Living With
MYELOMA
Treatment and
Side Effects Management

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

Welcome & Introductions

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S. Vincent Rajkumar, MD

Mayo Clinic

Thank you Dr. Rajkumar for volunteering your time and expertise for our program today.

The professional volunteers who present our patient education programs receive no financial compensation for their time.

Multiple Myeloma
Treatment and Side Effects Management

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Mayo Clinic Comprehensive Cancer Center

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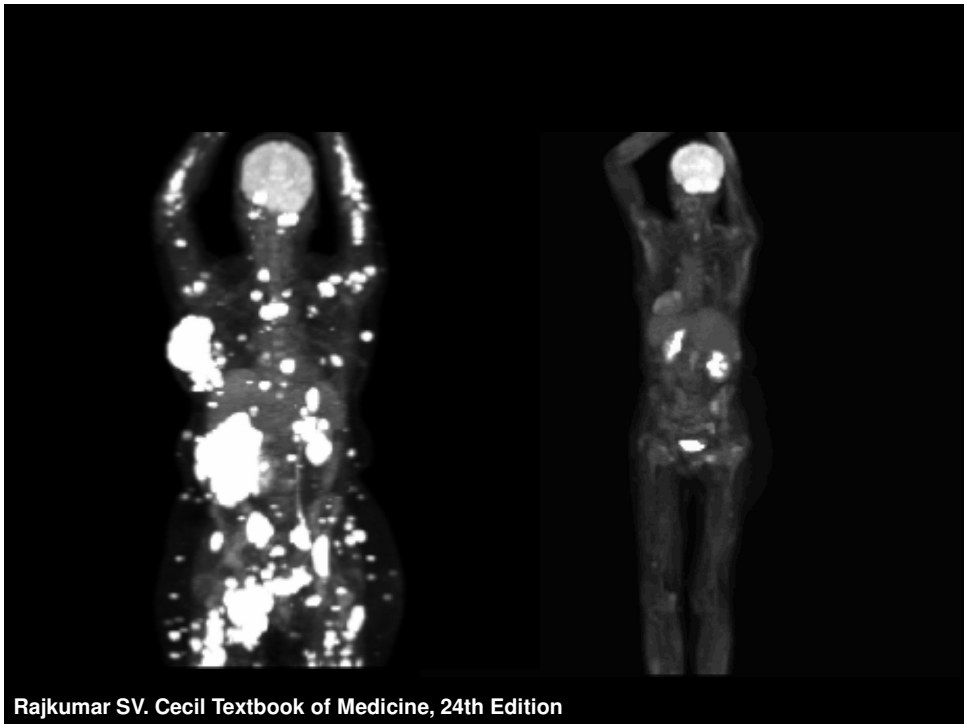
Myeloma

- 10% of all malignant hematologic neoplasms
- ~20,000 new cases each year in USA

Jemal A, CA Cancer J Clin 2009;59:225-249



Rajkumar SV. Cecil Textbook of Medicine, 24th Edition

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Survival

Study	3 year survival (%)
MP	42%
MPT	65%
VMP	70%
Rd	70%
2013	>80%

Median survival >7-10 Years

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PROGNOSIS IN MYELOMA

Prognostic determinant	Standard risk	High risk
Host factors	ECOG performance status 0-2 Normal renal function	ECOG performance status 3 or 4 Renal failure (serum creatinine ≥ 2.0) Advanced age
Tumor burden	Durie-Salmon stage I, II	Durie-Salmon stage III
Tumor biology (disease aggressiveness)	Hyperdiploidy t(11;14) t(6;14)	t(4;14)* t(14;16) t(14;20) 17p- High LDH High plasma cell proliferative rate High-risk signature on gene-expression profiling

Rajkumar SV et al. Blood 2011;118:3205-3211; Russell SJ et al. Lancet Oncology 2011

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Myeloma Risk-Stratification

High-Risk	*Intermediate-Risk*	*Standard-Risk*
▪ Del 17p (p53) ▪ t(14;16) (C-MAF) ▪ t(14;20) (MAF-B) ▪ High-risk GEP (gene expression profile) *Median survival ~3 years*	▪ t(4;14) (FGFR3/ MMSET)	All others including: ▪ Hyperdiploid (trisomies) ▪ t(11;14) (CCND1) ▪ t(6;14) (CCND3) *Median survival >7 years*

