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Transplantation in Multiple Myeloma

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At the end of the session, the participant will be able to:

- Describe the appropriate diagnostic workup for patients with newly diagnosed multiple myeloma and optimal treatment of transplant eligible patient
- Review current recommendations regarding timing of transplantation and post transplant maintenance
- Identify strategies to manage adverse effects of treatment in patients with multiple myeloma who receive treatment with systemic therapy in the frontline and/or relapsed setting
- List important factors to provide appropriate care and counsel for patients and families regarding diagnosis and supportive care

Meet Jane

- Jane is a very active 38 year-old mother of 2.
- Stays at home but trained as a nursing assistant. Wants to go back to school for RN degree
- On routine physical for school she has the following labs:

CBC values

- WBC count 3,300/µL
- Hemoglobin 9.1 g/dL
- Platelet count 158,000/µL

Chemistry Values

- Creatinine 1.3 g/dL
- Calcium 10.2 mg/dL
- Albumin 3.2 g/dL
- Total protein 10.4 g/dL

ARS Question

You look at her labs. Which of the result(s) would be most concerning?

a) *Anemia*. This is most likely from childbirth so not to worry. No further evaluation is needed

b) *Elevated Protein level.* Make sure she isn't eating too much protein in her diet

c) *Anemia and elevated total protein*. These can be signs of multiple myeloma

d) *Low white blood cell count*. She may have an infection.

ARS Question

What additional testing is to be anticipated?

a). Serum protein electrophoresis (SPEP)

b). Urine protein electrophoresis (UPEP)

c). Bone marrow aspiration and biopsy

d). Iron and anemia studies

e). All of the above

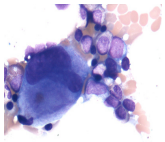
Case Presentation: Jane

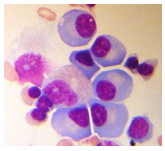
Additional labs were obtained:

- IgG 4,700 mg/dL and kappa 5,200 mg/dL
- M spike 3.8 g/dL
- Kappa free serum is 3500
- 24-hour urine < 0.16 g/24 hours
- β_2-microglobulin 3.9 mg/L
- Bone marrow biopsy showed 20% plasma cells
- Bone survey showed osteopenia, lytic lesions in bilateral femurs, calvarium
- *Diagnosis?*

→ *IgG Kappa MM , stage II ISS*

Multiple Myeloma: A Cancer of the Plasma Cells





- Healthy plasma cells produce immunoglobulins in response to foreign body invasion
- Myeloma cells produce abnormal immunoglobulin
  - 65% IgG; 20% IgA
  - 5% to 10% light chains (monoclonal kappa, lambda light chains, Bence Jones proteins)
  - Uncommon IgD, IgE, IgM, or nonsecretory disease

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Kyle RA, et al. Mayo Clin Proc. 2003;78:21-33.

20,000 Diagnosed With Multiple Myeloma Annually in United States; 10,000 Deaths

2011 Estimated New Cancer Cases Among US Males & Females

Rank	Cancer Type	Number Diagnosed	%
1	Prostate	240,890	15.1
2	Breast	230,480	14.4
3	Lung & Bronchus	221,130	13.8
4	Colon	141,210	8.8
5	Lymphoma	75,190	4.7
6	Melanoma	70,230	4.4
7	Bladder	69,250	4.3
8	Kidney	60,920	3.8
9	Thyroid	48,020	3.0
10	Endometrium	46,470	2.9
15	**Myeloma**	**20,520**	**1.3**
All Other Cancers		372,360	23.3
Total New Cases		1,596,670	100

2011 Estimated Cancer Deaths Among US Males & Females

Rank	Cancer Type	Number of Deaths	%
1	Lung & Bronchus	156,940	27.4
2	Colon	49,380	8.6
3	Breast	39,520	7.6
4	Pancreas	37,660	6.6
5	Prostate	33,720	5.9
6	Lymphoma	20,620	3.6
7	Liver	19,590	3.4
8	Ovary	15,460	2.7
9	Bladder	14,990	2.6
10	Esophagus	14,710	2.6
13	**Myeloma**	**10,610**	**1.9**
All Other Cancers		158,750	27.1
Total Cancer Deaths		571,950	100

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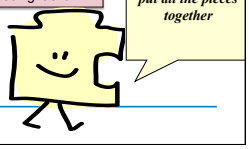
Howlader N, et al. (eds). *SEER Cancer Statistics Review, 1975-2008*, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER Web site in, 2012.

Initial Work-Up

Test	Possible Findings
CBC with differential	Anemia, thrombocytopenia
Chemistries	Renal insufficiency, hypercalcemia, decreased albumin, elevated LDH
β_2m	Often elevated
Serum protein electrophoresis	Presence of monoclonal protein
Urine protein electrophoresis	Presence of *Bence Jones* protein
Serum and urine immunofixation	Determines type of monoclonal protein
Free light chains	Elevation of the involved light chain

- Radiologic imaging
  - (Skeletal survey, MRI/CT, PET)
- Bone marrow biopsy



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CBC = complete blood count; β_2m = beta-2-microglobulin; LDH = lactate dehydrogenase.
Kyle et al, 2009b; NCCN, 2010.

MM Clinical Presentation

Disease Process	Clinical Presentation
M protein in serum or urine (97%)	Hyperviscocity with excessive M protein in the blood (common in IgA myeloma)
Clonal plasma cells (96%)	> 10% plasma cells in bone marrow
Skeletal involvement (80%)	Pain, reduced height, lytic lesions, pathologic fractures, osteoporosis, hypercalcemia
Anemia: Hgb < 12 g/dL (40%–73%)	Weakness, fatigue

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Hgb = hemoglobin.
Dispenzieri et al, 2009; Nau et al, 2008; Rajkumar, 2011.

Clinical Presentation (cont.)

Disease Process	Clinical Presentation
Renal insufficiency (20%–25%): light chain cast nephropathy (myeloma kidney)	Serum creatinine 2 mg/dL or greater
Hypercalcemia: Calcium > 11 mg/dL (13%–30%)	Anorexia, nausea, lethargy, polydipsia (excessive thirst), constipation, confusion
Neuropathy (20%)	Numbness, tingling, carpal tunnel syndrome (amyloidosis?)
Immune function deficiency (0.8–1.4 infections per patient-year)	Recurrent infections, bacteremia, pneumonia; "tumor fever" in < 1%

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Dispenzieri et al, 2009; Nau et al, 2008; Rajkumar, 2011.

