MULTIPLE MYELOMA: WHAT'S NEW?

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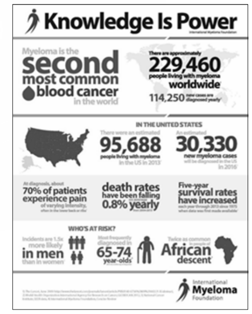
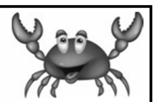
PLASMA CELL (MULTIPLE) MYELOMA

- In US
  - Most common lymphoid malignancy in African Americans; second in Caucasians
  - African Americans 2 x more than Caucasians
- Adults, usually > 50 years
  - Median age 68
  - Rare in adults before age 35
  - NOT found in children
- M/F ratio 3:2
- Median survival 3-4 years



LEARNING OBJECTIVES



- Review pathophysiology and lab diagnosis of plasma cell neoplasms with a focus on Multiple Myeloma
- Identify new molecular and Cytologic findings in Multiple Myeloma
- Identify targeted treatments based on molecular findings in Multiple Myeloma

ETIOLOGY OF MM

- Genetic causes ?
- Extension of MGUS
- Environmental/occupational exposures
- Radiation
- Chronic inflammation
- Infection (HH8)

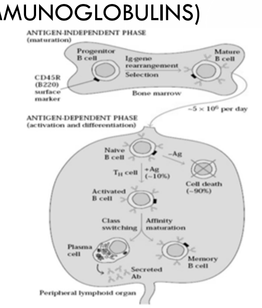
A 65-YEAR-OLD CAUCASIAN MAN WITH A DIAGNOSIS OF MULTIPLE MYELOMA THAT HAS RELAPSED IS BEING SEEN IN THE ONCOLOGY OUTPATIENT CENTER AND HAS BEEN MULTIPLY TRANSFUSED RECENTLY WHILE RECEIVING PREDNISONE, CYTOXAN, AND DARATUMUMAB. THE TYPE & SCREEN SHOWS THE PATIENT AS B, RH-POSITIVE WITH A POSITIVE ANTIBODY SCREEN ON ALL CELLS. THE RESULTS OF THE ANTIBODY PANEL ARE AS FOLLOWS:

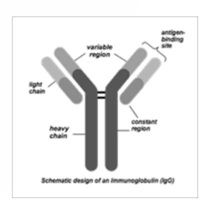
	D	C	c	E	e	f	V	C^w	K	k	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	P_1	M	N	S	s	Lu^a	Lu^b	Xg^a	LISS RT	LISS 37	LISS AHG	CC
1	+	+	0	0	+	0	0	+	0	+	0	+	+	+	0	+	0	0	+	0	+	0	+	0	0	0	2+	NT
2	+	+	0	0	+	0	0	0	0	+	0	+	0	+	0	+	+	+	0	+	0	0	+	+	0	0	2+	NT
3	+	0	+	+	0	0	0	0	0	+	+	+	+	0	0	+	+	0	+	0	+	0	+	+	0	0	1+	NT
4	0	0	+	0	+	+	0	0	+	+	+	+	+	0	+	0	0	+	+	+	+	0	+	0	0	0	1+	NT
5	+	0	+	0	+	+	0	0	0	+	0	0	+	+	0	+	+	0	+	0	+	0	+	0	0	0	2+	NT
6	0	0	+	0	+	+	0	0	0	+	0	0	+	0	+	0	0	0	+	0	+	0	+	0	0	0	1+	NT
7	0	0	+	0	+	+	0	0	0	+	+	0	+	+	0	+	+	+	0	+	0	+	+	0	0	0	2+	NT
8	0	0	+	+	+	+	+	0	0	+	0	+	0	+	0	+	+	+	0	+	+	0	+	0	0	0	2+	NT
9	0	0	+	0	+	+	0	0	+	0	+	0	0	+	0	+	0	+	+	0	+	0	0	+	0	0	1+	NT
10	+	+	+	0	+	+	0	0	0	+	+	+	+	0	0	0	0	0	+	0	+	0	+	+	0	0	1+	NT
11	+	0	+	0	+	0	0	0	0	+	+	0	+	0	0	+	+	+	+	0	0	0	+	+	0	0	1+	NT
AC	Patient Cells																								0	0	1+	NT

Key: RT- Room Temperature, 37- 37C, AHG – antihuman globulin phase, CC – Check Cells, NT – Not Tested

- A. Elution
- B. Treat the reagent RBCs with ficin
- C. Treat the patient's plasma with DTT
- D. Treat the reagent RBCs with DTT

B CELL MATURATION AND ANTIBODIES (IMMUNOGLOBULINS)





TYPES OF IMMUNOGLOBULINS

The Five Immunoglobulin (Ig) Classes

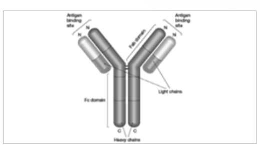
	IgM pentamer	IgG monomer	Secretory IgA dimer	IgE monomer	IgD monomer
Heavy chains	μ	γ	α	ε	δ
Number of antigen binding sites	10	2	4	2	2
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000
Percentage of total antibody in serum	6%	80%	13%	0.002%	1%
Crosses placenta	no	yes	no	no	no
Fixes complement	yes	yes	no	no	no
Fc binds to		phagocytes		mast cells and basophils	
Function	Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor	Main blood antibody of secondary responses, neutralizes toxins, opsonization	Secreted into mucus, tears, saliva, colostrum	Antibody of allergy and antiparasitic activity	B cell receptor

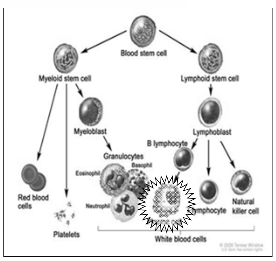
PLASMA CELL NEOPLASMS DIAGNOSIS

- Pathological
- Clinical
- Radiological
- Molecular/Cytogenetic

PLASMA CELL NEOPLASMS

- Proliferation of a single clone of Immunoglobulin-secreting plasma cells
- Results in increased serum levels of a single immunoglobulin or chain

