

# Management Update: Multiple Myeloma

*Presented by*

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# Introduction

- Multiple myeloma - clonal plasma cell neoplasm
- Monoclonal antibody production
- 1% of all cancer
- 10% of haematological malignancy
- Median age 65 years
- Incidence higher in African populations

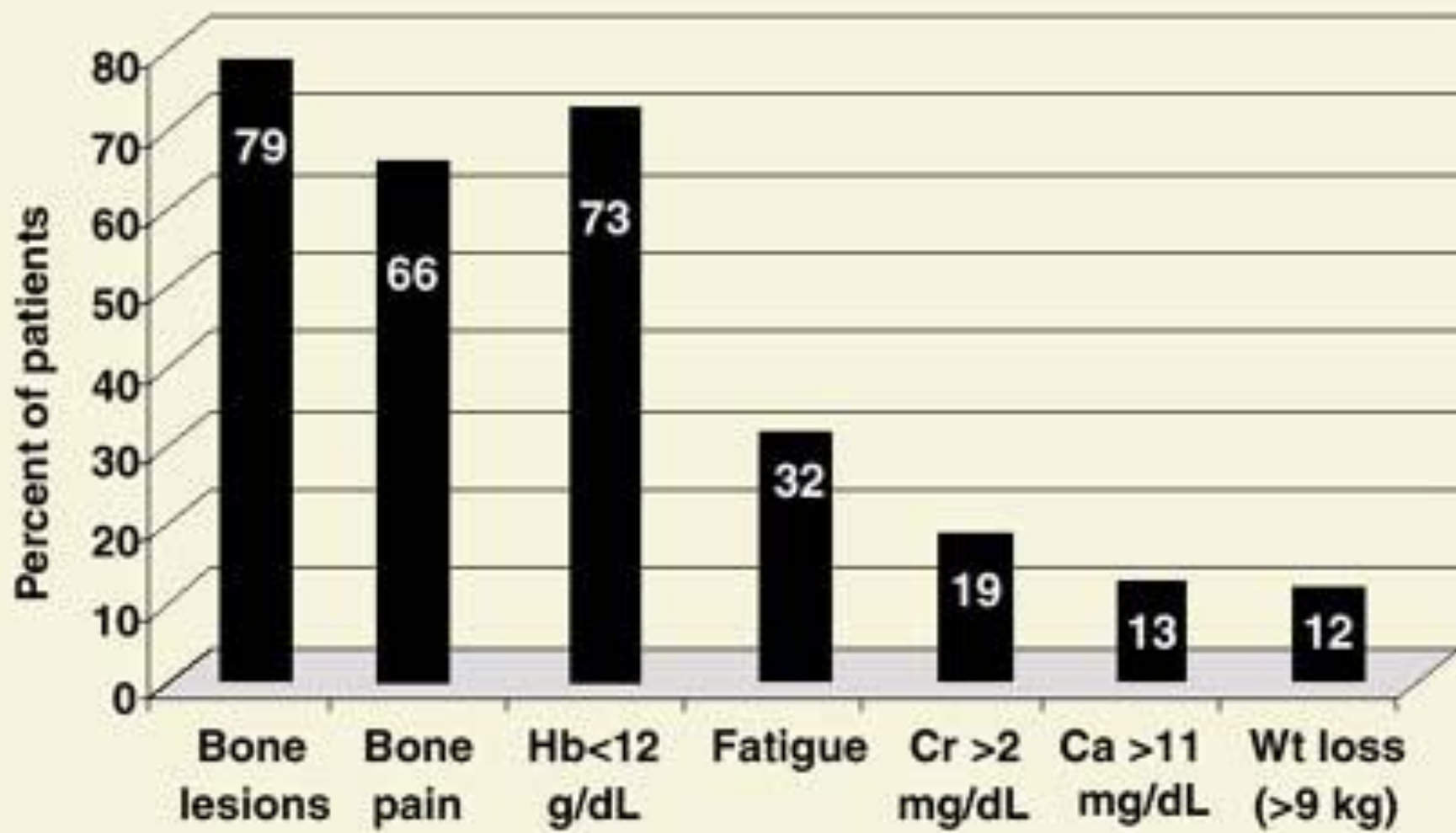
# Etiology

- Familial clustering
- African Americans
- Radiation
- Agriculture, Benzene, Radiation, Sheet metal work
- Chronic inflammatory disorders

## Clinical Presentation

Common clinical features include symptoms of-

1. Bone disease
2. Anaemia
3. Impaired renal function
4. Hypercalcaemia
5. Recurrent or persistent bacterial infection



## **Clinical Presentation(conti..)**

Other patients are diagnosed :

- The incidental detection of a raised (ESR)
- Symptoms of hyperviscosity.

# MM as Medical Emergency

- Spinal cord compression
- Hypercalcaemia and
- Renal failure

Patients require urgent specialist referral and treatment.

## Investigation and diagnosis

suspected myeloma



screening tests



Further tests to confirm the diagnosis.



Protein Electrophoresis of serum and concentrated urine.



- To confirm and type any M-protein present.
- Strong suspicion of myeloma but routine serum protein electrophoresis is negative.