**Presence of trisomies converts high risk into standard risk*

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Myeloma Risk-Stratification

*High-Risk**	*Intermediate-Risk**	*Standard-Risk*
▪ Del 17p ▪ t(14;16) ▪ t(14;20) ▪ GEP defined high-risk	▪ *t(4;14)*	▪ Hyperdiploid ▪ t(11;14) ▪ t(6;14)
CR appears critical	*Bortezomib (Velcade®) Critical*	*Excellent Outcome* regardless of how you treat

Outcome similar to standard risk if treated with bortezomib

**Presence of trisomies ameliorates high risk*

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Myeloma Drugs

Old Drugs	*New Active Drugs*	*New ?active drugs*
▪ Alkylators ▪ Steroids ▪ Anthracyclines (Adriamycin®, Doxil®) ▪ Bortezomib (Velcade®) ▪ Thalidomide (Thalomid®) Lenalidomide (Revlimid®)	▪ Carfilzomib (Kyprolis®) ▪ MLN 9708 ▪ Marizomib (NPI –52) ▪ Pomalidomide (Pomalyst®)	▪ Panobinostat ▪ Elotuzumab ▪ ARRY-520 ▪ Anti CD38 mo Abs ▪ Cyclin D inhibitors

Rajkumar SV. 2013

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Myeloma Treatment Strategies

Aggressive therapy

- Triplet or quadruplet induction
- Early transplant
- Lenalidomide maintenance

"Cure" Approach

Emphasis is on CR

Sequential Therapy

- Doublet or "mild" triplet induction
- Early or late transplant
- Maintenance based on risk

"Control" Approach

Emphasis is on QOL

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Approach for New Patients

Transplant Eligible	Transplant Ineligible
• ~~Melphalan-Containing Regimens~~	• Melphalan-Containing Regimens
• Non Melphalan Containing Regimens	• Non Melphalan Containing Regimens

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Induction Therapy: Transplant candidates

- Typically 4 cycles, then harvest stem cells
- Non-melphalan containing regimen

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Major Treatment Regimens

Doublets

- **TD**
- **RD**
- **VD**

Triplets*

- **VTD**
- **VRD**
- **Carfilz-Rd**
- **PAD**
- **VCD (CyBorD)**

***Other triplets: Anthracycline containing regimens; MLN9708-Rd**

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Additional Options in Transplant Ineligible Patients

- MP
- VMP
- MPT

EVOLUTION RANDOMIZED TRIAL VRD vs VCD vs VDCR

Response, n (%)	VDCR (n = 48)	VRD (n = 42)	VCD (n = 50)
CR	25%	24%	30%
≥ VGPR	58%	51%	44%
ORR (≥ PR)	88%	85%	82%

Kumar S, et al. Blood 2012;119(19):4375-82.

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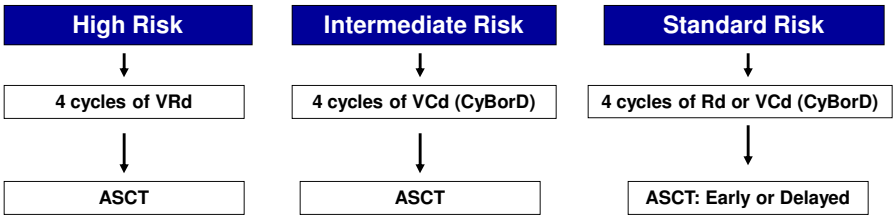
Transplant Eligible



Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110
v9 Revised and updated: Jun 2011

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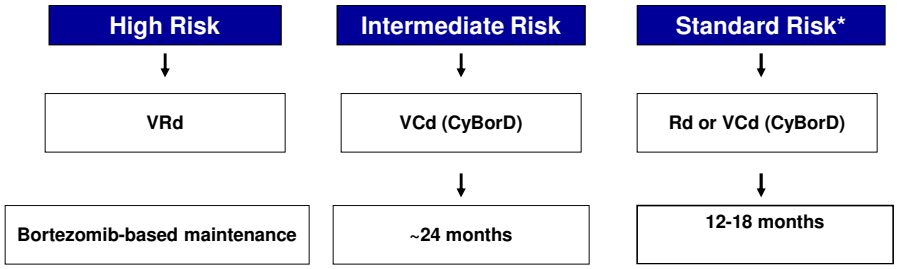
Transplant Ineligible



Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110
v9 Revised and updated: Jun 2011

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Lenalidomide Maintenance

Trial	Regimen	*n*	Median PFS (months)	*P* value for PFS	3-year overall survival rate (%)*	Median overall survival (months)	*P* value for overall survival	Second cancers (%)‡	Reported *P* value for second cancer incidence
McCarthy *et al.* (2012)[1]	Placebo Lenalidomide maintenance	229 231	27 46	<0.001	80 88	NR NR	0.03§	2.6 7.7	0.008
Attal *et al.* (2012)[2]	Placebo Lenalidomide maintenance	307 307	23 41	<0.001	84 80	NR NR	0.70	3.0 7.5	0.002
Palumbo *et al.* (2012)[3]	MP MPR MPR plus lenalidomide maintenance	154 153 152	13 14 31	<0.001	66 62 70	NR NR 45	NS	3 7 7	NR

Rajkumar SV. Nat Rev Clin Oncol 2012

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Newly Diagnosed Myeloma with special circumstances

- Plasma cell leukemia (PCL)
- Extensive extramedullary disease (EMD)
- Acute renal failure due to cast nephropathy

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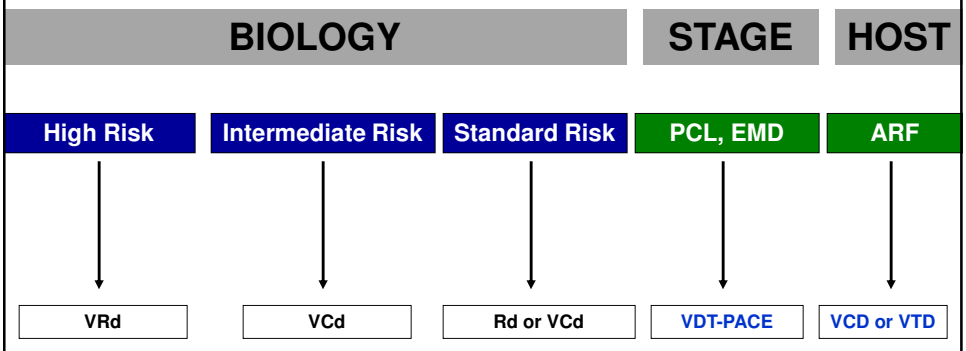
RISK-ADAPTED THERAPY



- Once weekly Dex (except VDT-PACE)
- Once weekly bortezomib (Velcade®) (except ARF; VDT-PACE)

PCL= Plasma cell leukemia; EMD= Extramedullary Disease; ARF= Acute renal failure
Rajkumar SV. Am J Hematol 2013; Nature Rev Oncol 2011

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Treatment of relapse

- Indolent relapse
- Aggressive relapse

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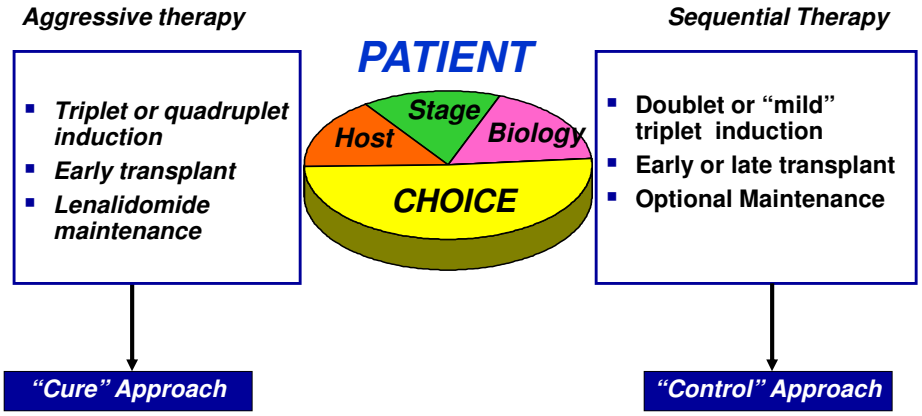
Myeloma Treatment