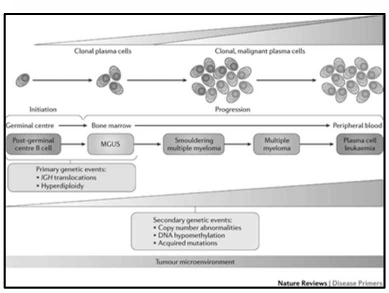




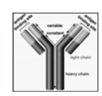
LAB EVALUATION FOR A SUSPECTED PLASMA CELL DISORDER

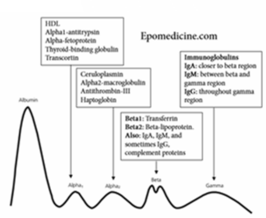
- Serum and urine protein electrophoresis
- Serum and urine immunofixation and Ig quantification and light chain types
- Serum free light chains
- Bone marrow examination
- Other labs

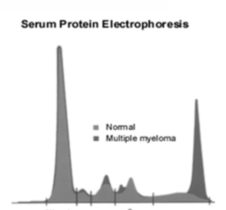
PROGRESSION OF MULTIPLE MYELOMA



SERUM PROTEIN ELECTROPHORESIS (SPEP)







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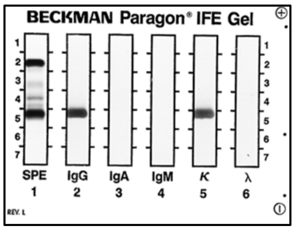
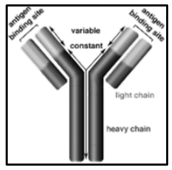
IMMUNOFIXATION, IFE





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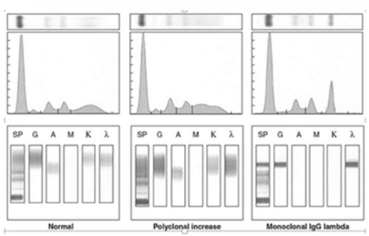
SERUM PROTEIN ELECTROPHORESIS (SPEP) IFE: SUBTYPES THE M-SPIKE COMPONENT



MORE ABOUT MONOCLONAL PROTEINS IN MM

- 75-85% have serum monoclonal IG
  - IgG >>> IgA; other types rare
  - Both heavy and light chain
  - M component- M Spike –Monoclonal Spike –on electrophoresis "paraprotein"
- **10-20% make light chains only**
  - Rapid renal excretion
  - Serum paraprotein may be absent
  - Found on urine electrophoresis (UPEP) or serum free light chain assays
- 5% Non-secretory myeloma (rare)
- Other causes of monoclonal proteins
  - B cell lymphomas
  - Autoimmune disease
  - HIV infection

SERUM FREE LIGHT CHAINS

- 2 types of light chains, kappa, κ and lambda, λ
- Each plasma cell produces only one type of heavy and light chain
- Heavy and light chains are produced separately within the plasma cells and are assembled to form a whole intact immunoglobulin
- Light chains attached to heavy chains: "bound light chains"; Light chains not attached to the heavy chains: **"FREE LIGHT CHAINS"**
- Plasma cells typically produce more light chains than are required to create whole immunoglobulins or monoclonal proteins
- THE EXCESS LIGHT CHAINS ENTER THE BLOODSTREAM AS "FREE LIGHT CHAINS"
- For myeloma patients, the amount of free light chain production is linked to the activity of myeloma cell growth

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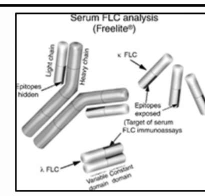
SERUM FREE LIGHT CHAINS

- **Abnormal ratio**
  - Level of either kappa or lambda is very high and the other light chain is normal/low
  - Indicates Myeloma
- **Normal ratio**, but increased levels of both kappa and lambda light chains
  - Indicates a disease other than myeloma, such as poor kidney function
  - Both light chains retained in the blood and not removed by the kidneys

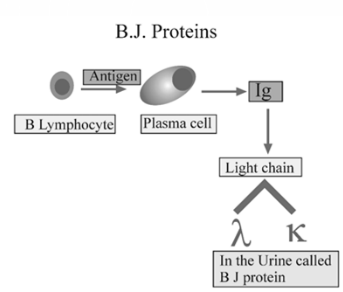


Normal levels of serum free light chains are*:

- Kappa: 3.3–19.4 mg/L or 0.33–1.94 mg/dL
- Lambda: 5.71–26.3 mg/L or 0.57–2.63 mg/dL
- Kappa/lambda ratio: 0.26–1.65*

*Note: In patients with renal impairment, it is recommended to interpret the results of the kappa/lambda ratio with a modified reference range of 0.37–3.1.

BENCE-JONES PROTEINS-FREE LIGHT CHAINS IN URINE



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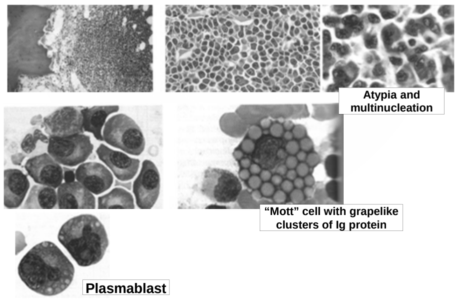
BONE MARROW FINDINGS



Atypia and multinucleation

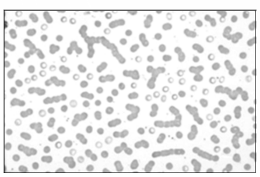
"Mott" cell with grapelike clusters of Ig protein

Plasmablasts

OTHER LAB FINDINGS

- Altered albumin to globulin ration
- β2 microglobulin -Surrogate marker for tumor burden
- CRP – Surrogate marker for IL-6 (IL-6 is a plasma cell growth factor)
- Serum viscosity (with very high M protein) CNS symptoms