Multiple Myeloma Disease Continuum

	Premalignant conditions		Plasma cell malignancy
	MGUS[1-4] (Monoclonal Gammopathy of Undetermined Significance)	**Smoldering Multiple Myeloma[1-5]**	**Multiple Myeloma**
M protein (per dL)	<3 g	≥3 g	M-spike or plasmacytoma
Clonal PC in bone marrow	<10%	≥10%	>10%
End-organ damage	None	None	1 or more CRAB criteria
Likelihood of progression	1% per year	10% per year for 5 years; 73% by 15 years	--
Symptoms	Asymptomatic	Asymptomatic	Symptomatic (~89%)
Active treatment	No	No	Yes

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1 Kyle RA, et al. *Mayo Clin Proc*. 2003;78:21-33.
2 International Myeloma Working Group. *Br J Haematol* 2003;121:749-57.
3 Jagannath, S. et al. *Clin Lymphoma Myeloma Leuk*. 2010 Feb;10(1):28-43.
4 Kyle RA, et al. *Curr Hematol Malig Rep*. 2010 Apr;5(2):62-9.
5 Mateos et al, *Blood* 114, Abstract 614, 2009

Disease Progression in Smoldering Multiple Myeloma and MGUS Patients

10% per year risk of progression: first 5 years

Important to identify ones who will need treatment; no benefit if tx too early

Disease Progression in SMM and MGUS Patients

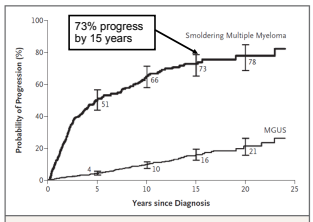

Figure 2. Probability of Progression to Active Multiple Myeloma or Primary Amyloidosis in Patients with Smoldering Multiple Myeloma or Monoclonal Gammopathy of Undetermined Significance (MGUS).
I bars denote 95% confidence intervals.

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Kyle RA, et al. N Engl J Med. 2007;356:2582-2590.

ARS Question

Which is NOT one of the "*CRAB*" criteria for diagnosis of myeloma?

1. Calcium elevation
2. Anemia
3. Bone lesions
4. Renal insufficiency or renal failure
5. Blood monoclonal proteins

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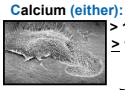
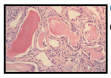
New Criteria "CRAB" Criteria: Myeloma Defining Event (MDE)

Calcium (either):
> 11mg/dl OR
≥ 1mg/dL above ULN

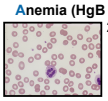


osteoclast

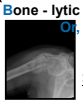
Renal dysfx (crea >2mg/dL OR (at least one):
eGFR ≤ 50
eGFR ↓ ≥35% in 1y
Bx confirmation)



Anemia (HgB <10g/dL OR 2g/dL below LLN)



Bone - lytic lesions on bone survey
Or, if x-rays neg., either):
≥ 3 hyperintense MRI foci
≥ 1 "large" MRI lesion
≥ 1 lytic lesion > 1cm PET/CT
≥ 3 small lytic PET/CT)



IMWG criteria, British Journal of Haematology 121: 749–57, 2003
Update in: Durie et al. Leukemia 20: 1467-73, 2006
Kyle, Rajkumar Leukemia 23: 3–9, 2009
Update Paris, 2011 (http://myeloma.org/pdfs/XIV-06_Panel2.pdf)

Arnett, T. www.bsoc.org.uk/gallery/arnett_osteoclast.jpg
Peter Maslak, ASH Image Bank 2004; 2004: 101227
Chapel et al. Essentials of Clinical Immunology 5th Ed., Blackwell Publishing
Peter Maslak, ASH Image Bank 2008; 2008: 8-00095.
Alexander et al. Eye 22: 1089-92, 2008

Multiple Myeloma Disease Staging: Two Systems

Stage	Durie-Salmon System[1]	International Staging System[2]
I	***All* of the following:** • Hemoglobin >10 mg/dL • Serum Ca normal or 12 mg/dL • By x-ray, normal bone or solitary bone plasmacytoma only • Low M-component production rates: IgG value <5 g/dL IgA value <3 g/dL Bence-Jones protein <4 g/24 hr	Serum beta-2 microglobulin <3.5 mg/L and Serum albumin ≥3.5 g/dL
II	**Fitting neither stage I nor III**	Not stage I or III
III	***One* or more of the following:** • Hemoglobin <8.5 mg/dL • Serum Ca >12 mg/dL • Advanced lytic bone lesions • Low M-component production rates: IgG value <5 g/dL IgA value <3 g/dL Bence-Jones protein <4 g/24 hr	Serum beta-2 microglobulin ≥5.5 mg/L

Jane is Stage II (B2M 3.9)

1. Durie BG, Salmon SE. Cancer. 1975;36:842-854.
2. Greipp PR, et al. J Clin Oncol. 2005;23:3412-3420.
3. Fonseca R, Bergsagel PL. *Diagnosis and Genetic Classification of Multiple Myeloma*. 2009 Cambridge University Press; Pages 1-17.

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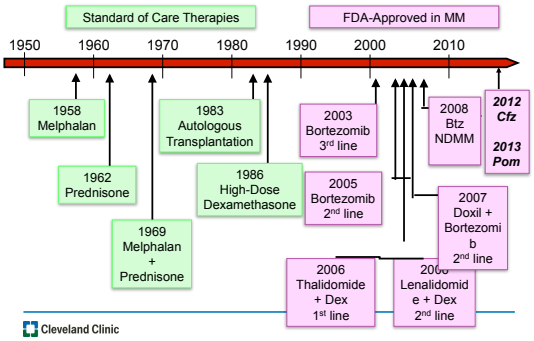
MM Treatment Options Have Expanded



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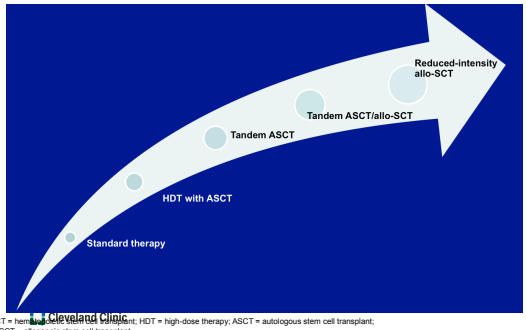
Advancements in HSCT



