortezomib; ORR = overall response rate; NR = not reached.

1. Kumar S, et al. *Blood* (ASH Annual Meeting Abstracts), Nov 2008; 112:91. 2. Richardson PG, et al. *Blood* (ASH Annual Meeting Abstracts), Nov 2008. 112:92. 3. Kumar S, et al. *Blood* (ASH Annual Meeting Abstracts), Nov 2008; 112:93. 4. Bensinger W, et al. *Blood* (ASH Annual Meeting Abstracts), Nov 2008; 112:94.

EVOLUTION
*Phase 2 Randomized Trial of 3- and 4-Drug Combinations**



EVOLUTION = Evaluation of Velcade, dexamethasone and lenalidomide with or without cyclophosphamide using targeted innovative oncology strategies in the treatment of frontline MM.

Kumar S, et al. *Blood (ASH Annual Meeting Abstracts)*. 2010;116(21):621.
Kumar S, et al. *Blood*. 2012 Mar 15. [Epub ahead of print]

EVOLUTION
Efficacy and Safety Results

Best Response across all cycles	VDCR N = 48	VRD N = 42	VDC N = 33	VDC mod* N = 17
ORR[2] (%)	88	85	75	100
CR[2] (%)	25	24	22	47
≥ VGPR[2] (%)	58	51	41	53
Median PFS[1]	710 days	NR	NR	NR
2-year OS[1] (%)	76	96	100	—
Safety[†] (%)				
1 or more ≥ grade 3 AEs[2]	83	76	79	88
AE resulting in discontinuation[2]	21	19	12	6
Neutropenia, ≥ grade 3[2]	44	10	30	24
Thrombocytopenia, ≥ grade 3[2]	15	12	12	0
PN, ≥ grade 3[2]	13	17	9	18

*VDC mod: VDC + cyclophosphamide day 15.
[†]2 deaths on study: both treatment-related and due to renal failure; one of these had renal insufficiency at time of diagnosis.
Median follow-up: ~18.5 months[1] or 20 months[2]

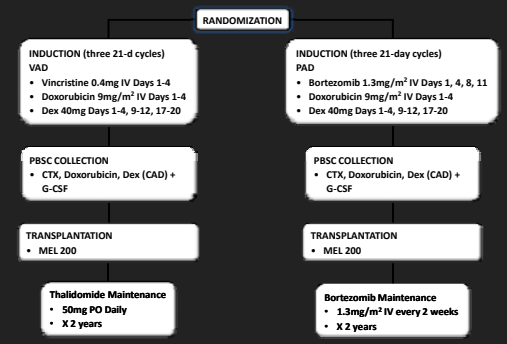
1. Kumar S, et al. *Blood (ASH Annual Meeting Abstracts)*. 2010;116(21):621.
2. Kumar S, et al. *Blood*. 2012 Mar 15. [Epub ahead of print]

Administration of bortezomib before and after autologous stem-cell transplantation improves outcome in multiple myeloma patients with deletion 17p

Kai Neben, Henk M Lokhorst, Anna Jauch, Uta Bertsch, Thomas Hielscher, Bronno van der Holt, Hans Salwender, Igor W Blau, Katja Weisel, Michael Pfreundschuh, Christof Scheid, Ulrich Duhrsen, Walter Lindemann, Ingo GH Schmidt-Wolf, Norma Peter, Christian Teschendorf, Hans Martin, Mathias Haenel, Hans G Derigs, Marc S Raab, Anthony D Ho, Helgi van de Velde, Dirk Hose, Pieter Sonneveld and Hartmut Goldschmidt

Neben K, et al. *Blood*. 2012;119(4):940-948.

Study Design



PBSC=peripheral blood stem cells

Neben K, et al. *Blood*. 2012;119(4):940-948.