PERIPHERAL BLOOD FINDINGS



Rouleaux

PLASMA CELL MYELOMA, SYMPTOMATIC, CLINICAL SIGNS AND SYMPTOMS

- COMMON
  - Bone pain (back, long bones, pelvis) and pathological fractures
  - Weakness, dizziness, fatigue (anemia)
  - Dehydration, urinary frequency (renal failure)
  - Headache
  - Infections (depressed normal immunoglobulin production, leukocytopenia
  - Fever
- LESS COMMON
  - Acute hypercalcemia
  - Symptomatic hyperviscosity
  - Neuropathy
  - Amyloidosis
  - Coagulopathy

OTHER LAB FINDINGS

- CBC – Anemia, leukocytopenia
- CMP – Hypercalcemia , increased levels of total protein, decreased albumin, increased BUN, creatinine
- ESR (elevated) >100
- 24-hour urine collection for quantification of the Bence Jones protein (light chains), protein, and creatinine clearance
- Markers of cell turnover/destruction - Uric acid, LDH

AMYLOIDOSIS

- Caused by a plasma cell that secretes light chains (common) or heavy chains (rare)
- Most commonly, light chains deposit in tissue as beta-pleated sheets
- Called "AL" amyloid for "Amyloid Light" chains
- Adults over 40, male predominance
- Clinical findings relate to deposition of amyloid in organs -Kidne in MM

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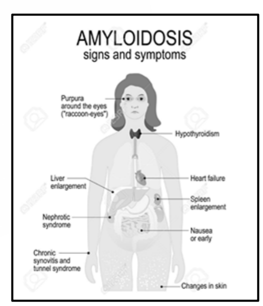


PLASMA CELL MYELOMA, SYMPTOMATIC – RADIOLOGIC SIGNS

- Lytic bone lesions seen on X-ray

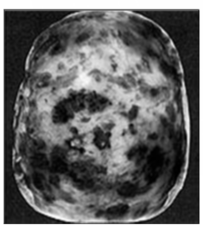
CRAB – DEFINES SYMPTOMATIC MULTIPLE MYELOMA

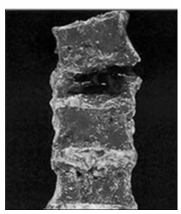
***Organ damage classified as "CRAB"** or any other significant clinical problem linked to myeloma progression such as recurrent infections or neuropathy unrelated to treatment

- **C** – calcium elevation (> 10 mg/dL)
- **R** – renal dysfunction (creatinine > 2 mg/dL or creatinine clearance < 40 ml/min)
- **A** – anemia (hemoglobin < 10 g/dL or > 2g/dL decrease from patient's normal)
- **B** – bone disease (one or more osteolytic lesions detected on skeletal radiography, WBLC CT, or PET/CT)

One or more "CRAB" features or other significant problem required for diagnosis of **Symptomatic Myeloma**

LYTIC BONE LESIONS – AUTOPSY

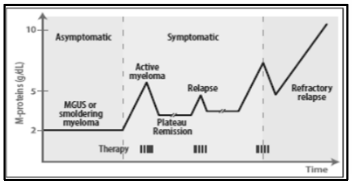


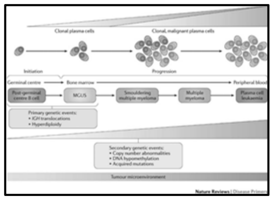


CALCIUM

- Lysis of bone leads to increased calcium in the blood
- 30% of patients have at time at presentation
- Key factors – IL6, IL1, RANKL, MIP1α and osteoblastic dysfunction

PROGRESSION OF MULTIPLE MYELOMA





RENAL DYSFUNCTION ("MYELOMA KIDNEY")

- CAUSES
  - Cast nephropathy
  - Light chain deposition disease
  - Primary amyloidosis
  - Hypercalcemia
  - Renal tubular dysfunction
  - Volume depletion
  - IV contrast dye, nephrotoxic meds

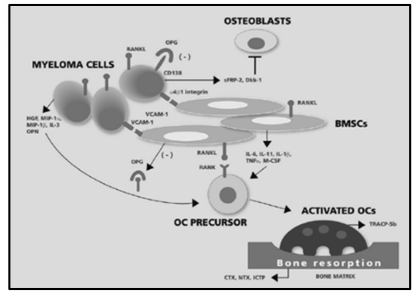
- Two main pathologic mechanisms:
  - Intracellular cast formation
  - Direct tubular toxicity by light chains

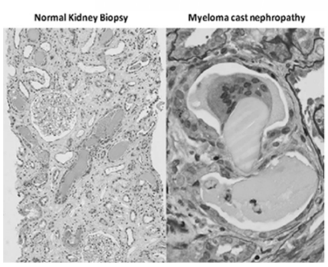
- Contributing factors to presence of renal failure due to multiple myeloma:
  - High rate of light chain excretion (tumor load)
  - Biochemical characteristics of light chain
  - Concurrent volume depletion

CAST NEPHROPATHY

- Most common pathological diagnosis on renal biopsy in multiple myeloma
- Due to light chains binding with Tamm-Horsfall mucoprotein, which is secreted by tubular cells in ascending loop of Henle, forming casts
- Multinucleated giant cells surround the casts
- Dehydration worsens cast nephropathy due to decreased flow in tubules, increased concentration of light chains

BONE LESIONS





- Treatment of renal failure
  - IV rehydration
  - Treatment of hypercalcemia
  - Treatment of MM
  - Plasmapharesis ?
  - Dialysis if necessary

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)

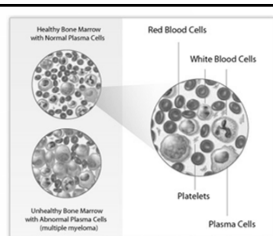
- Very common (5% of people over 70)
- Usually elderly patients with no symptoms
- African Americans > Caucasians (twice)
- Small monoclonal spike (IgG most common)
- Less than 10% clonal plasma cells in marrow
- No myeloma related organ/tissue impairment –NO CRAB

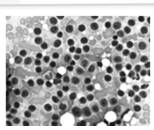
  CRAB: HyperCalcemia, Renal insufficiency, Anemia, Bone lesions

- No evidence of other B-cell proliferative disorder
- Increased risk for developing myeloma

ANEMIA

- Myeloma cells crowd out normal cells in BM
- Decreased production of red cells – anemia
- Can also be caused by treatments for MM