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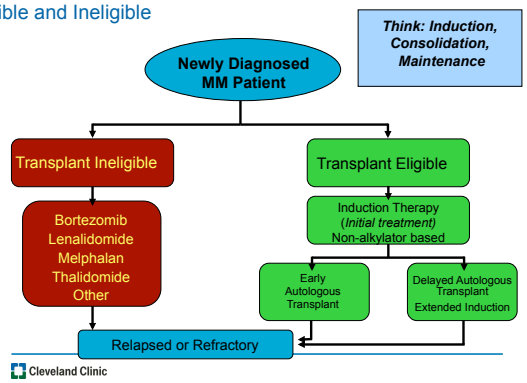
HSCT = hematopoietic stem cell transplant; HDT = high-dose therapy; ASCT = autologous stem cell transplant; allo-SCT = allogeneic stem cell transplant.

Primary Therapy for MM Differs Between Transplant Eligible and Ineligible



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Candidate for Transplantation Depends on Many Factors

Myeloma-Related Factors
- Type of myeloma
- Disease stage
- Disease aggressiveness
- Responsiveness to treatment
- Serum albumin
- Beta-2 microglobulin
- Chromosomal analysis

Patient-Related Factors
- Age
- Health/performance status
- Kidney, heart, lung, & liver function
- Donor availability
- Patient preference
- Insurance coverage
- Caregiver support

Transplant recommendations: IMWG guidelines
- Autologous: self-donation
- Syngeneic: identical sibling
- Allogeneic: related or unrelated donor, includes cord blood
- Reduced intensity ("mini") transplant: non-myeloablative
- Tandem transplants

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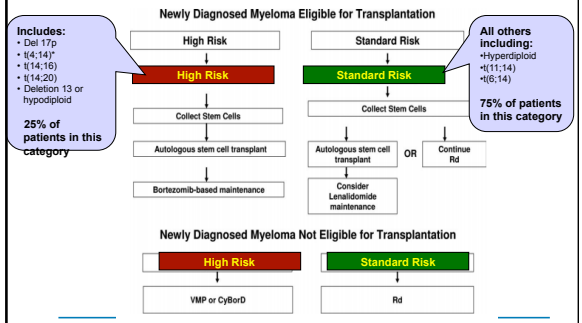
Kumar S et al. Blood. 2009;114(9):1729-1735

Trend Towards Risk-Stratification and Personalized Disease Treatment of MM



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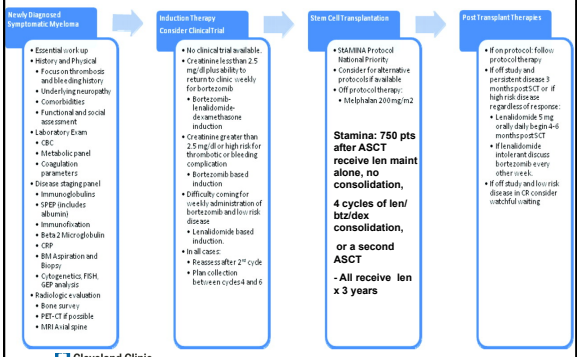
Rajkumar SV. Am J Hematol. 2011 Jan;86(1):57-65

Phases of Treatment: Newly Diagnosed Transplant Eligible



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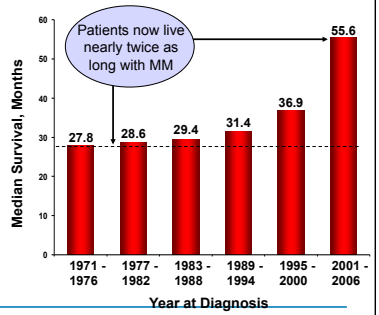
Giralt S. *Hematology* ASH Education Book. 2011; 2011(1):191-196.

MM Patients Are Living Longer Following Diagnosis

- Median survival newly diagnosed: ~5 years
  - Longer for younger patients
- 70,000 to 100,000 MM survivors in the US
  - Patients only, not caregivers/family



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Kumar S et al. Blood. 2008;111(5):2516-20

Questions Surround ASCT in the Era of Novel Agents

- Can we cure MM with transplant?
- Is sequential therapy better than transplant?
- Responses to treatment (similar to transplant) have been observed in the non-transplant setting
- The depth of response to treatment is important. CR: the single most important surrogate for long-term disease control and overall survival ….. But is a CR with standard therapy different in quality than the CR following transplant?
- Will we have a "BCR-ABL" test such as in CML to assess burden??

•What is the best way to treat MM in 2013?

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Roussel et al, 2010; Badros, 2010.

A Few Induction Regimens for MM…..

- Bortezomib/Dexamethasone
  - Bortezomib 1.3 mg/m^2 IV Days 1, 4, 8, 11
  - Dexamethasone 40 mg po Days 1–4, 9–12
  - Repeat every 3 weeks for 2–4 cycles
- Bortezomib/Thalidomide/Dexamethasone (VTD)
  - Bortezomib 1.3 mg/m^2 IV Days 1, 4, 8, 11
  - Thalidomide 200 mg po Days 1–21
  - Dexamethasone 20 mg on the day of and on the day after bortezomib
  - Repeat every 3 weeks x 3 cycles
- Lenalidomide/Dexamethasone
  - Lenalidomide 25 mg po Days 1–21 every 28 days
  - Dexamethasone 40 mg po Days 1, 8, 15, 22 every 28 days
  - Repeat every 4 weeks for 2 cycles

•Modern therapy for MM requires various parts

•Supportive care integral and will be discussed later

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MM = multiple myeloma; po = oral; IV = intravenous.
Blade et al, 2009; Palumbo et al, 2009

