MULTIPLE MYELOMA: WHAT'S NEW?

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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

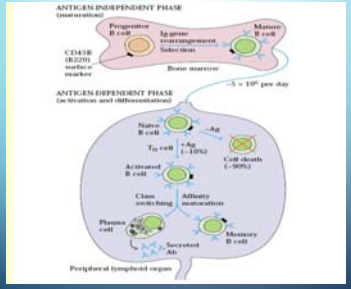
PLASMA CELL (MULTIPLE) MYELOMA

- 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

ETIOLOGY OF MM

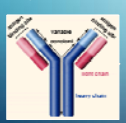
- Genetic causes ?
- Extension of MGUS
- Environmental/occupational exposures
- Radiation
- Chronic inflammation
- Infection (HH8)

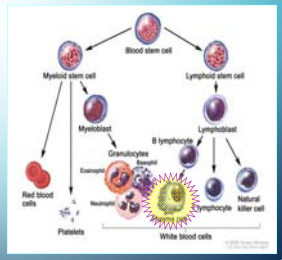
B CELL MATURATION



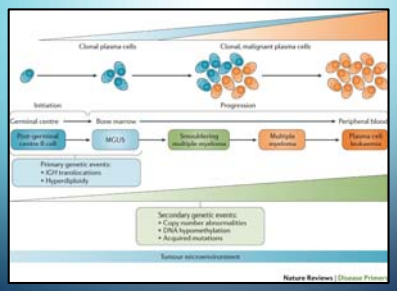
PLASMA CELL NEOPLASMS

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





PROGRESSION OF MULTIPLE MYELOMA



PLASMA CELL NEOPLASM DIAGNOSIS

- Pathological
- Clinical
- Radiological
- Molecular/Cytogenetic

LAB EVALUATION FOR A SUSPECTED PLASMA CELL DISORDER

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

SERUM FREE LIGHT CHAINS

- 2 types of light chains, kappa or lambda: light or 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:
  - The more myeloma cells, the greater the production of monoclonal protein.

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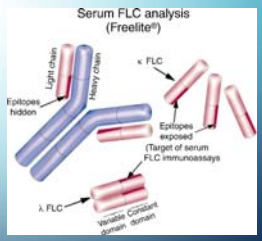
Normal levels of serum free light chains are*:

- 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.



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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

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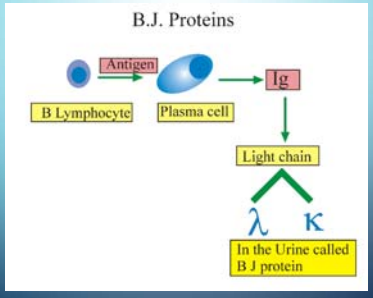
BENCE-JONES PROTEINS



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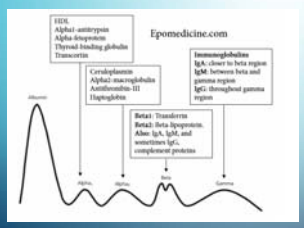
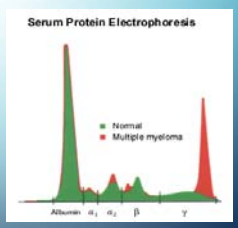
SERUM PROTEIN ELECTROPHORESIS (SPEP)





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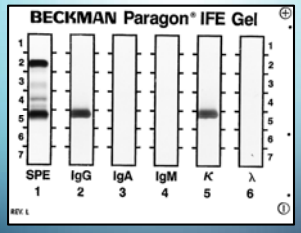
IMMUNOFIXATION, IFE