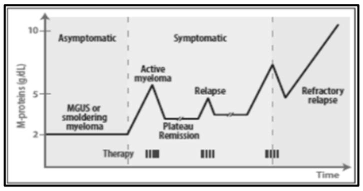




ASYMPTOMATIC (SMOLDERING) PLASMA CELL MYELOMA

- 10% or more clonal plasma cells in bone marrow (Myeloma level)
- **AND/OR**
- M protein in serum at IgG ≥3 g/dL, IgA >1 g/dL (Myeloma level)
- **NO** related endorgan or tissue impairment – **NO CRAB**

PROGRESSION OF MULTIPLE MYELOMA



CONCEPT OF MYELOMA DEFINING EVENTS (MDES)

Both criteria must be met:

1 • Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma

2 • Any one or more of the following myeloma defining events:

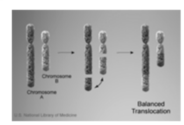
- A ◦ Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  - Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
  - Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177 µmol/L (>2 mg/dL)
  - Anemia: hemoglobin value of >2 g/dL below the lower limit of normal, or a hemoglobin value <10 g/dL
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT)
- B ◦ Clonal bone marrow plasma cell percentage ≥60%
- C ◦ Involved: uninvolved serum free light chain (FLC) ratio ≥100 (involved free light chain level must be ≥100 mg/L)
- D ◦ >1 focal lesions on magnetic resonance imaging (MRI) studies (at least 5 mm in size)

UPDATED CRITERIA FOR DIAGNOSIS OF MULTIPLE MYELOMA – REVISED INTERNATIONAL STAGING SYSTEM FOR MULTIPLE MYELOMA R-ISS

- From international cancer expert groups – IMWG & NCCN, 2016
- Added new biomarkers to the existing requirement for CRAB features
- These biomarkers were associated with inevitable development of CRAB in patients with smoldering myeloma
- The presence of 10% plasma cells in bone marrow, and any of the CRAB or any of the new 3 markers justifies the beginning of treatment
- Start treatment **early** before have end organ effects
- Updated laboratory and radiological variables

CYTOGENETICS TERMINOLOGY

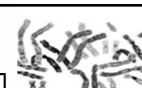
- Hyperdiploid -more than the usual diploid number of chromosomes
- Hypodiploid –less than the usual number of chromosomes
- Aneuploid - presence of an abnormal number of chromosomes in a cell, for example a human cell having 45 or 47 chromosomes instead of the usual 46
- Trisomy – three copies of chromosome
- Deletion- deletion of all or part of a chromosome
- Translocation –rearrangement of parts of chromosomes



MYELOMA DEFINING EVENTS (MDE)-”SLIMCRAB”

- **In the absence of “CRAB”, the SLIM criteria may be used**
  - **S**ixty percent (≥ 60%) clonal plasma Bone marrow cells
  - **Li** – Serum free Light chain ratio involved : uninvolved ≥ 100
  - **M** - 1 focal lesion (≥ 5mm each) detected by **M**RI; CT and PET-CT can also be used
- Don’t have to wait for end organ damage (CRAB) to start treatment
- “SLIM CRAB” for diagnosis

CYTOGENETICS FINDINGS



	Clinical setting in which abnormality is detected	
Cytogenetic abnormality	Smoldering multiple myeloma	Multiple myeloma
Trisomies	Intermediate-risk of progression, median TTP of 3 years	Good prognosis, standard-risk MM, median OS 7–10 years Most have myeloma bone disease at diagnosis Excellent response to lenalidomide-based therapy
t(11;14) (q13;q32)	Standard-risk of progression, median TTP of 5 years	Good prognosis, standard-risk MM, median OS 7–10 years
t(6;14) (p21;q32)	Standard-risk of progression, median TTP of 5 years	Good prognosis, standard-risk MM, median OS 7–10 years
t(4;14) (p16;q32)	High-risk of progression, median TTP of 2 years	Intermediate-risk MM, median OS 5 years Needs bortezomib-based initial therapy, early ASCT (if eligible), followed by bortezomib-based consolidation/maintenance
t(14;16) (q32;q23)	Standard-risk of progression, median TTP of 5 years	High-risk MM, median OS 3 years Associated with high levels of FLC and 25% present with acute renal failure as initial MDE
t(14;20) (q32;q11)	Standard-risk of progression, median TTP of 5 years	High-risk MM, median OS 3 years
Gain(1q21)	High-risk of progression, median TTP of 2 years	Intermediate-risk MM, median OS 5 years
Del(17p)	High-risk of progression, median TTP of 2 years	High-risk MM, median OS 3 years
Trisomies plus any one of the IgH translocations	Standard-risk of progression, median TTP of 5 years	May ameliorate adverse prognosis conferred by high risk IgH translocations, and del 17p
Isolated Monosomy 13, or Isolated Monosomy 14	Standard-risk of progression, median TTP of 5 years	Effect on prognosis is not clear
Normal	Low-risk of progression, median TTP of 7-10 years	Good prognosis, probably reflecting low tumor burden, median OS >7–10 years

Table 27.3 Risk-Stratification of Multiple Myeloma

High Risk	Intermediate Risk	Standard Risk[a]
17p deletion	t(4;14)	Hyperdiploidy
t(14;16)	Deletion 13 or hypodiploidy by conventional karyotyping	t(11;14)[b]
t(14; 20)		t(6;14)
High-risk signature on gene expression profiling		

Based on FISH analysis unless specified.
[a]LDH >ULN and β-2 microglobulin >5.5 may indicate worse prognosis.
[b]t (11;14) may be associated with plasma cell leukemia.
Adapted from Kumar SK, Mikhael JR, Buadi FK, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. *Mayo Clin Proc.* 2009;84:1095-1110.