Nursing Considerations for Selected Therapies

	Thalidomide	Lenalidomide	Bortezomib	Pegylated Liposomal Doxorubicin/ Bortezomib	High Dose Melphalan, Busulfan + Cytoxan
Peripheral neuropathy	✓		✓	✓	✓
Deep vein thrombosis	✓ More with dex	✓ More with dex			
Myelosuppression	✓ Neutropenia	✓ Neutropenia, thrombocytopenia, anemia	✓ Thrombocytopenia	✓ Neutropenia, thrombocytopenia, anemia	✓ Neutropenia, thrombocytopenia, anemia
Hypotension			✓		
Fatigue, weakness	✓	✓	✓	✓	✓
Sedation	✓				
Rash	✓	✓		✓	✓
Viral reactivation of herpes zoster			✓		✓
Gastrointestinal disturbance	✓ Constipation	✓ Constipation, diarrhea	✓ Nausea and vomiting, diarrhea	✓ Nausea and vomiting, diarrhea, constipation, mucositis/stomatitis	✓ Nausea, diarrhea, constipation, vomiting, mucositis
Renal		✓ Reduce dose for decreased CrCL			✓ Reduce dose for decreased CrCL

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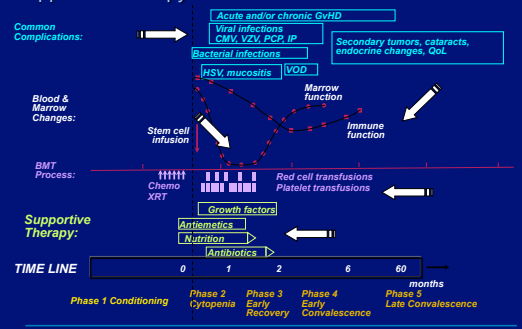
Doxil® [doxorubicin] [prescribing information]. Raritan, NJ: Centocor Ortho Biotech Products, LP; 2010; Revlimid® (lenalidomide) [prescribing information]. Summit, NJ: Celgene; 2012; Thalomid® (thalidomide) [prescribing information]. Summit, NJ: Celgene; 2012; Velcade® (bortezomib) [prescribing information]. Cambridge, MA: Millennium Pharmaceuticals, Inc; December 2012.

Stem Cell Transplant: Associated Side-effects and Supportive Therapy



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Types of HSCT

Categories	Stem Cell Source	Advantages	Disadvantages
Autologous	Patient	❖ Readily available stem cells ❖ Decreased incidence and severity of side effects ❖ Earlier engraftment ❖ Absence of GVHD	❖ Potentially contaminated cells ❖ Earlier relapse due to lack of GVT effect
Allogeneic	Related (sibling) or MUD	❖ Replacement of diseased or damaged marrow with healthy cells ❖ GVT effect	❖ Organ toxicity ❖ GVHD
Syngeneic	Identical twin	❖ See advantages of ASCT	❖ Lack of GVT effect

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MUD = matched unrelated donor; GVHD = graft-versus-host disease; GVT = graft-versus-tumor.
Logan et al, 2008.

SCT Options in Patients With MM

1) Myeloablative Single ASCT

2) Tandem Transplant
- Double Myeloablative ASCT
- Myeloablative ASCT: Myeloablative HLA-Matched Allo-SCT
- Myeloablative ASCT: Myeloablative HLA-Matched MUD SCT
- Myeloablative ASCT: RIC HLA-Matched Allo-SCT
- Myeloablative ASCT: RIC MUD Allo-SCT

3) Myeloablative Allo-SCT

4) RIC Allo-SCT

Auto-Auto and Auto-Allo Transplant BMT CTN 0102

- Designed to best define the role of allo in MM (n=710)
- If HLA matched sibs: randomized to RIC allo or 2nd auto
- **no benefit** (PFS or OS) when RIC allo used as consolidation therapy

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HLA = human leukocyte antigen; RIC = reduced-intensity conditioning.
Cooke et al, 2009; Krishnan A. et al. *Lancet Oncol.* 2011;12(13):1195-1203..

Risk Stratification Strategy

- At diagnosis, risk stratification helps guide the initial treatment
- Risk stratification may or may not lead to a better outcome (RR, PFS, and OS)
- Bortezomib and/or lenalidomide in patients with high-risk features such as high β_2m, del(13), t4;14 could overcome poor outcomes compared with conventional chemotherapy

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OS = overall survival; β_2m = beta-2-microglobulin. del(13) = deletion 13. RR= response rate; PFS= Progression free survival; OS= Overall survival; Lonial, 2010; Dispenzieri et al, 2007.

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Transplant Studies in Multiple Myeloma

Matt E. Kalaycio, MD, FACP

Chairman, Department of Hematologic Oncology and Blood Disorders
Director, Bone Marrow Transplant Program
Taussig Cancer Institute

Autologous Transplantation vs Conventional Chemotherapy For Newly Diagnosed Myeloma

		Pat (n)	CR	EFS (median months)	OS (median months)
Attal et al	Conventional	100	5	18	44
	HDT (8Gy TBI)	100	22	28**	57**
Fermand et al	Conventional	96	–	18.7	50.4 ST
	HDT	94	–	24.3**	55.3
*Blade et al	Conventional	83	11	34.3	66.9
	HDT (TBI)	81	30	42.5**	67.4
Child et al	Conventional	200	8.5	19.6	42.3
	HDT	201	44	31.6**	54.8**
*Barlogie et al.	Conventional	252	15	21	53 ST
	HDT (TBI)	258	17	25**	58

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Single ASCT (cont.)

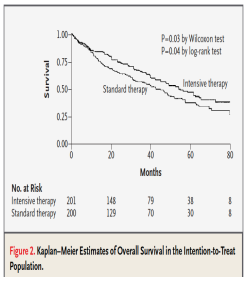

Figure 2. Kaplan–Meier Estimates of Overall Survival in the Intention-to-Treat Population.

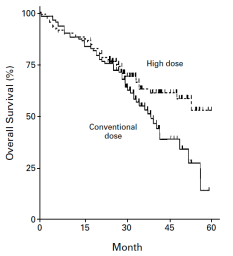

Figure 2. Overall Survival According to Treatment Group.

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Child et al, 2003; Attal et al, 1996.

Single ASCT (cont.)

- The NCCN has categorized single ASCT as a category 1 treatment option (high level of evidence with uniform consensus) for patients with MM
- In Europe, ASCT is also considered an important part of MM therapy for patients suitable for intensive chemotherapy
- Timing in which one should undergo transplant is unclear

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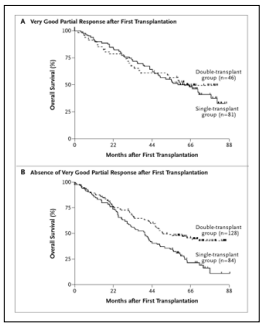
CR = complete response; EFS = event-free survival; NCCN = National Comprehensive Cancer Network.
Child et al, 2003; Attal et al, 1996; Palumbo et al, 2004; Kumar et al, 2009; NCCN, 2012.

