Multiple Myeloma

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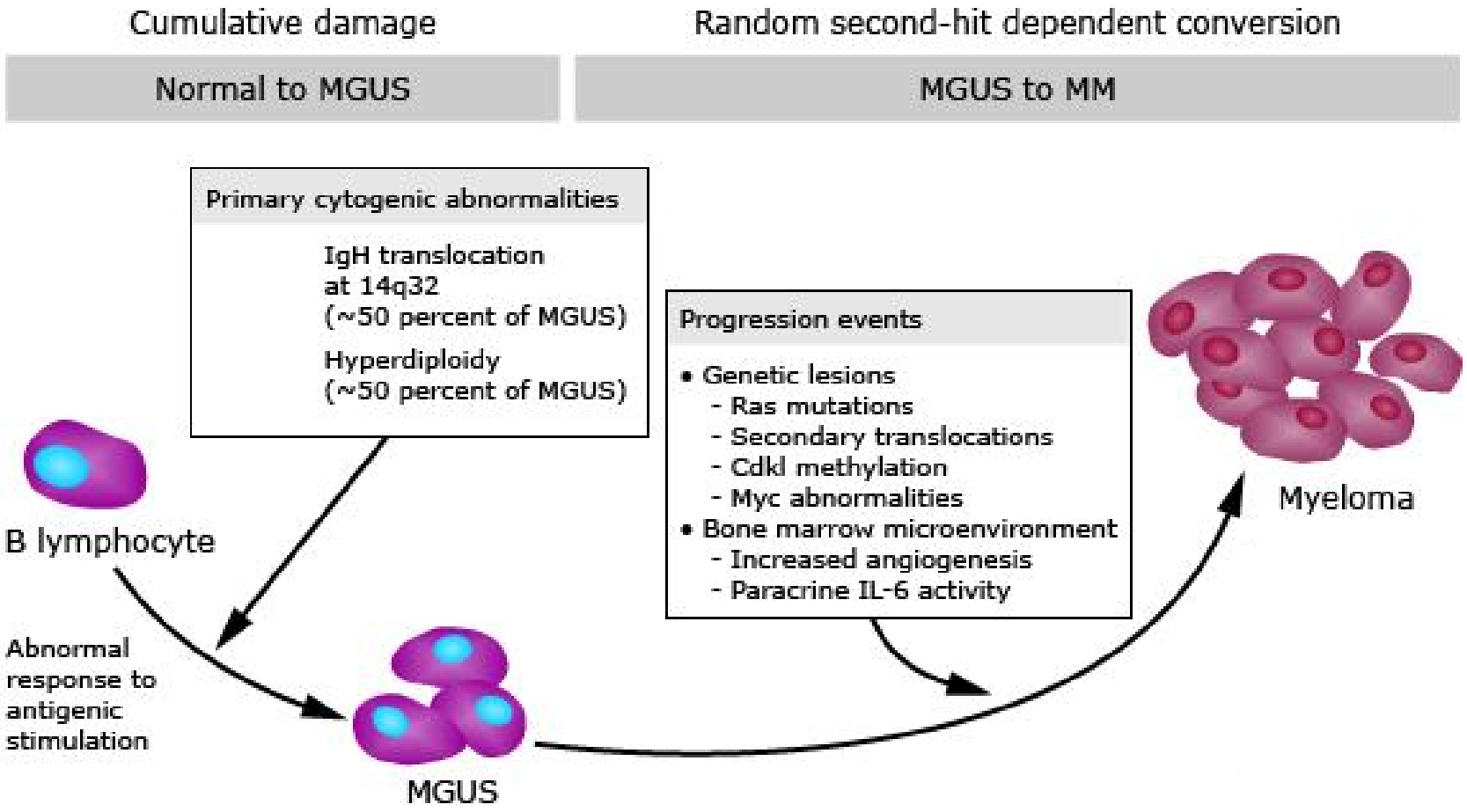
What is Multiple Myeloma?