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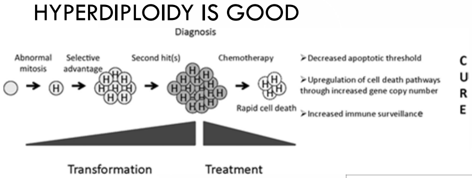
THERAPEUTIC OPTIONS

- Currently not curable
- High dose Chemotherapy with corticosteroids
- Bone Marrow/stem cell transplants
- Radiation
- Novel agents

Table 6. Myeloma treatment options

1.	Induction therapy
2.	High-dose chemotherapy with hematopoietic stem cell transplant
3.	Conservative use of radiation to preserve bone marrow
4.	Maintenance therapy
5.	Supportive care: • Pain medication • Anti-viral therapy • Bisphosphonates • Brace/corset • Growth factors • Kyphoplasty/vertebroplasty • Antibiotics • Exercise • Emergency care (e.g., dialysis, plasmapheresis, surgery, radiation)
6.	Management of drug-resistant or refractory disease
7.	Novel and experimental therapies: • Immunomodulatory drugs Thalomid® (thalidomide), Revlimid® (lenalidomide), Pomalyst® (pomalidomide) • Approved injectable proteasome inhibitors Velcade® (bortezomib) and Kyprolis® (carfilzomib), and oral proteasome inhibitor Ninlaro® (ixazomib); oral proteasome inhibitors oprozomib and marizomib in clinical trials • Histone deacetylase (HDAC) inhibitor Farydak® (panobinostat); HDAC inhibitor ACY-241 in clinical trials • Immunotherapies pembrolizumab, pidilizumab, lambrolizumab, CAR T cells in clinical trials • Monoclonal antibodies Darzalex® (daratumumab) and Empliciti® (elotuzumab); isatuximab (SAR650984) and siltuximab in clinical trials • Pan-tumor suppressor gene promoter selinexor in clinical trials

HYPERDIPLOIDY IS GOOD



CHEMOTHERAPY

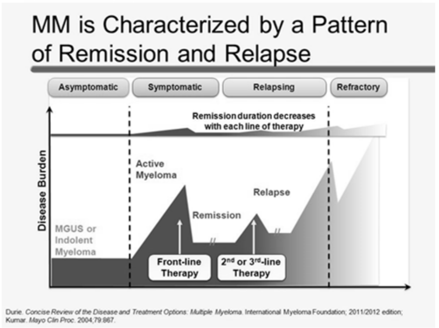
Chemotherapy - the treatment of disease by the use of chemical substances, especially the treatment of cancer by cytotoxic drugs

PLASMA CELL MYELOMA PROGNOSIS

- Prognosis:
  - Median survival ~ previously, 3 years (now 4 – 8 years)
  - 5 year survival rate (2007-2013) 49.6%
  - Before that, 5 year survival rate ~ 30%
  - Survival has increased with newer treatments

CHEMOTHERAPY TERMINOLGY

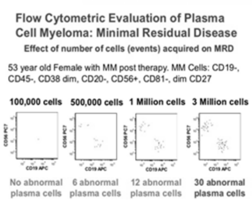
- **Induction therapy** –the 1st treatment given; often a standard set of treatments (or called Front line therapy)
- **Consolidation therapy** - a short course of chemotherapy, helps make the previous chemotherapy treatment and stem cell transplant work better -the goal of this therapy is to sustain a remission
- **Maintenance therapy** - given after a stem cell transplant or after induction therapy in people who don't have a stem cell transplant. A maintenance therapy drug is usually given in a low dose over a long period of time -the goal of this therapy is to sustain a remission
- **Remission** – all evidence of cancer is gone
- **Relapse** -a deterioration in someone's state of health after a temporary improvement
- **Minimal residual disease** MRD –the small number of cancer cells that remain after treatment, responsible for relapse



MITOTIC INHIBITORS -VINCRISTINE

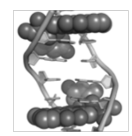
- Binds to tubulin, prevents chromosomes from separating during metaphase – leads to apoptosis
- Inhibits leukocyte production and maturation
- Side effects:
  - Peripheral neuropathy
  - Hyponatremia
  - Constipation
  - Hair loss

DETECTING MINIMAL RESIDUAL DISEASE (MRD)



ANTRHACYCLINE ANTIBIOTICS -DOXORUBICIN (ADRIAMYCIN)

- Mechanism of action -intercalates into DNA and stops DNA replication and RNA transcription
- Side effects:
  - Bone marrow suppression
  - Hair loss
  - Nausea and vomiting
  - Stomatitis
  - Typhilitis –acute inflammation of the bowel
  - Dilated cardiomyopathy leading to congestive heart failure
  - Palmar-plantar erythrodysesthesia PPE



ALKYLATING AGENTS: MELPHALAN (ALKERAN)

- Nitrogen mustard alkylating agents
- An alkylating agent adds an alkyl group (C_nH_{2n+1}) to DNA –inhibits DNA & RNA synthesis
- Side effects
  - Nausea and vomiting
  - Bone marrow suppression
  - Pulmonary fibrosis
  - Hair loss
  - Myelodysplastic syndrome

STEROIDS (CORTICOSTEROIDS)

- Prednisone and Dexamethasone
- Anti-inflammatory and anti-Myeloma effects
- Help reduce nausea & vomiting & fatigue
- May be used alone or in combination
- Side effects:
  - High blood sugar
  - Weight gain
  - Insomnia
  - Change in mood
  - Over time, suppress immune system and weaken bones

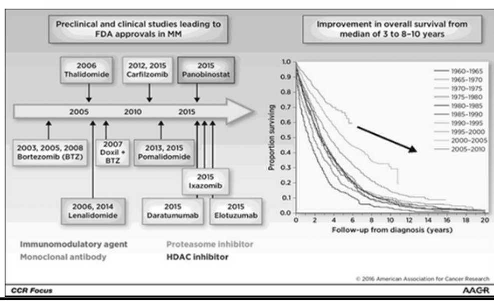
VAD –STANDARD INDUCTION THERAPY UNTIL RECENTLY

- Vincristine
- Adriamycin
- Dexamethasone

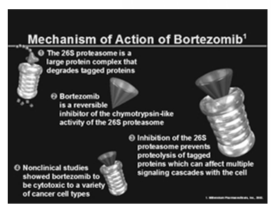
BORTEZOMIB (VELCADE)