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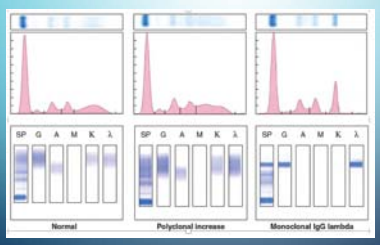
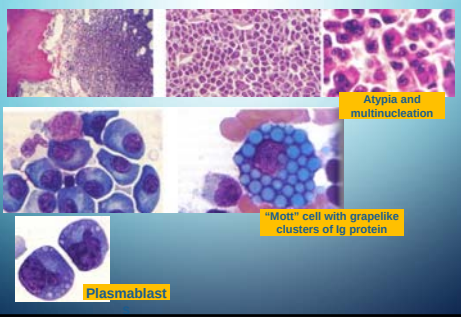
SERUM PROTEIN ELECTROPHORESIS (SPEP)
IFE: SUBTYPES THE M-SPIKE COMPONENT



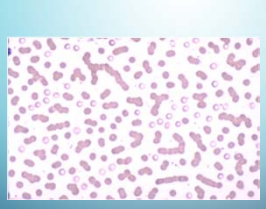
MORE ABOUT MONOCLONAL PROTEINS IN MM

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

BONE MARROW FINDINGS



PERIPHERAL BLOOD FINDINGS



OTHER LAB FINDINGS

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

OTHER LAB FINDINGS

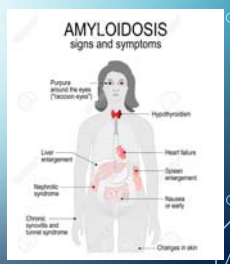
- Altered albumin to globulin ration
- β2 macroglobulin -Surrogate marker for tumor burden
- CRP – Surrogate marker for IL-6 (IL-6 is a plasma cell growth factor)
- Serum viscosity (with very high M protein) CNS symptoms

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

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- heart, CHF; kidney, nephrotic syndrome; peripheral nerves, neuropathy, etc.
- Bleeding due to binding of factor X to amyloid causing factor X deficiency



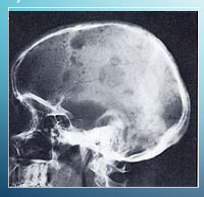
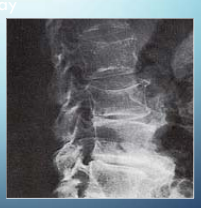
PATHOPHYSIOLOGY

Table 2. **Schema of pathophysiology**

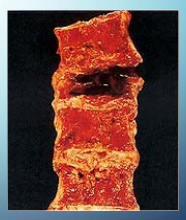
Skeletal Findings	• Solitary or multiple osteolytic lesions	• Diffuse osteoporosis (osteopenia)
Associated Effects of Bone Destruction	• Elevated serum calcium • Hypercalciuria (calcium increase in urine)	• Bone fractures • Loss of height (vertebral collapse)
Extramedullary (extraskeletal) Myeloma	• Soft tissue involvement, mostly common in head/neck area (e.g., nasopharynx); also in liver, kidney, and other soft tissue sites including skin	
Peripheral Blood	• Anemia • Abnormal clotting • Leukopenia	• Thrombocytopenia • Plasma cell leukemia • Circulating plasma cells • Circulating monoclonal B lymphocytes (precursors of myeloma cells)
Plasma Protein Changes	• Hyperproteinemia (elevated protein) • Hypervolemia (expanded volume) • Monoclonal immunoglobulins (IgG, IgA, IgD, IgE, IgM or light chains only)	• Narrowed anion gap (low serum sodium) • Elevated serum β2-microglobulin • Decreased serum albumin • Elevated serum IL-6 and C-reactive protein (CRP)
Kidney Abnormalities	• Proteinuria, casts without leukocytes or erythrocytes • Tubular dysfunction with acidosis (Fanconi syndrome)	• Uremia (kidney failure) • Amyloidosis or light chain deposition disease and renal dysfunction