Results

Overall results

	PFS	3 yr OS	Median OS
VAD (N = 182)	31.2 months	73%	Not reached
PAD (N = 172)	35.7 months	84%	

17q deletion results

	PFS			3 yr OS		
17q deletion present	17.6 mos	VAD	12.0 mos*	36%	VAD	17%†
		PAD	26.2 mos*		PAD	69%†
Lacking abnormality	35.7 mos			83%		

*P = .024
†P = .028

Neben K, et al. *Blood*. 2012;119(4):940-948.

Patient Case 1

- RS is a 68 y.o. male presented to ED after falling while taking down holiday lights. In the ED, x-rays confirmed he had broken his right hip. He was A&O x3 with no other signs of trauma or bleeding. Other past medical history includes HTN for which he is on lisinopril and Type 2 DM controlled with diet. Labs were as follows:
  - Hemoglobin: 8.9 gm/dL
  - Serum creatinine: 1.7 mg/dL
  - Calcium: 11.9 mg/dL
  - Albumin: 1.8 g/dL
  - β2microglobulin: 3.3 mcg/mL
  - Urine analysis= urine protein= M protein spike of IgA
  - Bone marrow = 19% plasma cells
  - Skeletal survey= multiple lytic lesions

Question 1 - Revisited

- What initial therapy would you initiate for RS?
  - A. Melphalan/prednisone
  - B. Steroids alone
  - C. Thalidomide/dexamethasone
  - D. Lenalidomide/high-dose dexamethasone
  - E. Other

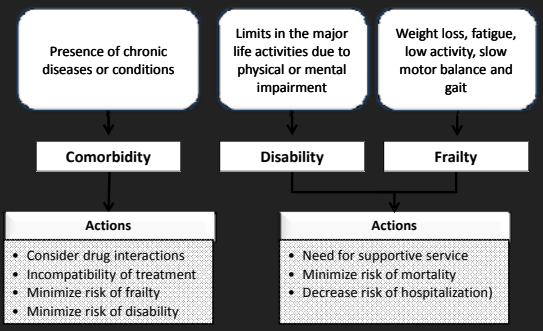
Administration Challenges, Adverse Effect Management and Comorbidities: Personalized Medicine in Multiple Myeloma

Case 2

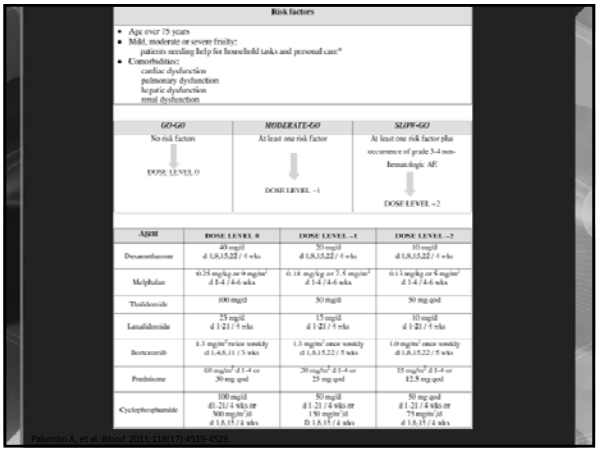
ST is a 76 y/o African American female who recently presented to her PCP for increasing pain in her back. PMH: Type 2 DM, HTN, CAD s/p stents, depression. ST was diagnosed with Stage IIIa IgG lambda multiple myeloma based on the following labs and exams:

- WBC: 12 X 10^9/L
- Serum creatinine: 1.7 mg/dL
- Hemoglobin: 8 gm/dL
- Calcium: 12 mg/dL
- Platelets: 112 X 10^9/L
- Albumin: 4 g/dL
- λ free light chains: 306 (0.57-2.63 mg/dL)
- Plasma viscosity: 2.47 X 10^{-3} (1.35-1.85)
- Skeletal survey shows multiple lytic lesions T8-T11
- β_2-microglobulin: 7 mcg/mL
- IgM: 9 (4-350 mg/dL)
- IgA: 5 (50-370 mg/dL)
- IgG: 6080 (620-1520 mg/dL)

Assessment for Vulnerability in Newly-Diagnosed MM Patients



Palumbo A, et al. *Blood*. 2011;118(17):4519-4529.