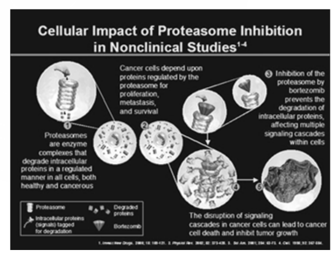
- First approved proteasome inhibitor, 2003
- Potentiates sensitivity to both conventional and novel therapeutic agents
- IV or subQ
- Mechanism of action:
  - Inhibits the 26S proteasome
  - Prevents proteolysis of proteins targeted (by ubiquitinylation) for removal
  - Disrupts homeostasis; leads to apoptosis
- Side effects:
  - Peripheral neuropathy
  - Bone marrow suppression
  - Herpres Zoster infections due to immunocompromise

BENCH TO BEDSIDE TRANSLATION OF NOVEL AGENTS NEW DRUGS HAVE IMPROVED SURVIVAL IN MM



PROTEASOME INHIBITORS





PROTEASOME INHIBITORS - BORTEZOMIB (VELCADE)

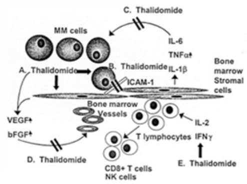
- Proteasomes – protein complexes that degrade proteins by breaking peptide bonds (proteolysis)
- Proteasome inhibitors –drugs that block the action of proteasome - Prevent protein breakdown
- Excess proteins cause cell cycle arrest and apoptosis
- Boron atom binds to the catalytic site of the 26S proteosome

IMMUNOMODULATORY AGENTS

- Immunomodulatory agents (IMiDs)
- Have become a key part of the treatment regimen for multiple myeloma.
- Stimulate natural killer cells and activate T cells ⟹ reducing the growth of myeloma cells

THALIDOMIDE

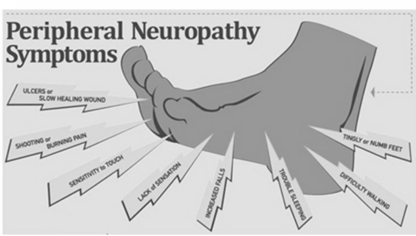
- First novel agent routinely used for multiple myeloma – oral
- Mechanisms of action:
  - Stimulation of T and NK cells
  - Anti-angiogenesis (decreases VEGF)
  - Suppresses MM growth factors (IL-6, TNF- α)
  - Inhibits adhesion to the stroma
- Side Effects:
  - Teratogenic
  - Peripheral Neuropathy
  - DVT/PE
  - Constipation
  - Sedation



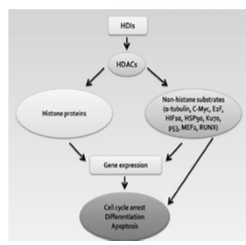
4 NEW DRUGS APPROVED IN 2015

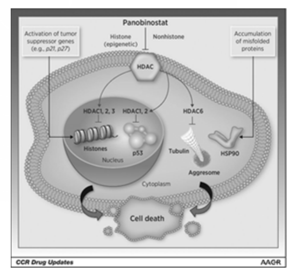
- Panibostat – deacetylase inhibitor, in combination with Bortuzimab and Dex
- Ixazomib –oral proteasome inhibitor, in combination with lenalinomide and Dex
- Elotuzumab – Mab that targets signaling lymphocyte activation molecule F7(SLAMF7), in combination with lenalinomide and Dex
- Daratumab – Mab targeting CD38, single agent

SIDE EFFECT OF THALIDOMIDE

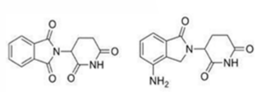


HISTONE DEACTYLASE INHIBITORS -PANOBISTAT



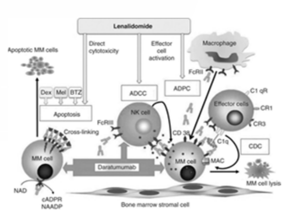


LENALIDOMIDE (REVLIMID)



Thalidomide   Lenalidomide

- Derivative of thalidomide –more potent
- Oral
- Fewer side effects:
  - No neuropathy
  - Less constipation
  - Less sedation
  - Less VTE
  - **MORE myelosuppression/cytopenias**
  - Maybe teratogenic



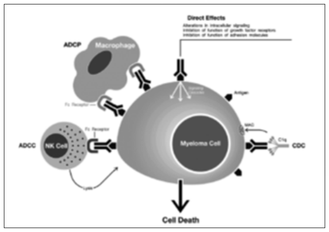
MONOCLONAL ANTIBODIES

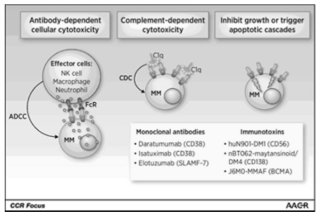
"Targeting" mAbs

Monoclonal antibody	Antigenic target
Elotuzumab	SLAMF7 (CS-1)
Daratumumab SAR650984	CD38
Siltuximab	IL-6
Tocilizumab	IL-6R
Dacetuzumab	CD40
MA5	MUC-1
BT-062*	CD138
IPH-2101†	KIR

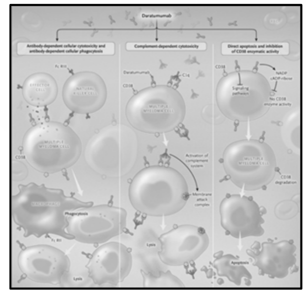
* Immunotoxin conjugate

HOW MABS CAN KILL MM CELLS



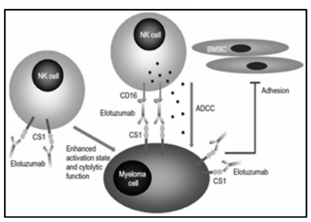


MECHANISMS OF **DARATUMUMAB** ACTION

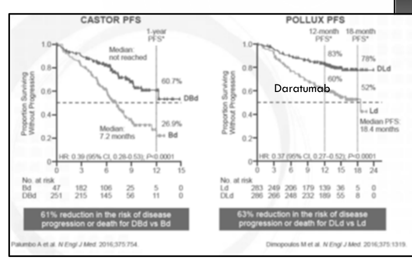


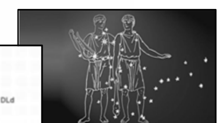
ELOTUZUMAB (EMPLICITI) – DIRECTED AGAINST SLAM7 (CS1