PLASMA CELL MYELOMA: SYMPTOMATIC – RADIOLOGIC SIGNS

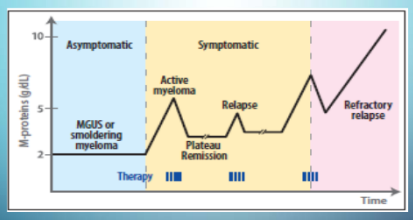
- Lytic bone lesions seen on X-ray

LYTIC BONE LESIONS – AUTOPSY

DISEASE PHASES



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

CRAB: HyperCalcemia, Renal insufficiency, Anemia, Bone lesions

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

Asymptomatic (Smoldering) Plasma Cell Myeloma

M-protein in serum at myeloma levels

AND/OR

10% or more clonal plasma cells in marrow

NO related organ or tissue impairment

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**

CALCIUM

- Lysis of bone leads to increased calcium in the blood
- 30% of patients have at time at presentation
- Key factors – IL6, IL1, RANKL, MIP 1a and osteoblastic dysfunction

RENAL DYSFUNTIONS: CAUSES OF RENAL FAILURE IN MM

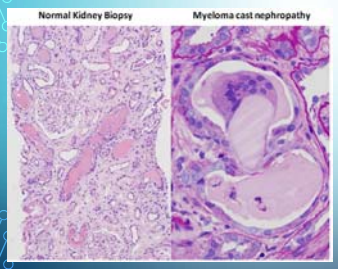
- Cast nephropathy
- Light chain deposition disease
- Primary amyloidosis
- Hypercalcemia
- Renal tubular dysfunction
- Volume depletion
- IV contrast dye, nephrotoxic meds

MYELOMA KIDNEY

- Two main pathogenetic 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

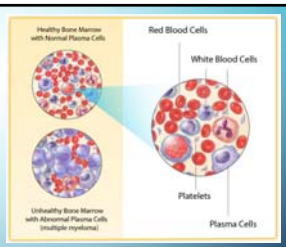
- Most common pathological diagnosis on renal biopsy in multiple myeloma
- Due to light chains binding with Tamm-Horsfall mucoprotein, which is secreted by tubular cells in ascending loop of Henle, forming casts
- Multinucleated giant cells surround the casts
- Dehydration worsens cast nephropathy due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

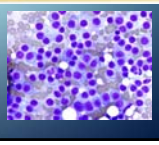


- Treatment of renal failure
  - IV rehydration
  - Treatment of hypercalcemia
  - Treatment of MM
  - Plasmapharesis ?
  - Dialysis if necessary

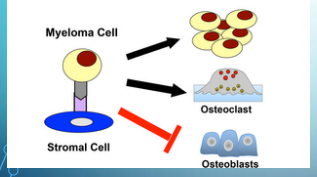
ANEMIA

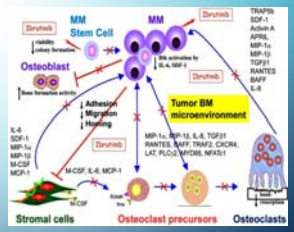
- Myeloma cells crowd out normal cells in BM
- Decreased production of red cells – anemia
- Can also be caused by treatments for MM





BONE LESIONS





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

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 **Li**ght chain ratio involved : uninvolved ≥ 100
  - **M** -1 focal lesion (≥ 5mm each) detected by **M**RI
- Don't have to wait for end organ damage (CRAB) to start treatment
- "SLIM CRAB" for diagnosis

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)

CYTOGENETICS FINDINGS

Cytogenetic abnormality	Smoldering multiple myeloma	Multiple myeloma
	Clinical setting in which abnormality is detected	
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 Isolated Monosomy 13, or Isolated Monosomy 14 Normal	Standard-risk of progression, median TTP of 5 years Standard-risk of progression, median TTP of 5 years Low-risk of progression, median TTP of 7-10 years	May ameliorate adverse prognosis confirmed by high risk IgH translocations, and del 17p Effect on prognosis is not clear Good prognosis, probably reflecting low tumor burden, median OS >7–10 years