- Cancer of the plasma cell

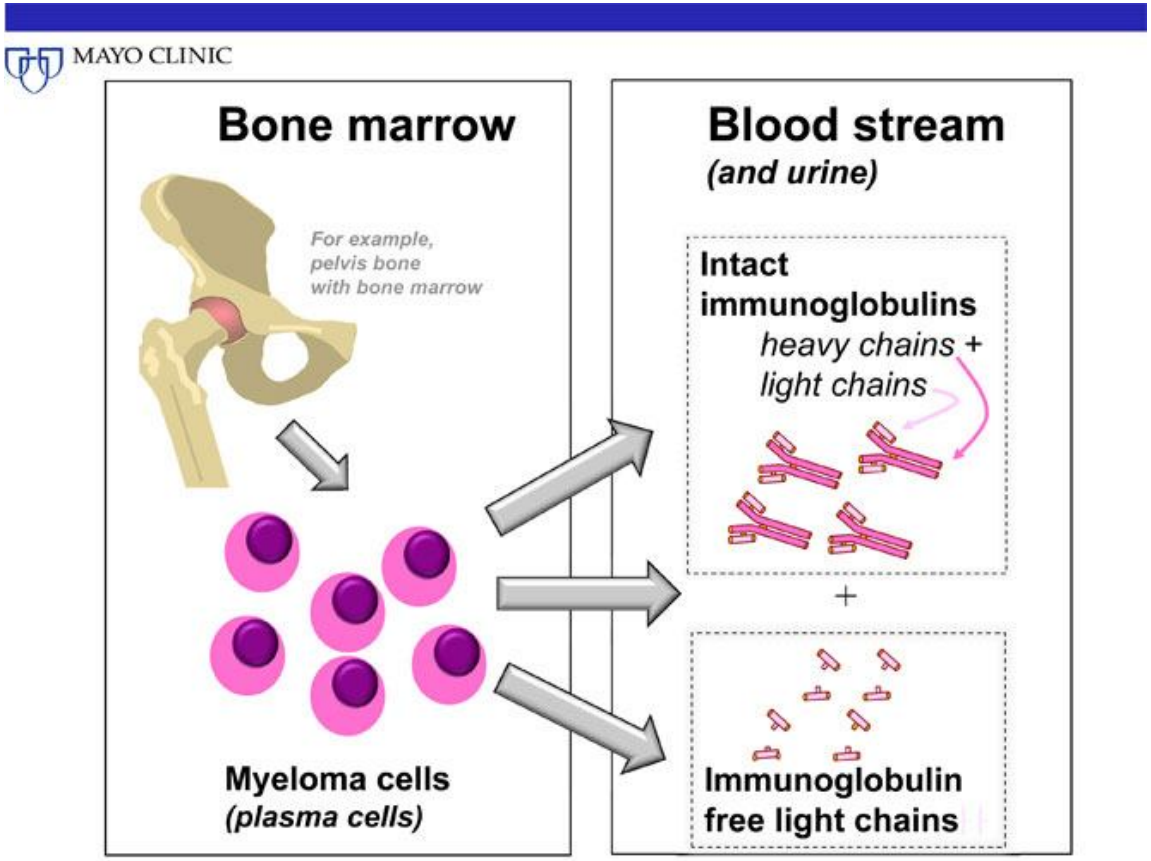
- Definition:
  B-cell malignancy characterised by abnormal proliferation of plasma cells able to produce a monoclonal immunoglobulin (M protein).

- This clone of plasma cells proliferates in the bone marrow.

Pathogenesis



MGUS: Monoclonal gammopathy of undetermined significance



IgG — 52 %
IgA — 21 %
IgD — 2 %
IgM — 0.5 %

κ or λ light chain only (Bence Jones) — 16%

Monoclonal myeloma plasma cells proliferate and overproduce M protein

From: International Myeloma Foundation

Incidence

- Myeloma develops in 1–4 per 100,000 people per year.

- MM is the second most common hematological malignancy in the U.S. (after non-Hodgkin lymphoma), and constitutes 1% of all cancers.