Single vs. Double Transplant

- A second transplant within a short time frame (~4 months)
- May only benefit patients not achieving very good partial response (VGPR; i.e., 90% reduction in M protein)
- Not all trials show improved survival
- Melphalan should be avoided prior to stem cell harvest
- Patients don't like second transplants



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Attal M et al. *N Engl J Med.* 2003;349:2495-2502;
Rajkumar SV et al. *Mayo Clin Proc.* 2005;80:1371-1382.

The goal of HD MEL with ASCT is CR

- CR correlates with PFS
- Definition of CR
  - Immunofixation vs Immunophenotypic vs Molecular
  - "Stringent" CR = normalization of the FLC ratio
- Duration of CR
- Newer treatment regimens achieve CR as often as ASCT

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CR rates with ASCT and newer regimens

	CR	CR		
Attal et al	22	29-37%	VRD	Richardson et al
Blade et al	30	35%	VTD	Rosinol et al
Child et al	44	67%	CRd	Jakubowiak et al
Barlogie et al.	17			
Attal et al 1	42			
2	50			
Cavo et al 1	33			
2	47			

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Richardson Blood 2010;116(5):679-686; Rosinol Blood. 2012 Aug 23;120(8):1589-96; Jakubowiak Blood. 2012 Aug 30;120(9):1801-9

CR rates improve with ASCT

CR %	After Induction	After ASCT #1	After ASCT #2	After Post-ASCT Rx
VTD N = 236	19	38	42	49
TD N = 238	5	23	30	34

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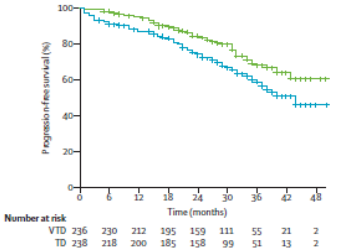
Cavo et al, Lancet 2010l

PFS with novel induction followed by ASCT



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Cavo et al, Lancet 2010l

ASCT vs Novel Agents

Palumbo et al, ASCO 2010, Abs 8015

- Ld x 4 cycles for induction
- Cytoxan + G mobilization
- Randomize
  - Mel/Pred/Len x6
  - Mel 200 x 2
- No maintenance
- Median F/U 12 months

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ASCT vs Novel Agents

Palumbo et al, ASCO 2010, Abs 8015

	MPR	MEL200
CR	14	25
>VGPR	57	62
PFS	91	91
OS	97	98

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Maintenance Therapy

- Maintenance therapy is the use of ongoing low intensity chemotherapy to eliminate or suppress the minimal residual tumor clone over a prolonged period of time
- Maintenance therapy is administered when the disease is in remission, either undetectable or at a low level
- The purpose of maintenance therapy is to prolong remission duration and thereby, life expectancy
- Immunomodulatory molecules are well suited for maintenance therapy, as they can be administered orally at low doses for a prolonged period of time

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Thalidomide Maintenance After ASCT

Author/Year	N	Thalidomide Dose (mg) / Duration	PFS / EFS	OS
Attal et al, 2006	597	Thalidomide 200 (median dose) vs. observation / progression	+	+
Spencer et al, 2006	243	Thalidomide 200 + prednisone vs. prednisone / 12 months	+	+
Maiolino et al, 2008	212	Thalidomide 200 + dexamethasone vs. dexamethasone / 12 months	+	NS
Barlogie et al, 2006*	668	Thalidomide 400 / progression	+	NS (+ in high-risk)
Morgan et al, 2010a*	820	Thalidomide 100 / progression	+ / -	NS (if optimal relapse Rx)
Lokhorst et al, 2010*	550	Thalidomide 50 / progression	+	-
Stewart et al, 2010	332	Thalidomide 200 + prednisone vs. observation / 48 months	+	NS

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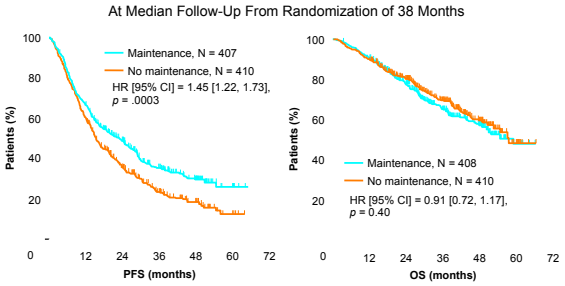
*Thalidomide also given as part of induction therapy.
PFS = progression-free survival; EFS = event-free survival; OS = overall survival; NS = not significant.

Thalidomide Maintenance: MRC Trial



❖ Thalidomide maintenance improves PFS but without an OS advantage

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HR = hazard ratio; CI = confidence interval.
Morgan et al, 2010b.

Lenalidomide Maintenance: CALGB 100104 Schema

CALGB, ECOG, BMT-CTN

Registration → Restaging Days 90–100 → Randomization

D-S Stage 1-3, ≤ 70 years
≥ 2 cycles of induction
Attained SD or better
≤ 1 yr from start of therapy
≥ 2 x 10^6 CD34 cells/kg

Mel 200 ASCT → CR PR SD → Placebo / Lenalidomide* 10 mg/d with ↑↓ (5–15 mg)

Patient stratification based on diagnostic β_2m level and prior thalidomide and lenalidomide use during induction

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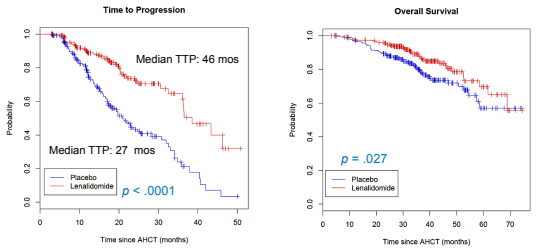
CALGB = Cancer and Leukemia Group B; ECOG = Eastern Cooperative Oncology Group; BMT-CTN = Blood and Marrow Transplant Clinical Trials Network; CR = complete response; PR = partial response; SD = stable disease; β_2m = beta-2-microglobulin.
McCarthy et al, 2011.