CYTOGENTICS TERMINOLOGY

- Diploid – normal number (2) of chromosomes per cell
- Hyperdiploid -more than the usual diploid 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; trisomy is a type of aneuploidy
- Deletion- deletion of all or part of a chromosome
- Translocation –rearrangement of parts of chromosomes

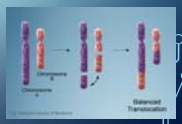


Table 27.3 Risk-Stratification of Multiple Myeloma

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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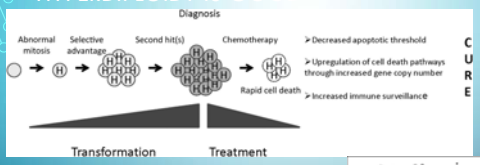
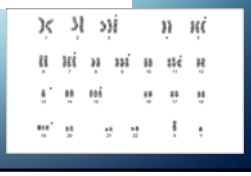
HYPERDIPLOIDY IS GOOD



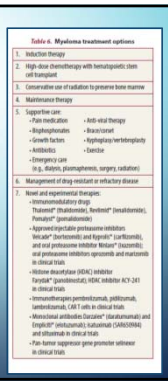


PLASMA CELL MYELOMA PROGNOSIS

- Prognosis:
  - Median survival ~ 3 years
  - ~ 10% survival for 10 year
  - Survival has increased

THERAPEUTIC OPTIONS

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



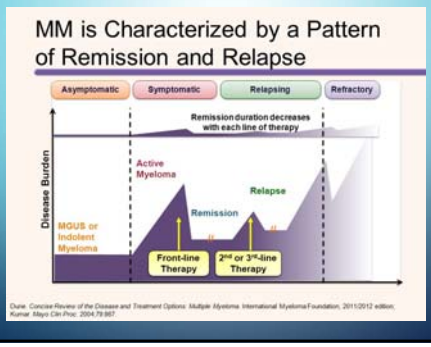
CHEMOTHERAPY

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

CHEMOTHERAPY TERMINOLOGY

- **Induction therapy** –the 1st treatment given, often a standard set of treatments
- **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

MM is Characterized by a Pattern of Remission and Relapse

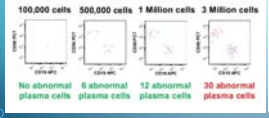


DETECTING MINIMAL RESIDUAL DISEASE (MRD)

Flow Cytometric Evaluation of Plasma Cell Myeloma: Minimal Residual Disease

Effect of number of cells (events) acquired on MRD

53 year old Female with MM post therapy. MM Cells: CD19-, CD45-, CD38 dim, CD20-, CD56+, CD81-, dim CD27



International Myeloma Working Group (IMWG) MRD Criteria[1]

MRD negative: absence of aberrant clonal plasma in bone marrow aspirate, ruled out by an assay with minimum sensitivity of 1:10^5 nucleated cells or higher (ie, 10^{-5} sensitivity)

Sustained MRD negative: MRD negativity in the marrow (flow or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart; subsequent evaluations can be used to further specify the duration of negativity (eg, MRD negative at 5 years)

Imaging plus MRD negative: MRD negativity as defined by flow or NGS, plus disappearance of every area of increased tracer uptake found at baseline, a preceding PET/CT, decrease to less mediastinal blood pool SUV, or decrease to less than that of surrounding normal tissue

Based on flow cytometry or NGS (such as Euroflow standard operation procedure for MRD detection in MM, or other validated equivalent methods; LymphoSIGHT, or other validated equivalent method)

1. Kumar S et al. Lancet Oncol. 2016; 17:e328-346.

ALKYLATING AGENTS: MELPHALAN (ALKERAN)