Risk Factors

- Age - over 65 years old
- Gender - Men > Women (1.4:1)
- Race - black Americans > white Americans.
- Radiation
- Family history
- Workplace exposures - petroleum-related industries
- Obesity

Clinical Presentations

- Bone disease & hypercalcemia
- Recurrent infections
- Anemia and fatigue
- Renal failure due to multiple causes
- Neuropathy
- Asymptomatic in a minority of the patients

Screening and Diagnosis

- Blood and urine tests
- X-rays
- Magnetic Resonance Imaging (MRI)
- Computerized Tomography (CT)
- Bone marrow examination

Criteria for Diagnosis

MGUS

- **<30 g/L M spike**
  <10% PC

Smoldering/Asymptomatic MM

∀ ≥30 g/L M spike

- **OR**

∀ ≥10% PC

Active MM

- **>10% PC**
- **M spike+**

- **AND**

CRAS

No anaemia, bone lesions, normal calcium and kidney function (no CRAS)

Kyle RA. N Engl J Med 2002; 346: 564

Staging for Multiple Myeloma

- Durie-Salmon System (DSS)-1970s
  - Monoclonal immunoglobulin
  - Calcium
  - Bone damage
  - Hemoglobin

- International Staging System (ISS)-2005
  - Beta(2)- microglobulin
  - Serum albumin

International staging system (ISS)

Stage	Criteria	Median survival (months)
I	B2M <3.5 mg/L and serum albumin ≥3.5 g/dL	62
II	•B2M <3.5 mg/L, but serum albumin <3.5 g/dL •B2M 3.5 – 5.5 mg/L irrespective of the serum albumin	44
III	B2M ≥5.5 mg/L	29

•B2M: Beta(2)- microglobulin

Treatment Options

- The stage of the disease
- The symptoms
- The person's age and general health

- Inactive disease is asymptomatic disease that does not require immediate treatment.

- **Solitary plasmacytomas:**
  These are often treated with radiation therapy. If the plasma cell tumor is not in a bone, it may be removed with surgery.

- **Early myeloma:**
  Smoldering myeloma and stage I disease.
  Patients with bone disease from myeloma are often started on a bisphosphonate.

- **2011 NCCN Guidelines:**

  Progression to stage II or higher disease should be replaced by the term progression to symptomatic disease.

Treatment Options

- Chemotherapy
  - Traditional chemo
  - Immunomodulating agents: Thalidomide / Lenalidomide
  - Target agent: Bortezomib (Velcade®)

- Stem cell transplantation (SCT)
  - Autologous / Allogeneic

Is stem cell transplantation an option?

- European: < 65 years
- United States: age-limit is not used.

- NOT considered for transplantation:
  - Age >77 years
  - Direct bilirubin >2.0 mg/dL
  - Serum creatinine >2.5 mg/dl unless on chronic stable dialysis
  - ECOG performance status 3 or 4 unless due to bone pain
  - New York Heart Association functional status Class III or IV

Treatment for MM is best categorized on the basis of the patient's age and prognostic factors:

(1) Young, newly diagnosed patients who are potential transplant candidates

(2) High-risk patients who are potential transplant candidates

(3) Newly diagnosed elderly patients who are not transplant candidates.

- Chromosomal abnormalities: *(2009 International Myeloma Workshop)*
  - High-risk (25%): presence of t(4;14) or deletion 17p13 detected by fluorescence in situ hybridization.
  - Standard-risk (75%): t(11;14) detected by fluorescence in situ hybridization.

- ISS stages II and III and high serum beta(2)-microglobulin levels are suggestive of higher risk disease.