Risk factors

- Age over 75 years
- Mild, moderate or severe frailty:
  patients needing help for household tasks and personal care*
- Comorbidities:
  cardiac dysfunction
  pulmonary dysfunction
  hepatic dysfunction
  renal dysfunction

GO-GO	MODERATE-GO	SLOW-GO
No risk factors	At least one risk factor	At least one risk factor plus occurrence of grade 3-4 non-hematologic AE
↓ DOSE LEVEL 0	↓ DOSE LEVEL –1	↓ DOSE LEVEL –2

Agent	DOSE LEVEL 0	DOSE LEVEL –1	DOSE LEVEL –2
Dexamethasone	40 mg/d d 1,8,15,22 / 4 wks	20 mg/d d 1,8,15,22 / 4 wks	10 mg/d d 1,8,15,22 / 4 wks
Melphalan	0.25 mg/kg or 9 mg/m² d 1-4 / 4-6 wks	0.18 mg/kg or 7.5 mg/m² d 1-4 / 4-6 wks	0.13 mg/kg or 6 mg/m² d 1-4 / 4-6 wks
Thalidomide	100 mg/d	50 mg/d	50 mg qod
Lenalidomide	25 mg/d d 1-21 / 4 wks	15 mg/d d 1-21 / 4 wks	10 mg/d d 1-21 / 4 wks
Bortezomib	1.3 mg/m² twice weekly d 1,4,8,11 / 3 wks	1.3 mg/m² once weekly d 1,8,15,22 / 5 wks	1.0 mg/m² once weekly d 1,8,15,22 / 5 wks
Prednisone	60 mg/m² d 1-4 or 50 mg qod	20 mg/m² d 1-4 or 25 mg qod	15 mg/m² d 1-4 or 12.5 mg qod
Cyclophosphamide	100 mg/d d1 -21/ 4 wks or 300 mg/m²/d d 1,8,15 / 4 wks	50 mg/d d 1-21 / 4 wks or 150 mg/m²/d D 1,8,15 / 4 wks	50 mg qod d 1-21 / 4 wks or 75 mg/m²/d d 1,8,15 / 4 wks

Palumbo A, et al. *Blood*. 2011;118(17):4519-4529.

Case 2

- It has been decided to treat ST with lenalidomide + bortezomib + dexamethasone (RVD)
- Lenalidomide 25 mg days 1-21 + low-dose vs. high dose dexamethasone Q28days
  - Low dose: 40 mg days 1, 8, 15, 22
  - High dose: 40 mg days 1-4, 9-12, 17-20
  - N = 445
  - 1- year OS = 87% (high dose) vs. 96% (low dose) , *P* = .0002
  - DVT = 26% vs. 12%, *P* = .0003
  - Infection or pneumonia = 16% vs. 9%, *P* = .04
  - Fatigue = 15% vs. 9%, *P* = .08

Rajkumar SV, et al. *Lancet Oncol*. 2010;11(1):29-37.

Case 2: Patient ST

- She also has prexisting diabetes with peripheral neuropathy on gabapentin 300mg TID.
- What is your recommendation?

Peripheral Neuropathy (PN)

- Higher risk of PN
  - In patients presenting with subclinical PN
  - After prolonged therapy
  - In elderly patients
- Clinical manifestations include sensory symptoms, motor symptoms, and autonomic dysfunction

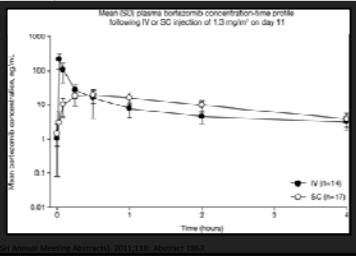
Bortezomib Dose Modification with PN

Severity	Action
Grade 1	Continue as scheduled
Grade 1 w/ pain or grade 2	Reduce dose per course to 1.0 mg/m²
Grade 2 w/ pain or grade 3	Withhold bortezomib treatment until PN resolves, reinitiate at a dose of 0.7 mg/m² once weekly
Grade 4	Discontinue therapy

Palumbo A, et al. *Blood*. 2008;111:3968-3977.
Argyriou AA, et al. *Blood*. 2008;112:1593-1599.