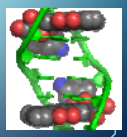
- Nitrogen mustard alkylating agents
- An alkylating agent adds an alkyl group (C_nH_{2n+1}) to DNA
- Side effects
  - Nausea and vomiting
  - Bone marrow suppression
  - Pulmonary fibrosis
  - Hair loss
  - Myelodysplastic syndrome

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

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



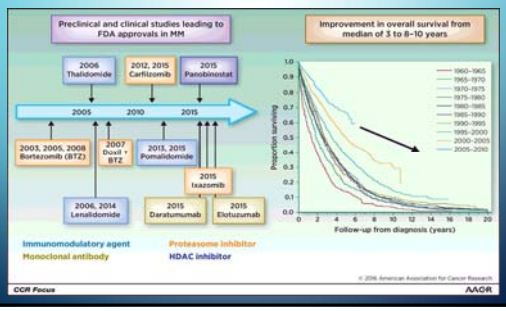
STEROIDS (CORTICOSTEROIDS)

- Prednisone and Dexamethasone
- Anti-inflammatory and anti-Myeloma effects
- Help reduce nausea & vomiting
- 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

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

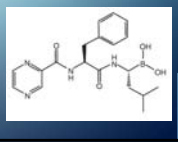


PROTEASOME INHIBITORS – BORTEZOMIB (VELCADE)

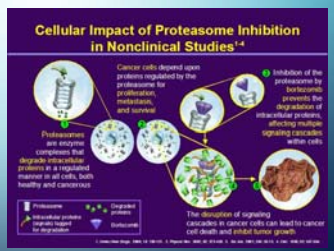
- Proteasomes – protein complexes that degrade proteins by breaking peptide bonds (proteolysis)
- Proteasome inhibitors –drugs that block the action of proteasome - Prevent protein breakdown
- Excess proteins cause cell cycle arrest and apoptosis
- Boron atom binds to the catalytic site of the 26S proteosome

BORTEXOMIB (VELCADE)

- First approved proteasome inhibitor
- 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 ubquitinylation) for removal
  - Disrupts homesstasis; leads to apoptosis
- Side effects:
  - Peripheral neuropathy
  - Bone marrow suppression
  - H Zoster infections due to immunocompromise



PROTEASOME INHIBITORS – BORTEZOMIB



CARFILZOMIB (KYPROLIS)

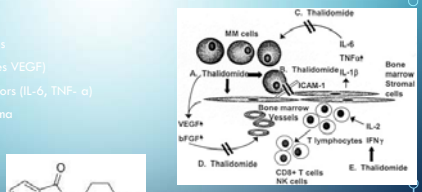
- Proteosome inhibitor
  - Binds irreversibly, given by IV infusion (2 d/wk)
  - Active in 22% of MM pts refractory to Velcade and Revlimid (and may be more powerful than velcade in up-front therapy but studies ongoing)
  - Mainly Hematologic toxicity, Peripheral Neuropathy RARE (despite being similar to Velcade)
  - FDA Approved July 2012 (only for those that are relapsing after prior velcade and revlimid)
  - 2015 approved in combo with Rev/dex

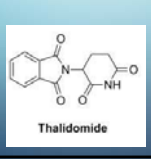
IMMUNOMODULATORY AGENTS

- 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- a)
  - Inhibits adhesion to the stroma
- Side Effects:
  - Teratogenic
  - Peripheral Neuropathy
  - DVT/PE
  - Constipation
  - Sedation