PFS and OS at Median Follow-Up of 34 Months



❖ 35 deaths in the lenalidomide arm and 53 deaths in the placebo arm

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TTP = time to progression.
McCarthy et al, 2011.

Lenalidomide Maintenance Post-Transplant: The IFM 2005-02: Study Design

Phase III Randomized, Placebo-Controlled Trial
N = 614 Patients, From 78 Centers, Enrolled Between 7/2006 and 8/2008

Patients < 65 Years, With Non-Progressive Disease, ≤ 6 Months After ASCT in First-Line

Randomization: Stratified According to β_2m, del(13), VGPR

Consolidation: Lenalidomide alone 25 mg/day po Days 1–21 q28days for 2 months

Arm A Placebo (n = 307) until relapse

Arm B Lenalidomide (n = 307) 10–15 mg/d until relapse

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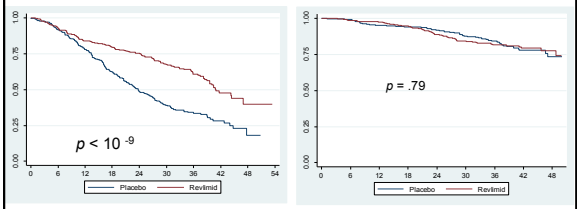
IFM = Intergroupe Francophone du Myelome; del(13) = deletion 13; VGPR = very good partial response;
Attal et al, 2011.

Lenalidomide Maintenance Post-Transplant: IFM 2005-02: PFS From Randomization (4/2011)

Median F/U: 36 months post-random, 46 months post-diagnosis



Placebo (n = 307)
Len (n = 307)

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Attal et al, 2011.

ASCT Summary

- New drugs have CR rates approaching ASCT
- CR increased further by ASCT
- CR increased further by Post-transplant therapy
  - Is prolonged therapy as good as intensive, short course treatment?
- IMiD maintenance: Possible increase in 2° malignancies
  OS benefit so far in 1 study
  PFS benefit in all 3 studies

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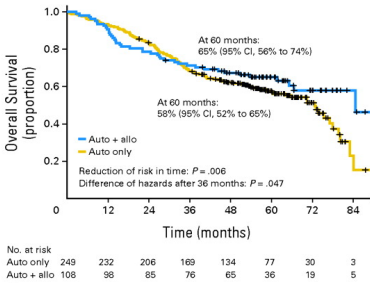
Auto-Allo Tandem?



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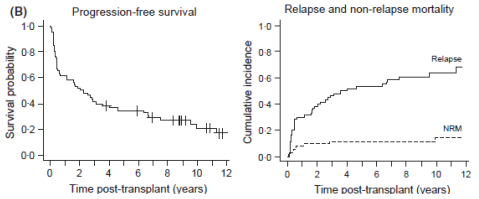
Björkstrand B et al. JCO; 29:3016-22, 2011

Late relapses



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Sahebi et al, Br J Haematol, 2012

International Myeloma Working Group Consensus Statement Regarding the Current Status of Allogeneic Stem-Cell Transplantation for Multiple Myeloma

Henk Lokhorst, Hermann Einsele, David Vesole, Benedetto Bruno, Jesus San Miguel, Jose A. Pérez-Simon, Nicolaus Kröger, Philippe Moreau, Gosta Gahrton, Cristina Gasparetto, Sergio Giralt, and William Bensinger

JCO; 2010

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Stem cell transplant for myeloma

- Single ASCT current standard of care
  - Tandem ASCT in select patients
  - Timing uncertain
- Post ASCT treatment SOC
  - Consolidation vs maintenance
- No standard role for Allogeneic transplant

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Nursing Considerations and Supportive Care in Myeloma

Beth Faiman PhDc, MSN, APN-BC, AOCN

Remember Jane?

- Diagnosed with IgG Kappa Multiple Myeloma, ISS stage II.
- Kappa free-serum is also significantly elevated at diagnosis, m spike
- Goals: Control disease, prevent treatment or disease/related complications
- Wants to undergo Autologous transplant upfront as part of clinical trial
- Induction regimen
  - Bortezomib 1.3 mg/m2 IV Day 1, 4, 8, 11 q21days
  - Dexamethasone 40 mg Day 1, 2, 4, 5, 8, 9, 11, 12 q21days
  - Lenalidomide 15 mg PO d 1-14, q21 days

ARS Case Study

You are the nurse caring for Jane prior to transplantation.

What supportive care therapy would you consider to be important to start prior to C1?

1) Granulocyte stimulating factor (GCSF)
2) Platelet transfusions
3) Bone marrow transplant
4) Bisphosphonates, acyclovir
5) None of the above

ARS Case Study: Question 1

Jane complains of numbness and pain in her feet after cycle 1 of bortezomib, lenalidomide and dexamethasone. What would you anticipate to be the correct intervention?

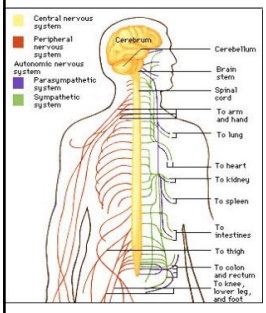
1. Continue bortezomib. She needs to go to transplant.
2. Hold Bortezomib until pain resolves. Then continue at full dose.
3. Hold Bortezomib until pain resolves. Then reduce the dose of bortezomib to 1.0mg/m2 days 1, 4, 8 and 11 IV.
4. Hold bortezomib until pain resolves. Then reduce the dose of bortezomib1.0mg/m2 days 1, 4, 8 and 11 and give SC.
5. Either 3 or 4.

Peripheral Neuropathy (PN)

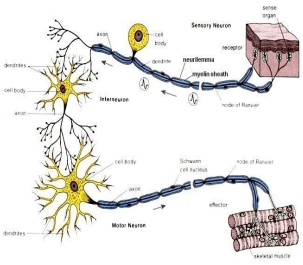
- Damage to the peripheral nervous system caused by injury, inflammation, or degeneration of peripheral nerve fibers
  - Can affect QOL, compromise optimal treatments
- Incidence of PN is increasing
  - More neurotoxic drugs have been developed
  - Patients are living longer, multiple treatment regimens
- Multifactoral
  - Older age, chemotherapy dose/duration
  - Prior cisplatin or vinca alkaloids
  - Co-administration with other neurotoxic agents
  - Pre-existing conditions such as DM, ETOH, HIV positive, female gender, Vit B12 deficiency/B6 toxicity

Tariman et al, 2008; Thalomid® prescribing information, 2007; Velcade® prescribing information, 2009.