Bortezomib SQ vs. IV

Pharmacokinetics	C_{max} (ng/mL)	T_{max} (min)	AUC_{last} (ng.hr/mL)
SQ	20.4	30	155
IV	223	2	151
Pharmacodynamics	E_{max} (%)	E_{max} (min)	AUE_{72hr} (%.hr)
SQ	63.7	120	1714
IV	69.3	5	1383



Moreau P, et al. *Blood* (ASH Annual Meeting Abstracts). 2011;118. Abstract 1863.

Bortezomib SQ vs. IV

Adverse Events, %	Bortezomib SQ n = 147	Bortezomib IV n = 74
Any grade (treatment-related)	95 (84)	99 (91)
Grade ≥ 3 (treatment-related)	57 (39)	70 (55)
Serious	36	35
Grade 3/4 hematologic toxicity, %		
Hemoglobin level	14	12
White blood cell number	8	18
Absolute neutrophil count	22	28
Platelet count	18	23
Peripheral neuropathy, %	38*	53
Grade ≥ 2	24†	41
Grade ≥ 3	6‡	16

*P = .044 †P = .012; ‡P = .026

Moreau P, et al. *Lancet Oncol.* 2011;12:431-440.

Case 2

ST is a 76 y/o African American female who recently presented to her PCP for increasing pain in her back. PMH: Type 2 DM, HTN, CAD s/p stents, depression. ST was diagnosed with Stage IIIa IgG lambda multiple myeloma based on the following labs and exams:

- WBC: 12
- Scr: 1.7
- β_2-microglobulin: 7 mcg/ml
- Hgb: 8
- Ca: 12
- IgG: 6080 (620-1520 mg/dL)
- Plts: 112
- Albumin: 4
- IgM: 9 (4-350 mg/dL)
  - λ free light chains: 306 (0.57-2.63 mg/dL)
  - λ IgA: 5 (50-370 mg/dL)
- Plasma viscosity: 2.47 (1.35-1.85)
- Skeletal survey shows multiple lytic lesions T8-T11

Treatment of Bone Disease in MM

- NCCN guidelines
  - Bisphosphanates
  - Radiation for palliation, pain, cord compression, fracture
- Denosumab
  - FDA approved for the prevention of skeletal-related events in patients with bone metastases from solid tumors (NOT in multiple myeloma)

The NCCN Clinical Practice Guidelines in Oncology™ Multiple Myeloma (Version 1.2012). © 2011 National Comprehensive Cancer Network, Inc. Available at: NCCN.org. Accessed [March 13, 2012]. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

Treatment of Bone Disease in MM

- Denosumab
  - 120 mg SQ vs. zoledronic acid, N = 1176 (only 10% MM)
  - CrCl >30 mL/min
  - Noninferior
- Ibandronate 6 mg, N=40
  - CrCl 30-59 mL/min, N=10
  - CrCl <30 mL/min, N=9
    - AUC 65% higher vs CrCl >60 mL/min, p<0.01
    - Cmax similar
    - No changes in renal function or SCr
- Pamidronate 30 mg over 30 min x 3 days
  - Case report, MM patient receiving dialysis
- Bisphosphonates in elderly MM

Bergner R, et al. *J Clin Pharmacol.* 2007;47(8):942-950; Henry DH, et al. *J Clin Oncol.* 2011;29(9):1125-1132. 29:1125-1132; Trimarchi H, et al. *Nat Clin Pract Nephrol.* 2006;2(8):459-463; Mehta J, et al. *Blood.* 2010;116(13):2215-2223.