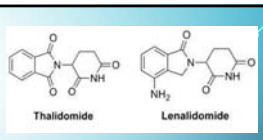


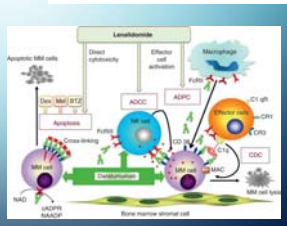


SIDE EFFECT OF THALIDOMIDE

LENALIDOMIDE

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



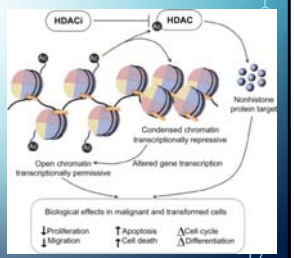


4 NEW DRUGS APPROVED IN 2015

- 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 angent

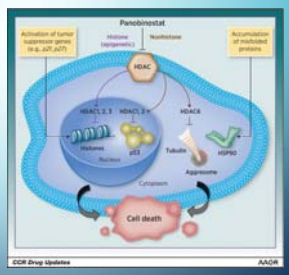
HISTONE DEACTYLASE INHIBITORS (HDACI)

- Hi



PANOBISTAT (FARYDAK)

- Not useful as a monotherapy
- Side effects:
  - Pancytopenia
  - Fatigue
  - Nausea
  - Diarrhea
  - Insomnia



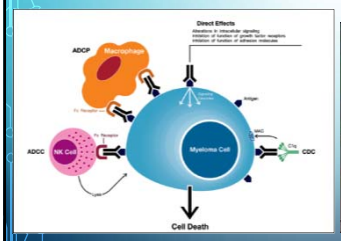
MONOCLONAL ANTIBODIES

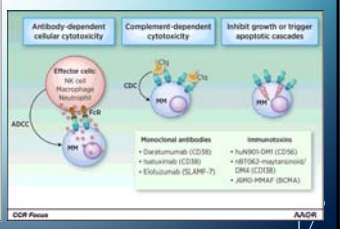
"Targeting" mAbs

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

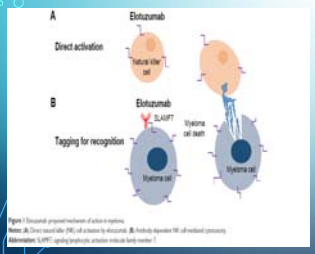
* Immunotoxin conjugate

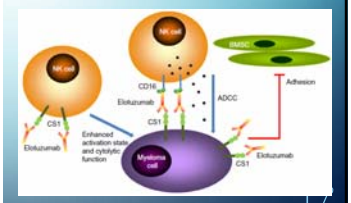
HOW MABS CAN KILL MM CELLS





ELOTUZUMAB – DIRECTED AGAINST SLAM7

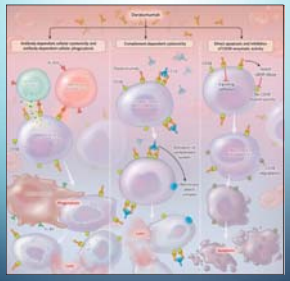




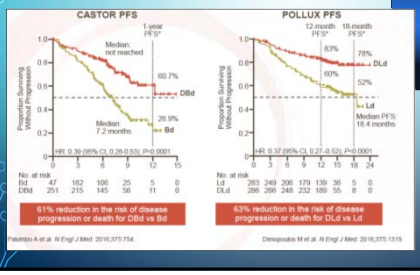
DARATUMAB, DARA (DARZALEX)

- Human IgG antibody (mAb) that targets CD38
- CD38 – a transmembrane protein abundantly expressed on malignant plasma cells
- IV infusion
- Works well in combination or as a single agent

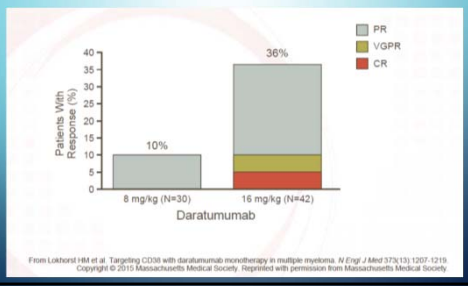
MECHANISMS OF DARATUMUMAB ACTION



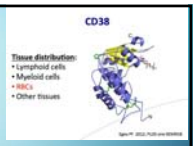
DARA COMBINATIONS WITH OTHER THERAPIES IN RELAPSED-REFRACTORY MM – 2016 NEJM –CASTOR AND POLLUX STUDIES