VAD regimen

Vincristin 0.4mg/day
Adriamycin 9mg/m2 } qd d1-4 **q4w x 4 cycles**

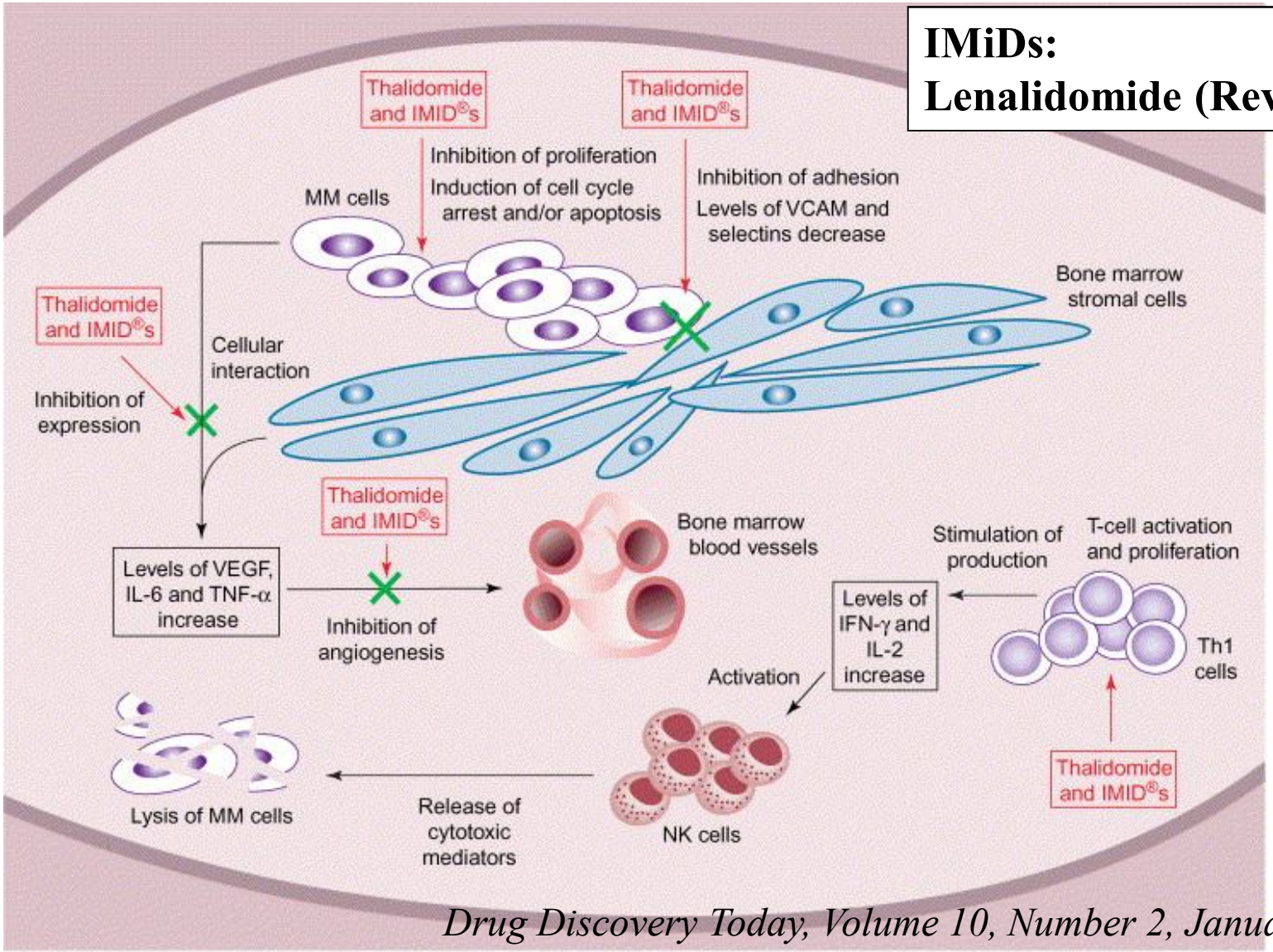
Deamethasone 40mg/day - qd d1-4, 9-12, 17-20

- Adverse effect:
  - Cardiac injury thrombotic events, and alopecia.

- Given these risks, and the higher response rates of new agents (thalidomide, lenalidomide, and bortezomib).