VTE and MM

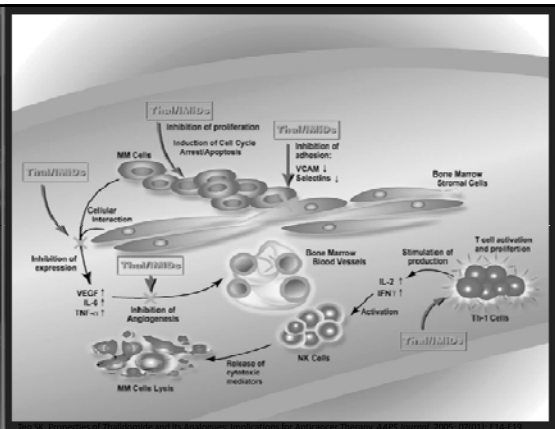
- Increased incidence of VTE
  - Estimation varies 3% - 10%
- Mechanisms behind VTE in MM not known
  - Possible roles for procoagulant antibody formation, paraprotein interference within fibrin structure, activated protein C resistance and endothelial damage.

ASCO Guidelines: Lyman GH, et al. *J Clin Oncol.* 2007;25(34):5490-5505.

Thalidomide and Lenalidomide

- Addition to therapy regimen improves response rates
  - Thalidomide alone: 25-35%
  - Thalidomide plus dexamethasone: 50%
  - Thalidomide, dexamethasone, alkylating agent: 70%
- Mechanism of action
  - Inhibits angiogenesis and induces apoptosis
  - Inhibits TNF-a and type 1 helper T-lymphocytes
  - Induces IFN-β and type 2 helper T-lymphocytes

ASCO Guidelines. Lyman GH, et al. *J Clin Oncol.* 2007;25(34):5490-5505.
Palumbo A, et al. *Leukemia.* 2007; 1-10.



Teo SK. Properties of Thalidomide and its Analogues: Implications for Anticancer Therapy. *AAPS Journal.* 2005; 07(01): E14-E19. DOI: 10.1208/aapsj070103

VTE and Thalidomide

- Serum thrombomodulin levels
  - Decreased during 1st month of thalidomide therapy
  - Gradual recovery over following two months
- Protease activated receptor-1 (PAR-1)
  - Endothelial exposure altered by thalidomide after doxorubicin exposure
  - Can increase thrombin binding to the vascular endothelium
- Activated protein C (APC)
  - Patients with APC resistance in absence of factor V Leiden had higher incidence of DVT when treated with thalidomide

Corso A, et al. *Ann Hematol.* 2004;83(9):588-591.
Kaushal V, et al. *J Thromb Haemost.* 2004;2(2):3273-84.
Zangari M, et al. *Blood Coagul Fibrinolysis.* 2002;13(3):187-192.

Therapy-specific Incidence of VTE

Therapy	Incidence	Comments
Thalidomide alone	1-3%	
Thalidomide + dexamethasone	17-26%	Thal/dex vs dex: 17% vs 3%
Thalidomide + chemotherapy	12-28%	
Oral melphalan + prednisone	1.5-2%	
Melphalan + pred + thalidomide	12-18.5%	

Dunkley S, Gaudry L. J Thromb Haemost. 2007;5:1323-1325.
Palumbo A, et al. J Thromb Haemost. 2006;4:1842-1845.
Palumbo A, et al. *Lancet.* 2006;367:825-831.
Kyle RA, Rajkumar SV. *N Engl J Med.* 2004;351(18):1860-1873.
ASCO Guidelines. Lyman GH, et al. *J Clin Oncol.* 2007;25(34):5490-5505.
Rajkumar SV, et al. *J Clin Oncol.* 2006;24(3):431-436.
Singhal S, et al. *N Engl J Med.* 1999;341:1565-1571.
Zangari M, et al. *Blood.* 2001;98:1614-1615.