1/3 OF REFRACTORY MM PATIENTS RESPONDED TO DARA ALONE



EFFECTS ON TRANSFUSION TESTING



- 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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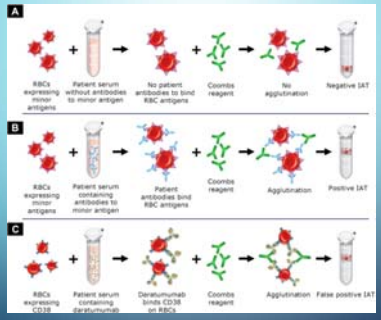

DTT-treating RBCs eliminates the interference in DARA-patient samples

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

TREATMENT OF RED BLOOD CELLS

- Dithiothreitol (DTT)
  - Disrupts daratumumab binding, allowing detection of underlying atypical alloantibodies in patient plasma
  - Test in conjunction with a k positive cell to confirm effectiveness of DTT treatment
  - Antigens sensitive to DTT include; Kell blood group antigens, Yt^a, Do^a/Do^b
- Adsorptions using ZZAP and untreated RBC's failed to remove interference
- Other methods of mitigating anti-CD38 interference
  - Neutralization using recombinant soluble human CD38 or daratumumab idiotype antibody
    - Neither reagent is widely available at this time
  - Antigen-typed cord cells have been used for the antibody screen as an alternative to DTT-treated cells

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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 phenotype or 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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MANAGING PATIENTS ON DARATUMUMB

- 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
    - Even if phenotypically similar RBCs are selected, AHG crossmatch will still be incompatible
- Transfusion emergently required: uncrossmatched ABORh compatible RBCs can be given per local transfusion service practices

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MANAGING PATIENTS ON DARATUMUMAB

- Hospitals establish procedures to inform the transfusion service whenever any patient is scheduled to begin taking daratumumab
- Set up notification in EMR when daratumamb 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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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

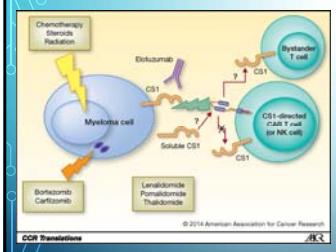
Table 12. **Clinical trial phases**

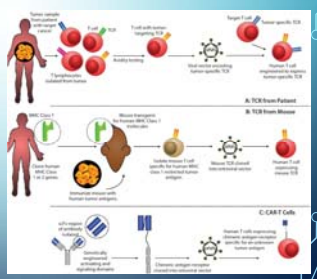
I	Early testing to assess dosing, tolerance, and toxicity in patients
II	Further testing to evaluate how effective treatment is at the dose and schedule selected
III	Comparison of the new treatment with prior treatment(s) to determine if the new treatment is superior
IV	Usually carried out after FDA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

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

ADOPTIVE T CELL THERAPY MECHANISM OF ACTION





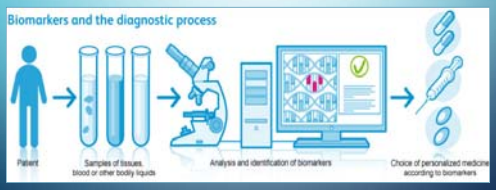
TRANSPLANT OPTIONS

Table 16 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 SJLM • 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 do 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

TUMOR MARKERS

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

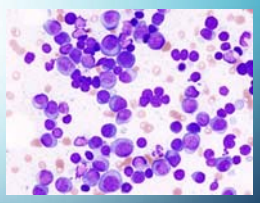


THE IDEAL TUMOR MARKER

- 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

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



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 compression fractures
- Acyclovir with Velcade
- Dialysis
- Collect stem cells BEFORE too much myelotoxic therapy (avoid mel and >4 cycles REV)

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.