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Randomized Trials

- **MM 020:** MPT vs Rd (18 mo) vs Rd (indef)
- **DFCI/IFM:** VRd vs Transplant

Upcoming

- **E1A11:** CRd vs VRd
- **SWOG:** VRd vs VRd plus elotuzumab

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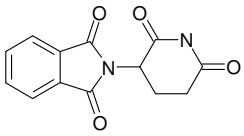
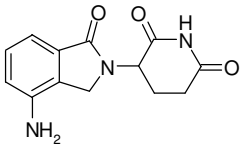
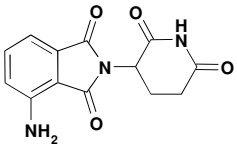
Thalidomide (Thalomid®)	Lenalidomide (Revlimid®)	Pomalidomide (Pomalyst®)
		
100-200 mg/d	15-25 mg/d	1-4 mg/d
Neuropathy Constipation Sleepiness Blood Clots	Low Blood Counts Rash Blood Clots	Low Blood Counts Rash

Structurally similar, but functionally different both qualitatively and quantitatively

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Bortezomib (Velcade®)

Neuropathy
GI side effects
Low blood counts
Infections

Carfilzomib (Kyprolis®)

Low Blood Counts
Infections
Shortness of breath

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Side-Effect Management

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Dexamethasone (Decadron®) Dosing

Doublets

- Td
- Rd
- Vd

Triplets

- VCd
- VTd
- VRd

Lowers Risk of Clots, Pneumonias, Rash, Cardiac Side Effects, etc, etc

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Bortezomib (Velcade®) Dosing and Prevention of Neuropathy

Lower risk of grade 3 or higher neuropathy with once-weekly dosing vs twice-weekly

Similarly, lower risk with SQ versus IV dosing

Palumbo A et al. JCO 2010;28:5101-5109

Mateos M. Lancet Oncol 2010; 11: 934–941; Moreau P. et al. Lancet Oncol 2011;12:431-40

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Blood Clots

- Prevention versus Treatment
- Blood thinners:
  - Aspirin
  - Coumadin
  - Low Molecular weight Heparin

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Stomach Ulcers and Bleeding

- Lower Dex dose
- Prilosec or similar drugs
- Antacids

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OTHER GENERAL TIPS

- Dex at bedtime
- VCD (CyBorD) instead or Vel/Dex
  - Once-weekly
  - SQ
  - 3 on 1 off
- Lower dose of Lenalidomide in Elderly

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Infection Prophylaxis

- Induction Phase
  - Bacterial Prophylaxis
    - All patients should receive antibacterial prophylaxis during induction
    - Bactrim SS daily for 4 months
    - If sulfa allergy or induction with Lenalidomide: Levaquin or Penicillin can be used
  - Viral Prophylaxis
    - Prophylaxis for herpes zoster with Bortezomib containing Regimens
    - Acyclovir 400mg BID or Valacyclovir 500mg daily
  - Pneumocystis Prophylaxis
    - Bactrim prophylaxis recommended if long term steroid therapy planned

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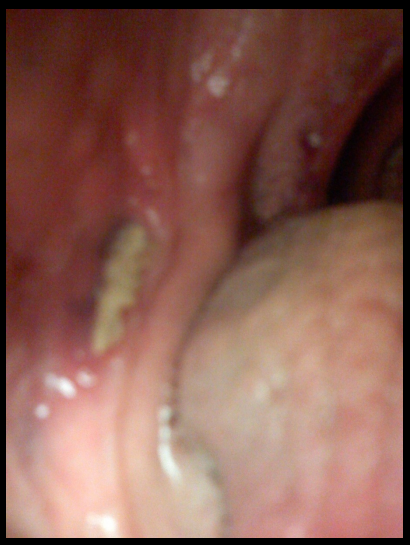
Supportive Care: Bisphosphonates

- All patients who have documented bone disease
- Not indicated in smoldering MM
- Pamidronate or Zoledronic acid

Lacy MQ. Mayo Clin Proc Aug 2006



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Supportive Care

- **Pain meds**
- **Kyphoplasty or Vertebroplasty**
- **Radiation**

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NEWS & VIEWS

HAEMATOLOGICAL CANCER

Redefining myeloma

S. Vincent Rajkumar, Giampaolo Merlini and Jesus F. San Miguel

The current definition of multiple myeloma is outdated. The diagnosis requires evidence of overt end-organ damage, preventing initiation of early therapy when the malignancy is at its most susceptible stage. We propose an evidence-based approach using more-sensitive and highly specific biomarkers to update the definition of this disease.