ASCO Recommendations

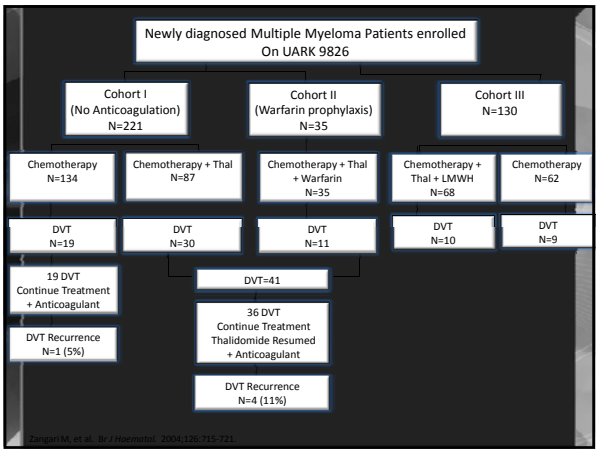
- Routine anticoagulation for VTE prophylaxis is not recommended for *ambulatory* patients receiving chemotherapy
- Patients receiving thalidomide or lenalidomide with dexamethasone or chemotherapy warrant prophylaxis

ASCO Guidelines. Lyman GH, et al. *J Clin Oncol.* 2007;25(34):5490-5505.

LMWH Literature

Study	Therapy	Prophylaxis	Methods	Results
GIMEMA	MP vs MPT	Enoxaparin 40mg	Chemotherapy randomized Prophylaxis due to protocol amendment	17% vs 9% did not complete 6 cycles MPT therapy; before/after 20% vs 3.1% as a subgroup
UARK 9826	Chemo +/- thalidomide	Enoxaparin	3 cohorts; amended protocol from low-dose fixed warfarin; open-label	DVT: 11/35 vs 30/87 vs 19/134

Palumbo A, et al. *Lancet.* 2006;367:825-831.
Zangari M, et al. *Br J Haematol.* 2004;126:715-721.
Alikhan R, et al. *Blood Coagul Fibrinolysis.* 2003;14:341-346.



Zangari M, et al. *Br J Haematol*. 2004;126:715-721.

Prophylactic Low-dose Aspirin

- 105 patients were treated with vincristine, doxorubicin, dexamethasone, and thalidomide (VAD-t)
- High rate of venous thrombosis noted after 35 patients in the trial
- Low-dose aspirin initiated in 26 of the original 35 patients
- Thrombosis
  - 19% who received aspirin from start of enrollment
  - 15% who received aspirin after the study started
  - 58% of those who never received aspirin

Baz R, et al. *Mayo Clin Proc*. 2005;80:1568.

Prophylactic Low-dose Aspirin

Study	Methods		Therapy
I	Retrospective	Amendment	Thal/dex + clarithromycin; ASA added to regimen
II	Prospective	Randomized	Dexamethasone, ± thalidomide & ASA, ± clarithromycin
III	Prospective	Descriptive	Lenalidomide & ASA

Summary of TEs in studies I to III

Thromboemolic events	Grade 2 (percent)	Grade ¾ (percent)	Grade 5 (percent)	Comments
Study I: BLT-D	8	9	-	No TEs after ASA was added to study regimen
Study II: Randomized BLT-D				
Group 1	-	6.6	-	Thalidomide, dexamethasone, clarithromycin (if needed) and ASA
Group 2	-	21.4	-	Dexamthasone and clarithromycin (if needed)
Study III: BiRD	-	10.8	1.4	

Niesvizky R, et al. *Leuk Lymphoma*. 2007;48(12):2330-2337.

Prophylactic Low-dose Aspirin

- Not designed to assess thromboembolic risk
- No *a priori* definition of TE risk factors
- 3 study designs

Table IV. Rate of thrombosis in patients receiving low-dose aspirin with thalidomide/dexamethasone

	Total number of patients	Number of patients (%): Thrombosis	Number of patients (%): No Thrombosis
Thalidomide/ dexamethasone: Low-dose aspirin	15	1 (6.6)	14 (93)
Dexamethasone: No Aspirin	14	3 (21.4)	11 (79)
OR 3.82 (exact 95% CI, 0.25, 214.45); Fisher's exact *p* value (2-sided)=0.33.			

Niesvizky R, et al. *Leuk Lymphoma*. 2007;48(12):2330-2337.