Mechanism of IMiDs

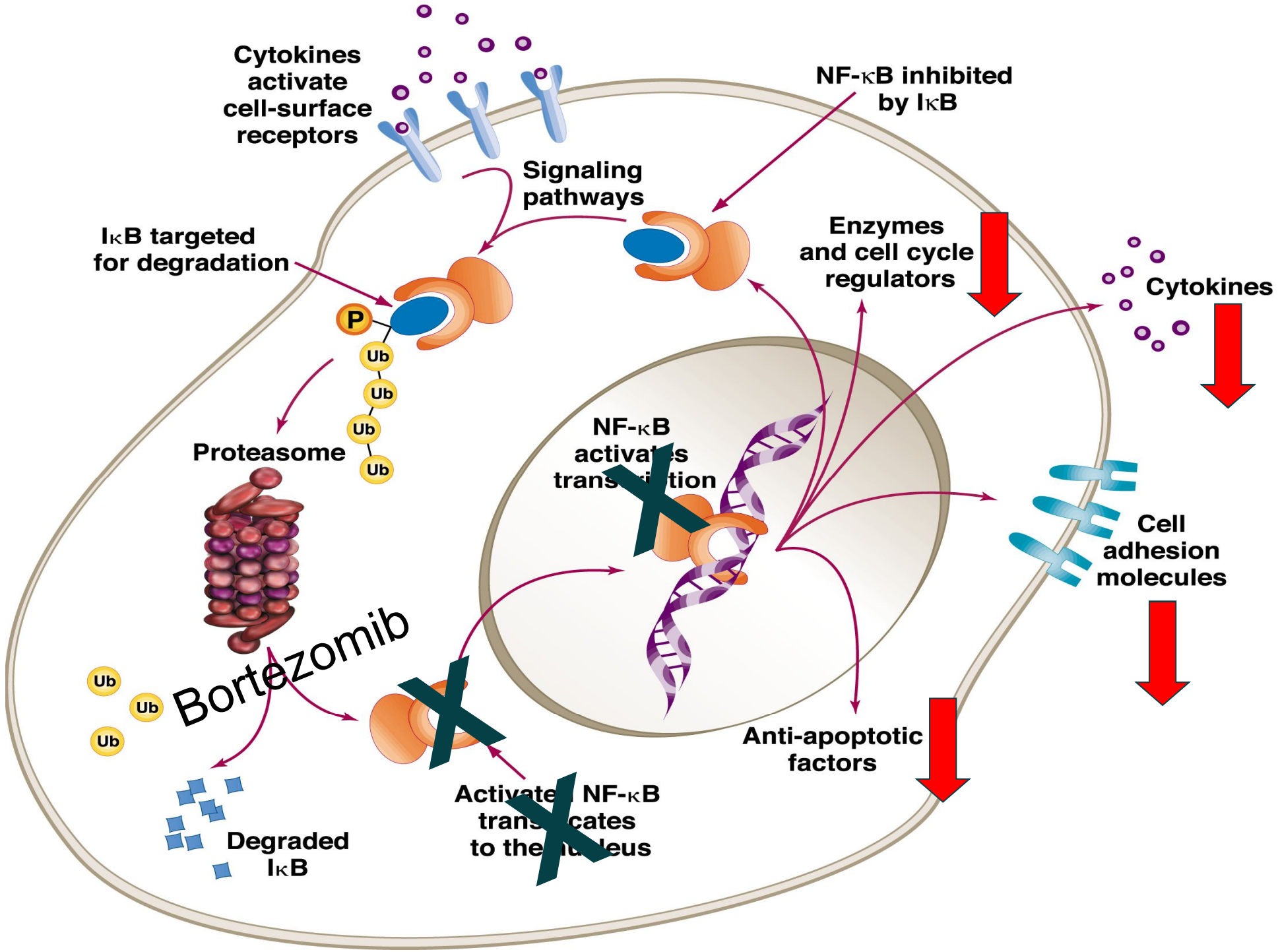
IMiDs:
Lenalidomide (Revlimid®)