Peripheral Nervous System



Peripheral nerve fiber



Nervous System. Online. Available: http://universe-review.ca/R10-16-ANS.htm , accessed 6/12/12.

PN: Management Strategies

- Regular monitoring at each treatment visit and neurotoxicity assessment using a well-established PN assessment tool preferably at the beginning of each treatment cycle
- Treatment dose and schedule modifications
- Pharmacologic and non-pharmacologic interventions
- Patient education

Tariman et al, 2008; Wickham, 2007; Thalomid® prescribing information, 2012; Velcade® prescribing information, 2012.

Bortezomib: Comparing SQ vs. IV Administration

Design:

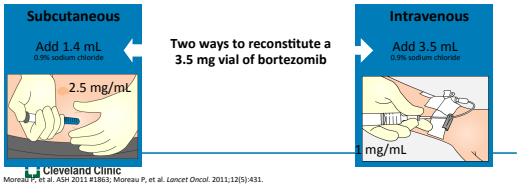
- 222 patients received SQ or IV btz
- 1.3 mg/m^2 on days 1, 4, 8, and 11
- Pts received a median of 8 cycles of btz

Results:

- No efficacy differences detected
- Significantly less neuropathy 38% SQ vs. 53% IV
- gastrointestinal

Bortezomib is FDA-approved for SQ.

Recommended injection sites: thigh and abdomen.



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Moreau P, et al. ASH 2011 #1863; Moreau P, et al. *Lancet Oncol.* 2011;12(5):431.

Case Study (cont.)

- Cycle 2 (Feb): bortezomib given SC and weekly days 1, 8, 15 and 21 of a 28-day cycle
- Cycle 3 (March): no new disease/ treatment related complications. Starts pamidronate.
- Undergoes Pre-transplant screening, stem cell harvest
- After 4 cycles: Proceeds with ASCT at the end of April
- Bone marrow biopsy 1 month after transplant confirms a complete remission (no evidence of increased plasma cells) but residual m protein

	KAPPA, FREE, SERUM	K/L RATIO
Mo/Ref Rng	3.3 - 19.4 mg/L	0.26 - 1.65
January	3500.0 (H)	>1255.83 (H)
February	911.9 (H)	>379.96 (H)
March	939.4 (H)	391.42 (H)
April	550.0 (H)	110.00 (H)
May	419.1 (H)	83.82 (H)
Sept	93.7 (H)	>39.04 (H)
November	5.8 (H)	>23.25 (H)
January	7.4	1.48
February	5.4	1.08

Component	Serum M Spike
Mo/ Ref Rng	0.00 g/dL
January	3.8
March	1.75
April	0.93 – PRIOR TO ASCT
August	0.21 – Starts LEN
Sept	0.00 No M Spike Detected
November	0.00 No M Spike Detected
January	0.00 No M Spike Detected
February	0.00 No M Spike Detected

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Disease and Treatment Related Side Effects: Infections in MM

- A leading cause of death in myeloma patients
  - –Risk further increased by cytotoxic therapy, transplant, and glucocorticoids
- Immunoglobulin levels decreased
  - –Hyporesponsive to antigen stimulation
  - –Deficient antibody production
- Infiltration of bone marrow by plasma cells
- Interventions
  - –Prompt reporting of symptoms
  - –IV Ig prophylaxis
  - –Poor response to pneumococcal and influenza vaccines (STILL GIVE)
  - –No ZOSTAVAX; give herpes zoster oral prophylaxis (bortezomib, carfilzomib)

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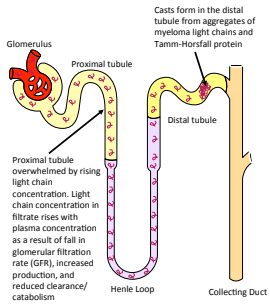
Renal Complications in MM Patients

Renal complications

- 25% to 50% have renal impairment at ANY TIME during disease
- 30% to 40% have elevated serum creatinine at presentation
- Treat: Hydrate, avoid dehydration, correct hypercalcemia, NO NSAIDS, dyes



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Dimopoulos MA, Terpos E. *Hematology Am Soc Hematol Educ Program.* 2010;2010:431-436; Bayraktar UD, et al. *Am J Hematol.* 2011;86(2): 224-227; Iggo N, et al. *QJM.* 1997;90:653-656; Dimopoulos MA, Terpos E. *Hematology.* 2010:431-436; Image adapted from Servier Medical Art

General Disease Related Side Effects: Bone Disease in MM

- Malignant cells produce osteoclast-activating factors that destroy bone cells
  - –Leads to osteolysis, bone pain, and pathologic fracture
- Bisphosphonates inhibit bone destruction
  - –Monitor patients for:
    - ➢Acute phase reactions
    - ➢Renal dysfunction
    - ➢Osteonecrosis of the jaw

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Management of Musculoskeletal System: Bone

- Osteonecrosis
  - – Evaluation with x-rays (panoramic) or MRI
  - – Prompt orthopedic referral for evaluation
  - – Pain assessment with appropriate pharmacological interventions
  - – Discontinue steroid use
  - – Avascular necrosis (3%)
- Osteoporosis
  - – Bone density
  - – Consider supplementation with calcium 1,000 mg/day and vitamin D 400 IU/day
  - – IV/PO bisphosphonates

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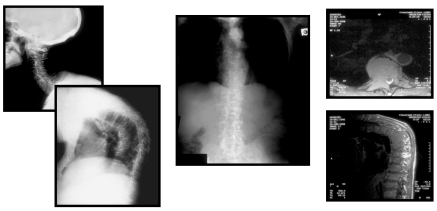
MRI = magnetic resonance imaging; IU = international units; IV = intravenous; PO = orally.
Kyle et al, 2007; Faiman et al, 2008; Faiman et al, 2013 *in press.*

Bone Complications: A Result of Disease and Treatment



- Compression fractures
  - Vertebroplasty, kyphoplasty
  - Radiation (if plasmacytoma) but avoid to protect bone marrow
  - Bisphosphonates

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General Disease and Treatment Related Side Effects: Thromboembolic Events: Risk in MM

- MM is intrinsically hypercoagulable disease associated with a higher risk of thromboembolic events
  - This may lead to DVT or PE
- Higher risk for DVT/PE in patients treated with conventional chemotherapies plus novel therapies such as
  - Thalidomide, lenalidomide or pomalidomide
  - Doxorubicin, high-dose corticosteroids

DVT = deep-vein thrombosis; PE = pulmonary embolism.
Rome et al, 2008; Musallam et al, 2009; Menon et al, 2008.