Prophylactic Aspirin

Study	Therapy	Prophylaxis	Methods	Occurrence of thrombosis
Knight[1]	Lenalidomide + dexamethasone (2 studies)	Low-dose aspirin	Preliminary report	20/87 w/ erythropoeitin 4/83 w/o erythropoeitin 0/23 w/ ASA 52/668 w/o ASA
Zonder[2,3]	Lenalidomide + dexamethasone	Full-dose aspirin	Preliminary report After protocol amendment	9/12 w/o ASA 6 % w/ ASA[1] 19 % w/ ASA[2]

1. Knight R, et al. *N Engl J Med*. 2006;354(19):2079-2080.
2. Zonder JA, et al. *Blood*. 2006;108(1):403.
3. Zonder JA, et al. *Blood*. 2010;116(26):5838-41.

Warfarin

- Low-dose warfarin
  - 1 mg daily
  - Has been studied as prophylaxis for central venous catheter thrombosis
- Full anticoagulation
  - Goal INR 2-3

Coumadin (warfarin sodium) package insert. Princeton, NJ: Bristol-Myers Squibb; 2011.

Fixed Low-Dose Warfarin

Study	Therapy	Prophylaxis	Methods	Results
Miller[1]	MM: VAD-t or VDT CLL: FT	1mg if ≤ 70 kg 2mg if > 70 kg	No concurrent ASA; baseline hypercoagulable work-up; duration of treatment coincided with therapy (avg 4 months)	No significant difference; compared to historical controls
UARK 9826[2]	Chemo +/- thalidomide	1mg warfarin	Cohort 2 (chemo + thal and warfarin)	DVT: 11/35 (c+t+w) vs 30/87 (c+t) vs 19/134 (c) Trial stopped
Weber[3]	Thalidomide vs thal/dex	1mg warfarin	Protocol amendment	16/40 patients receiving thal/dex continued trial, but switched to therapeutic dose of warfarin or LMWH

1. Miller KC, et al. *Leuk Lymphoma*. 2006;47(11):2339-2343.
2. Zangari M, et al. *Br J Haematol*. 2004;126(5):715-721.
3. Weber D, et al. *J Clin Oncol*. 2003;21(1):16-19.

Risk Assessment Model

Individual risk factors	Recommended therapy
Obesity (≥ 30 kg/m^2)	If no risk factor or any one risk factor is present: Aspirin 81-325 mg once daily
Previous venous Thromboembolism	
Central venous catheter or pacemaker	
Associated disease: •Cardiac disease •Diabetes •Chronic renal disease •Immobilization •Acute infection	If two or more risk factors are present: LMWH (equivalent to enoxaparin 40mg once daily) OR Full-dose warfarin (target INR 2-3)
Surgery •General surgery •Trauma •Any anesthesia	
Medications: Erythropoietin	
Blood clotting disorders	
Myeloma-related risk factors •Diagnosis •Hyperviscosity	
Myeloma therapy •High-dose dexamethasone (≥ 480 mg/month) •Doxorubicin •Multiagent chemotherapy	LMWH (equivalent to enoxaparin 40mg once daily) Full-dose warfarin (target INR 2-3)

Palumbo A, et al. *Leukemia*. 2008;22(2):414-423.

VTE Prophylaxis

- Risk factors:
  - Individual
    - History of VTE, age, obesity, cardiac disease, immobilization, presence of central catheter, surgical procedures
  - Disease-related
    - Multiple myeloma diagnosis, hyperviscosity
  - Therapy-related
    - Immunomodulatory therapy (thalidomide, lenalidomide) in combination with high-dose steroids

Gay F, Palumbo A. *Med Oncol*. 2010;27(suppl 1):S43-S52.

VTE Prophylaxis Options

- If none or 1 individual or MM-related risk factor present:
  - Aspirin (81 mg to 325 mg daily)
- If 2 or more individual or myeloma-related risk factors present:
  - Low molecular weight heparin (LMWH)
  - Full dose warfarin (target INR 2-3)
- Therapy-related risk factors should be considered high-risk:
  - LMWH or full dose warfarin

Gay F, Palumbo A. *Med Oncol*. 2010;27(suppl 1):S43-S52.