Drug Discovery Today, Volume 10, Number 2, January 2005

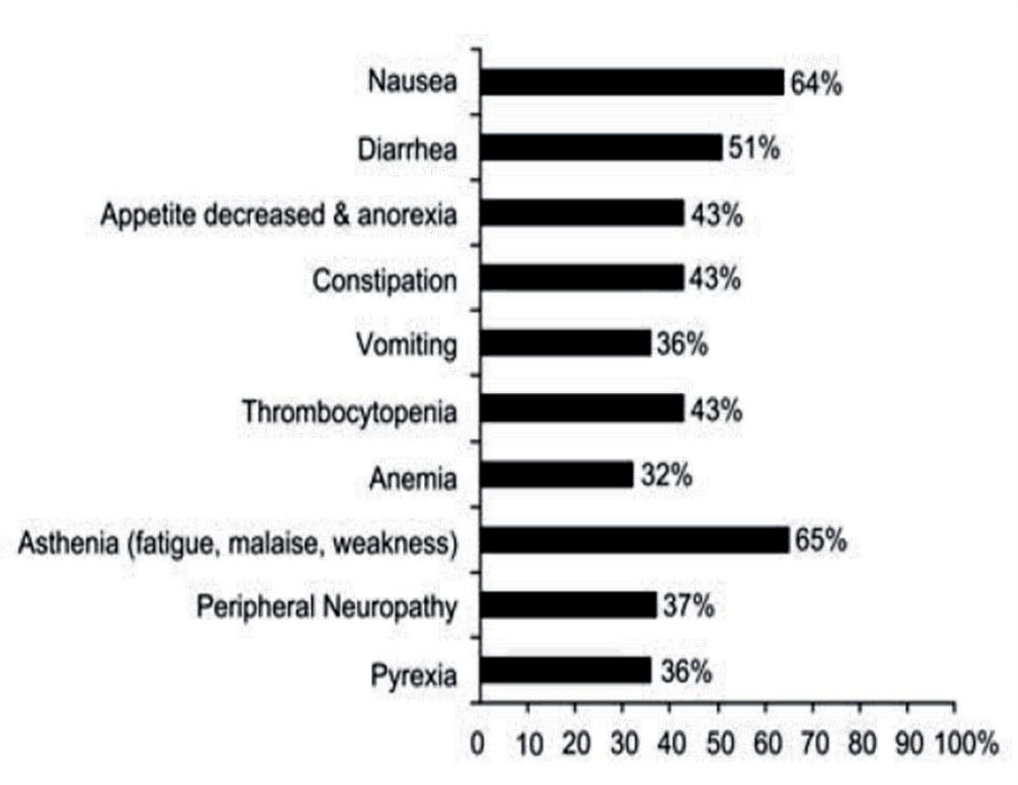
Side effects of IMiDs

- Thrombotic events
  - DVT
  - Pulmonary embolus
- Drowsiness and somnolence
- Peripheral neuropathy
- Dizziness and orthostatic hypotension
- Neutropenia (painful nerve damage)


Cytokines activate cell-surface receptors
NF-κB inhibited by IκB
Signaling pathways
IκB targeted for degradation
P
Ub
Ub
Ub
Ub
Proteasome
Enzymes and cell cycle regulators
Cytokines
NF-κB activates transcription
Cell adhesion molecules
Bortezomib
Ub
Ub
Ub
Anti-apoptotic factors
Activated NF-κB translocates to the nucleus
Degraded IκB

Bortezomib (Velcade®)

- A proteasome inhibitor
- Has shown good efficacy as a single agent and in combination in patients
  - With relapsed multiple myeloma
  - As initial treatment, including prior to autologous stem cell transplantation
- Is well-tolerated, including in combination