Rajkumar, S. V. *et al. Nat. Rev. Clin. Oncol.* advance online publication 31 July 2012; doi:10.1038/nrclinonc.2012.128

Multiple myeloma is unique among cancers in that a clinician's opinion on whether or not 'end-organ' damage is present is required to make a diagnosis of malignancy.

between MGUS and myeloma, in which the risk of progression to malignancy in the first 5 years following diagnosis is 10% per year.[5] SMM includes a heterogeneous population

Key points

- The current status quo in which the definition of myeloma requires the presence of serious end-organ damage needs to change
- Highly specific biomarkers are being developed that can identify patients with smoldering multiple myeloma who have an almost inevitable risk of progression to multiple myeloma within 2 years
- These markers promise to usher in a new definition for myeloma that will enable therapy at an early susceptible stage of malignancy and help prevent destructive end-organ damage

treatment options for myeloma, until recently, were limited: alkylators, cortico-

Rajkumar SV, Merlini G, San Miguel JF. Nat Rev Clin Oncol 2012

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Biomarkers of High Predictive Value in "SMM"

- **BM Plasma cells 60% or more**
- **Free light chain ratio 100 or more**
- Absence (<5%) of normal PCs by immunophenotyping
- Deletion 17p
- ≥3 focal lesions on MRI studies
- Evolving pattern
- Unexplained decrease in CrCl ≥25% accompanied by a rise in urinary M protein or serum FLC levels
- Immunopariesis

Rajkumar SV, Merlini G, San Miguel JF. Nat Rev Clin Oncol 2012

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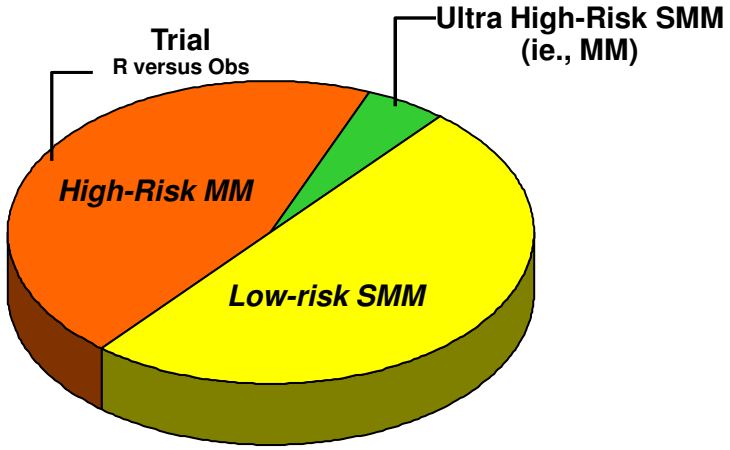
High-Risk Smoldering Multiple Myeloma



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Contact

- rajks@mayo.edu
- @VincentRk (Twitter)
- @MayoMyeloma (Twitter)

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Question and Answer Session

Dr. Rajkumar's slides are available for download at www.LLS.org/programs

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MYELOMA ONLINE CHAT

- **Every Tuesday evening from 8:00 PM – 10:00 PM ET**
- **Visit www.LLS.org/chat to register or for more information**

The Leukemia & Lymphoma Society's (LLS) Co-Pay Assistance Program offers financial assistance to qualified myeloma patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

- **WEBSITE: www.LLS.org/copay**
- **TOLL-FREE PHONE: (877) LLS-COPAY**

For more information about myeloma and other LLS programs, please contact an LLS Information Specialist.

- **TOLL-FREE PHONE: (800) 955-4572**
- **EMAIL: infocenter@LLS.org**