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VTE: Signs and Symptoms

DVT

- Slight fever, Tachycardia
- Unilateral swelling, erythemia, warm extremity
- Cyanosis/cool skin if venous obstruction
- Dull ache, pain, tight feeling over area and palpation
- Homan's Sign not always positive
- Distension superficial venous collateral vessels
- ULTRASOUND

PE

- Anxiety
- Sudden shortness of breath
- Worsening chest discomfort
- Rapid pulse and heart rate
- Low grade fever
- Pleural friction rub, crackles followed by diminished breath sounds, wheezing
- SPIRAL CT/VQ SCAN

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Rome et al, 2008.

Thromboembolic Events: Prophylaxis

- Mechanical
  - Ambulation, Exercise is the most effective prophylactic strategy
  - Sequential compression devices
  - Antiembolism stockings- questionable
- Steroid dose reduction
  - Decreased risk of VTE in ECOG trial
  - Dexamethasone reduced dosing 40mg weekly
    - DVT: 26% RD vs 12% Rd (p=0·0003)
    - Infection/Pneumonia: 16% vs 9% (p=0·04)

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Rome et al, 2008 Rajkumar SV et al. Lancet Oncol. 2010;11(1):29-37

Thalidomide and Lenalidomide: Thromboembolic Event Management

- Symptom assessment at baseline and each visit
- Thromboembolic event: Prophylaxis
  - Full-dose warfarin
  - LMWH or full-dose heparin for high-dose dexamethasone, doxorubicin, or multiagent chemotherapy independent of risk factors
  - LMWH or full-dose heparin for patients with ≥ 2 risk factors
  - Aspirin for low-risk patients only
- Risk factors include
  - Drugs (EPO)
  - History of thromboembolic events
  - Obesity
  - Concurrent cardiac or renal disease, diabetes, acute infection
  - Surgery

LMWH = low-molecular-weight heparin; EPO = erythropoietin.
Palumbo et al, 2007; Rome et al, 2008

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Myelosuppression

- General recommendations- all novel agents
  - Monitor signs and symptoms
  - Monitor CBC and differential
  - Educate on signs and symptoms of neutropenic fever, anemia, thrombocytopenia
- Myelosuppression management
  - Growth factor therapy
  - Dose reduction as appropriate
  - Transfusion as indicated

CBC = complete blood count.
Miceli et al, 2008.

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Overview of GI Side Effects

- Novel therapeutics can cause serious GI side effects
  - Constipation- stool softeners, laxitives
  - Diarrhea- loperamide, diet (cdiff, stool culture)
  - Nausea and/or Vomiting: Ginger, peppermint, small meals, 5ht3 receptor antagoist, motility agents
  - Weight loss – small meals, secondary causes??
- Onset, duration, aggravating/alleviating factors
- Diarrhea common in lenalidomide maintenance post transplant

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Smith et al, 2008.

Overall Recommendations

- Effective management includes
  - Monitoring patients carefully
  - Educating patients and caregivers about what to expect during treatment
  - Appropriate prophylaxis
  - Pharmacologic and non-pharmacologic interventions
- Effective management leads to
  - Increased adherence to therapy
  - Improved QOL
  - Prevention of serious adverse events

QOL = quality of life

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Faiman et al, 2008; Faiman, 2011

List of Important Factors When Providing Care: Assessment and Management

On-going and Individualized for Each Patient

What is the risk of VTE?	Increased if prior VTE, receiving IMiDs, etc.	
Bone health	MM bone disease confirmed? Imaging yearly; Vitamin D, Calcium	
Infectious diseases	Is your patient at high risk for infection? (neutropenia; hypogam) (myelosuppression from disease/ treatment)	– Wkly CBC, differential for 8 wks with lenalidomide – Acyclovir prophylaxis with bortezomib, carfilzomib – IV Ig for recurrent infections (a result of hypogammaglobulinemia)
GI	Antiemetic prior to bortezomib, doxorubicin	Assess for diarrhea (btz, len) constipation (thal, dox)
Neurologic	Review increased risk of PN with bortezomib and thalidomide	Prompt intervention can prevent irreversible PN symptoms
Renal	Avoid renal toxic agents, 24-hr urine albumin (bisphosphonates), dose reduction (lenalidomide, melphalan, opioids, acyclovir)	
Disease Monitoring	SPEP, UPEP, 24-hr urine, sFLC monthly	
Health Maintenance	Cancer and Cardiovascular surveillance	
Survivorship	Financial, Psychosocial issues (years life lost, retirement)	

IMiDs = immunomodulatory drugs

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IMF, 2011; Kyle et al, 2007; NCCN, 2012; Smith et al, 2008: Faiman et al, 2011; Miceli et al, 2011

New "New Drugs": Relapsed MM

- **Carfilzomib**, no significant PNP, appears at least as effective as bortezomib;
  - FDA Approved June, 2012 for RRMM failed bortezomib, imid
- **Pomalidomide**, tolerated about as lenalidomide, but more effective
  - FDA Approved February,2013 for RRMM failed bortezomib, rev
- **Elotuzumab**, humanized antibody against CS1, promising in Ph2 with Rd
- **Azacitidine**, DNA methylation inhibitor, OS benefit in MDS
- **Panobinostat**, histone deacetylase inhibitor, promising in Ph1/2 with Bort/Dex,

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Conclusions

- The landscape of MM continues to change
- Nurses are critical in the management of MM related side effects
- There is no clear consensus but guidelines exist to help "guide" our decisions regarding transplantation and side effect management
- Future research will aim at providing clarity and best management strategies
  - Optimal induction, consolidation, maintenance

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Hausheer et al, 2006; Faiman, 2011

Thank you!

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