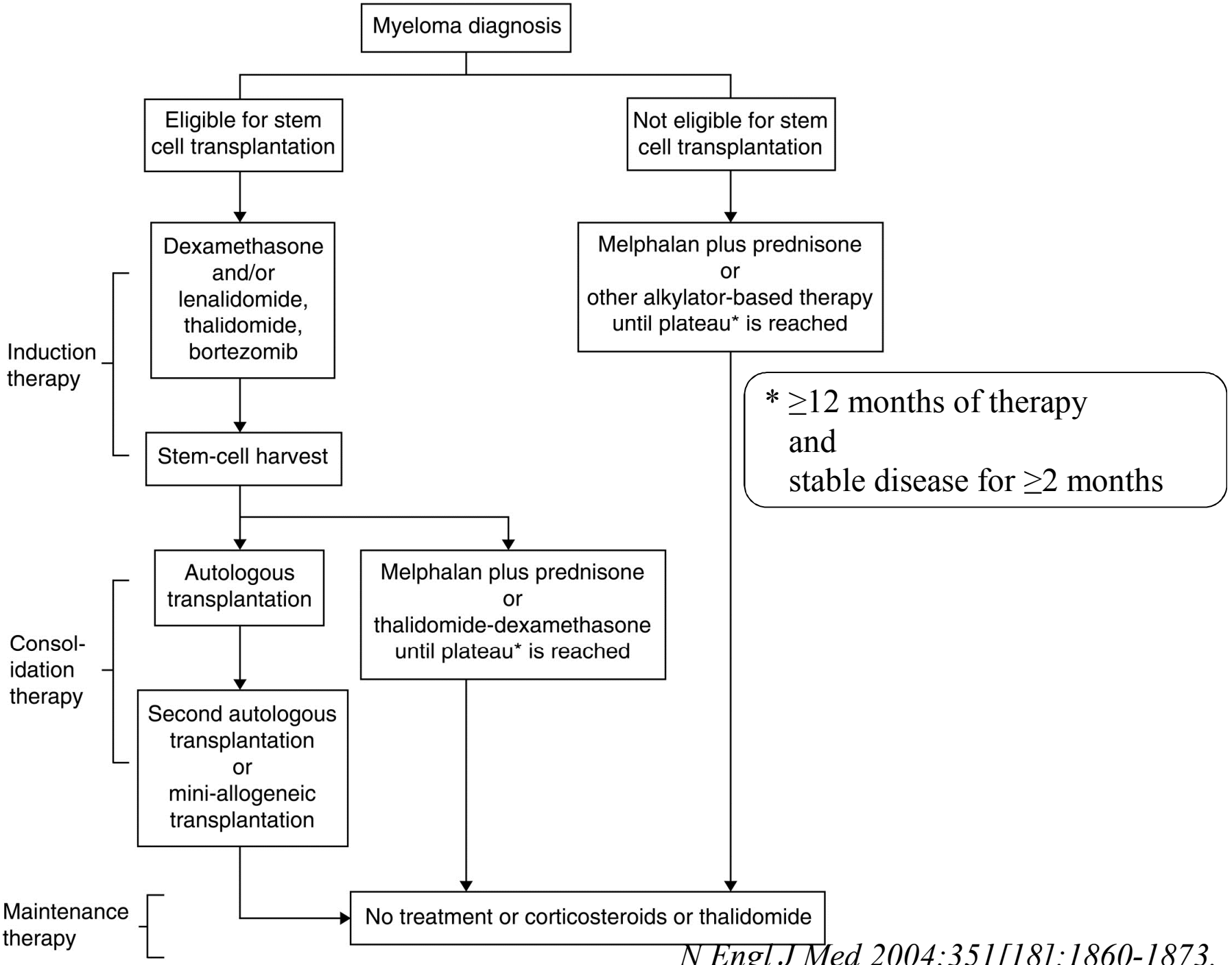


San Miguel J et al. Oncologist 2006

Not transplant candidates

- **MP regimen** (q6w x 9 cycles)
  - Melphalan (Alkeran®) 9mg/m^2 po qd d1-4
  - Prednisone 60 mg/m^2 po qd d1-4

- **CTD regimen** *Blood. Aug 4 2011;118(5):1231-8.*
  - Cyclophosphamide, thalidomide, and dexamethasone
  - Higher response rates than MP regimen
  - CTD was not associated with improved survival outcomes



N Engl J Med 2004;351[18]:1860-1873.

Patients with refractory disease or relapse

- If the MM relapse occurs longer than 6 months after the initial therapy, then the initial regimen can be used again.

- 2011 NCCN MM guidelines (salvage therapy)
  - Cyclophosphamide, dexamethasone and bortezomib/lenalidomide
  - Primary treatment of amyloidosis

ASCO guidelines for treating bone loss

MM patients with lytic disease or osteopenia on plain radiographs or imaging studies

↓

Intravenous pamidronate 90 mg deliver over at least 2 hrs
or
zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks.

↓

Continue therapy for 2 yrs & consider stopping in patients w/ responsive or stable disease; further use at physician's discretion

Kyle RA et al. J Clin Oncol. 2007; 25: 2464-72

Adjunctive Therapy for Complications

- Skeletal complications
  - 85% of patients have lytic bone disease
  - Fractures: bisphosphonates (P.O)
  - Spinal cord compression: corticosteroid (reduce swelling)
  - Bone pain: local radiotherapy
- Infection: prophylactic antibiotics and IVIG
- Anemia: erythropoietin
- Renal failure: bortezomib-based therapy