- For patients previously treated 1 – 3 times
- Used with Dex and Lenalinomide



DARA COMBINATIONS WITH OTHER THERAPIES IN RELAPSED-REFRACTORY MM – 2016 NEJM –CASTOR AND POLLUX STUDIES

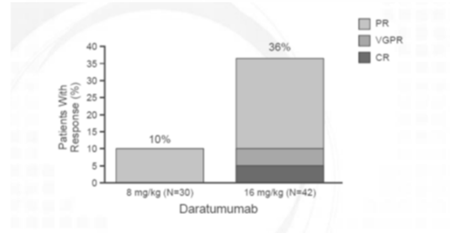




DARATUMUMAB, DARA (DARZALEX)

- Human IgG antibody (mAB) that targets **CD38**
- CD38 – a transmembrane protein abundantly expressed on malignant plasma cells; also functions in cell adhesion, signal transduction, and calcium signaling
- IV infusion
- Works well in combination or as a single agent

1/3 OF REFRACTORY MM PATIENTS RESPONDED TO DARA ALONE

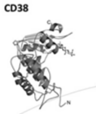


From Lokhorst HM et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med* 373(13):1207-1219. Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

EFFECTS ON TRANSFUSION TESTING

CD38

Tissue distribution:
- Lymphoid cells
- Myeloid cells
- RBCs
- Other tissues



Egea PF 2012, PLOS one 0034918

- CD38 is weakly expressed on red blood cells
  - Anti-CD-38 binds to CD38 on reagent RBCs causing panreactivity in vitro
  - Positive indirect antiglobulin (IAT) tests
  - Agglutination may occur in all media and all methods
    - Saline, low ionic strength saline, polyethylene glycol
    - Gel, tube, solid phase
  - Reactions are usually weak (1+), but stronger reactions have been observed in solid phase (up to 4+)
- **Anti-CD38 could mask a clinically significant alloantibody**

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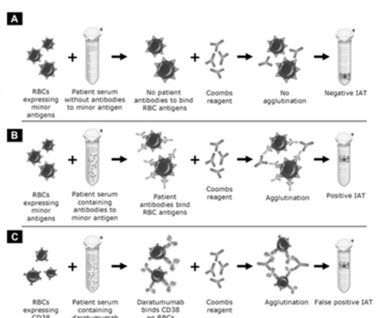
TABLE 4. DTT-sensitive blood group systems*

Blood group system name	ISBT symbol	Transfusion reaction potential
Dombrock	DO	Immediate/delayed, mild to severe
Indian	IN	Very rare, decreased cell survival with IN1
John Milton Hagen	JMH	Delayed (rare)
Kell	KEL	Immediate/delayed, mild to severe
Knops	KN	No
Landsteiner-Wiener	LW	Delayed, none to mild
Lutheran	LU	No to moderate
Raph	RAPH	No to moderate
Cartwright	YT	Delayed (rare); mild

* Adapted from the Blood Group Antigen Facts Book.[15]



MANAGING PATIENTS ON DARATUMUMAB

- Anti-CD38 interference may cause delays in issuing RBCs
- Before a patient begins anti-CD38 treatment
  - Perform baseline ABORh and antibody screen
  - Perform baseline genotype
- After a patient has begun anti-CD38 treatment
  - ABORh performed normally
  - Perform antibody screen and identification using DTT treated RBCs

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DTT-treating RBCs eliminates the interference in DARA-patient samples

Patient	DARA dose (mg/kg/wk)	Days from last dose	Ab screen & panel result	Panel result using DTT-RBCs
1	8	7	Panreactivity	Negative
2	8	7	Panreactivity	Negative
3	8	13	Panreactivity	Negative
4	16	0	Panreactivity	Negative
5	16	0	Panreactivity	Negative

Chapuy 2015, Transfusion 55:1545

MANAGING PATIENTS ON DARATUMUMAB

- Crossmatch
  - Antibody screen negative (using DTT-treated cells)
    - IS or electronic crossmatch ABORh compatible, K matched RBCs
  - Known alloantibody
    - Give phenotypically similar RBCs
    - May perform AHG crossmatch using DTT-treated donor cells
  - Transfusion emergently required: uncrossmatched ABORh compatible RBCs can be given per local transfusion service practices

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MANAGING PATIENTS ON DARATUMUMAB

- Hospitals should establish procedures to inform the transfusion service whenever any patient is scheduled to begin taking daratumumab
- Set up notification in EMR when Daratumumab is ordered by physician for ABORh, Antibody Screen, DAT, and genotyping testing to be ordered
- Daratumumab-mediated positive indirect globulin tests **may persist for up to six months** after the last daratumumab infusion
- Provide wallet card to patient to notify other blood of potential interference with testing and results of genotype/phenotype

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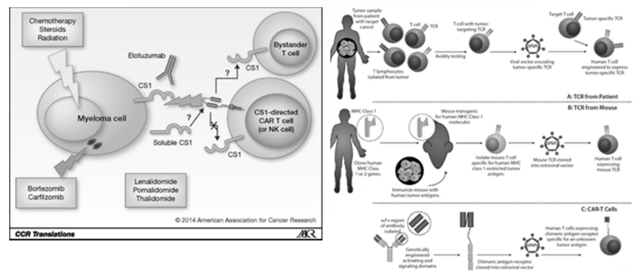
ADOPTIVE T CELL THERAPY MECHANISM OF ACTION



OTHER DRUGS IN DEVELOPMENT

- Selective inhibitor on nuclear export (SINE) Selinexor
- Checkpoint inhibitors
- Vaccines - against MAGE-A3 protein, found on the surface of multiple myeloma cells in high-risk patients