Summary

- Evaluate patient specific risk factors
  - Concern for thrombocytopenia—especially with lenalidomide
  - Renal function
- Thalidomide-associated therapy
  - Full dose warfarin for high risk patients
  - LMWH for low to moderate risk patients
- Lenalidomide-associated therapy
  - Aspirin
    - UK Thrombosis Prevention Trial

VTE Prophylaxis in MM: Guidelines

- NCCN guidelines
  - Aspirin 81-325 mg (low risk outpatients)
  - Warfarin, INR 2-3
  - LMWH
  - Fondaparinux
  - UFH
- CHEST guidelines
  - Prophylactic LMWH or LDUH over no prophylaxis
  - Aspirin is not addressed for cancer patients
  - VKAs

The NCCN Clinical Practice Guidelines in Oncology™ Venous Thromboembolic Disease (Version 2.2011). © 2011 National Comprehensive Cancer Network, Inc. Available at: NCCN.org. Accessed [April 3, 2012]. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
Kahn SR, et al. *Chest*. 2012; 141(2 Suppl):e195S-226S.

VTE Prophylaxis in MM: New Agents

- Rivaroxaban
  - FDA approved:
    - To reduce the risk of stroke and systemic embolism in patients with nonvalvular Afib
    - Prophylaxis of deep vein thrombosis (DVT) in patients undergoing knee or hip replacement
- Dabigatran

Xarelto (rivaroxaban) package insert. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2011.
Pradaxa (dabigatran etexilate mesylate) package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2012.

Patient Case 3

- 67 year old female was induced with VAD-t (vincristine, doxorubicin, dexamethasone, thalidomide)
- She has received 2 cycles of chemotherapy and now presents to the hospital with unilateral pain and swelling in her left lower leg.
- The VAD-t therapy has been effective, so her physician wants her to receive 2 more cycles of induction therapy before her stem-cells are harvested
  - Would you proceed with therapy?
  - Would you recommend thromboprophylaxis?

Patient Case 4

- 73 year old male presents with refractory multiple myeloma
- He is not a candidate for transplant and was previously treated with MP (melphalan plus prednisone).
- His medical history is significant for a DVT of idiopathic cause when he was 55
- His physician wants to treat him with thal/dex (thalidomide) since he previously responded to MP.
  - Would you proceed with therapy?
  - Would you recommend thromboprophylaxis?

Bortezomib and Herpes Zoster Reactivation

- Incidence of herpes zoster in randomized Phase 3 frontline MM trials

Trial	Bortezomib Arm No Prophylaxis	Bortezomib Arm with Prophylaxis	Control Arm
VISTA	13%	3%	4%
IFM 2005-01*	NA	9%	2%
HOVON-65/GMMG-HD4	15%	9%	2%

*No antiviral prophylaxis for herpes zoster was specified in the protocol.

- Retrospective analysis of 125 patients on bortezomib and antiviral prophylaxis found no VZV reactivation
  - 100% compliance
  - Well tolerated

VZV= Varicella-zoster virus
San Miguel, et al. *N Engl J Med*. 2008;359:906-917.
Harousseau, et al. *J Clin Oncol*. 2010;28(30):4621-4629.
Sonneveld, et al. *Blood*. 2008;112. Abstract 653.
Vickrey E, et al. *Cancer*. 2009;15(1):229-232.
Chanan-Khan A, et al. *J Clin Oncol*. 2008;26(29):4784-4790.

MM Summary

- Treatment decisions
  - Transplant candidate?
  - Renal function
  - Comorbidities
  - Multidrug regimens are preferred
- Supportive care
  - VTE prophylaxis recommended with thalidomide/lenalidomide regimens
  - Bisphosphonates are preferred for bone disease
  - Patient specific factors are very important
  - Zoster prophylaxis for bortezomib regimens

Question & Answer Session