Table 12. **Clinical trial phases**

I	Early testing to assess dosing, tolerance, and toxicity in patients
II	Further testing to evaluate how effective treatment is at the dose and schedule selected
III	Comparison of the new treatment with prior treatment(s) to determine if the new treatment is superior
IV	Usually carried out after FDA approval to assess cost-effectiveness, quality of life impact, and other comparative issues

TRANSPLANT OPTIONS

Table 10. **High-Dose Therapy (HDT)**

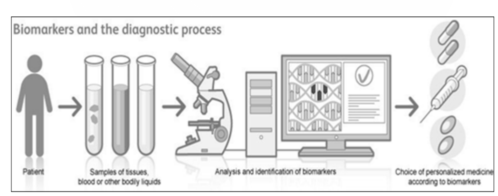
TRANSPLANT TYPE	ADVANTAGES	DISADVANTAGES
Single Autologous	• 50% excellent remissions • At least as good as standard therapy regarding overall survival and probably better for patients with high Sβ2M • Basis for strategies to produce true remission or long-term cure • New preparative regimens may produce true complete remission	• Relapse pattern similar to standard chemotherapy • More toxic and expensive • Patients who decisively benefit from transplant not clearly identified • Maintenance therapy may still be required/recommended
Double Autologous	• 2002 update of French data indicates survival benefit for subset of patients not in CR or VGPR • Excellent results with tandem transplant *(see text)*	• Role of double versus single still unclear • Much more toxic and expensive versus single • No survival benefit if in CR or VGPR after first transplant
Traditional Allogeneic	• No risk of contamination of marrow/stem cells with myeloma • Possible graft-versus-myeloma effect to prolong remission	• Even for HLA identical siblings, significant risk of early complications and even death • Risk of complications unpredictable • Restricted to age < 55 • More toxic and expensive versus autologous
Reduced-intensity conditioning (RIC) allogeneic transplant or "Mini-Allo"	• Less toxic form of allo • Preparative chemotherapy usually well tolerated • Results in anti-myeloma immune graft	• Still produces graft-versus-host disease • Full benefits still unclear • Risk of initial mortality approximately 17% • Not recommended for myeloma patients outside the context of a clinical trial
Identical Twin	• No risk of myeloma contamination in transplanted cells • Much less risky than allogeneic transplant	• No graft-versus-myeloma effect • Need identical twin < 55

ADOPTIVE T CELL THERAPY

- In clinical trials in myeloma & other cancers
- Patients have their T cells removed and activated with chimeric antigen receptors (CARs)
- CARs are proteins that allow T cells to recognize a specific antigen on tumor cells (CD19, CD38, CD40, CD44, CD47, ICAM1, NCAM1, CD74, CD81, CD86, CD200, IGF1R, CD307, CD317, SLAM7, PD-L1, CD138, and B-cell membrane antigen, BCMA)
- These cells are then reintroduced into the body, they will start multiplying, and with help from the engineered receptor, will locate tumor cells with the targeted antigen and destroy them

TUMOR MARKERS

- Patients' genes and proteins are increasingly being measured to diagnose and manage their cancers
  - Examples: BRCA1, HER2/neu, CEA, AFP
- These markers can help in designing personalized treatment



THE IDEAL TUMOR MARKER

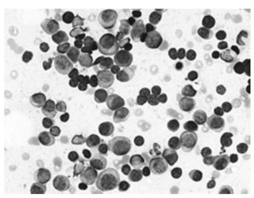
- Testing requirements:
  - Easily available source of tissue – e.g., blood sample
  - Simple and reproducible test
  - Accurate
- Clinical requirements:
  - Found in nearly all patients
  - Accurately correlates with disease to:
    - Predict patient outcome
    - Monitor response to treatment

CONCLUSIONS

- Between the 1960's and the 1990's, the prognosis MM survival was dismal
- Survival improved with high dose chemo and Stem cell transplant
- Survival is improving with these newer agents and SCT
- Huge advances in MM treatment but patients still relapse, so newer treatments/combos are being studied

B-CELL MATURATION ANTIGEN, BCMA

- A tumor marker for myeloma (?)
  - Shed from tumor cells into the blood
  - Correlates with disease status
  - Accurately measures the current disease status
  - Can be used to quickly determine response to treatment
  - In vitro studies promising
- Phase I clinical trial for use in CAR therapy and antibody conjugate (2017)



QUESTIONS?

10 STEPS TO BETTER CARE
A UNIQUE TOOL FOR DIAGNOSTIC AND TREATMENT INFORMATION

One of the most daunting aspects of being diagnosed with multiple myeloma is learning about – and understanding – an unfamiliar disease that is quite complicated. From diagnosis to long-term survival, the 10 Steps to Better Care* will guide you through the myeloma journey:

1. **Know what you're dealing with. Get the correct diagnosis.**
2. **Tests you really need.**
3. **Initial treatment options.**
4. **Supportive care and how to get it.**
5. **Transplant: Do you need one?**
6. **Response Assessment: Is treatment working?**
7. **Consolidation and/or maintenance.**
8. **Keeping Track of the Myeloma: Monitoring without mystery.**
9. **Relapse: Do you need a change in treatment?**
10. **New Trials: How to find them.**

Visit **10steps.myeloma.org** to gain a better understanding of the disease and diagnosis, and proceed through the steps to learn the best tests, treatments, supportive care, and clinical trials currently available.

As always, the International Myeloma Foundation (IMF) urges you to discuss all medical issues thoroughly with your doctor. The IMF is here to equip you with the tools to understand and better manage your myeloma. Visit the IMF website at myeloma.org or call the IMF InfoLine at 800-452-CURE (2873) or 818-487-7455 to speak with our trained information specialists about your questions or concerns. The IMF is here to help.

SUPPORTIVE THERAPY

- Aspirin
- Bisphonates – monthly for 1 year, then q 3 months
  - Dental evaluation before to avoid dental extractions & risk of osteonecrosis
- Surgery to repair fractures
- Kyphoplasty/Vertebroplasty for vertebral body compression fractures
- Acyclovir with Bortexomid (Velcade)
- Intravenous immunoglobulin prophylaxis for frequent infections
- Dialysis
- Collect stem cells BEFORE too much myelotoxic therapy (avoid mel and >4 cycles REV)