Immunofixation and SFLC assessment

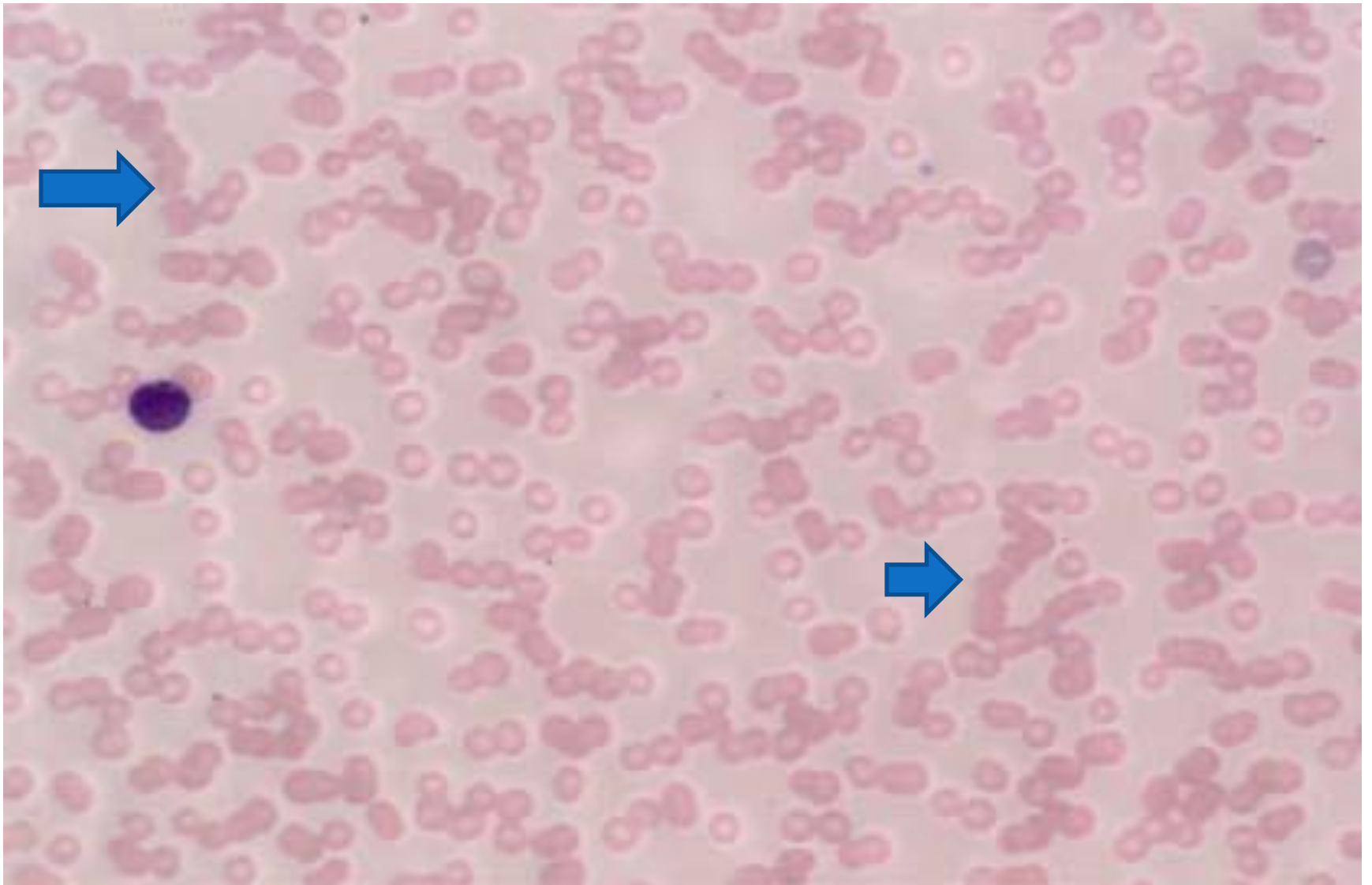


# **Initial investigations in patients with myeloma**

## **A. Screening Test**

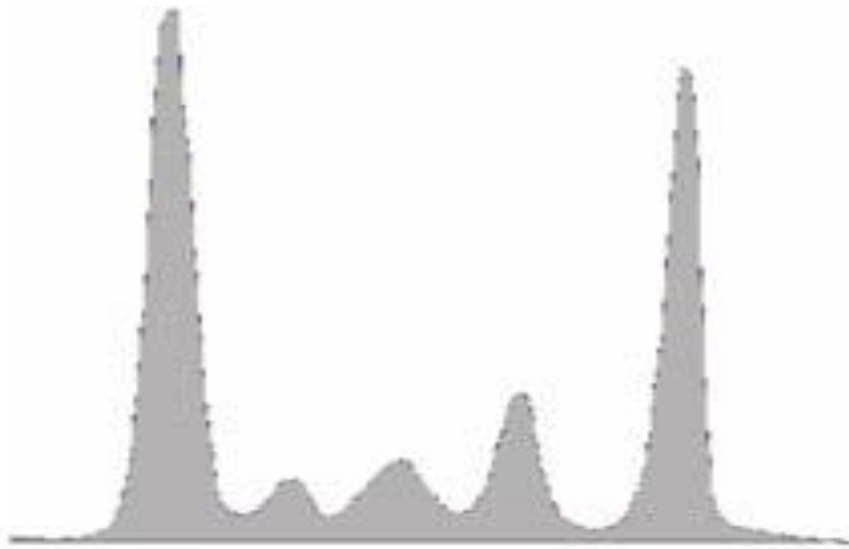
1. Full blood count (FBC), ESR or Plasma Viscosity
2. Electrophoresis of serum and concentrated urine
3. Calcium, Albumin
4. Urea, Creatinine
5. X-ray of symptomatic areas.

# PBF



## **B. Tests to establish diagnosis**

1. Bone marrow aspirate + trephine biopsy with plasma cell Phenotyping
2. Immunofixation of serum and Urine



Serum protein electrophoresis – Monoclonal gammopathy



A

Albumin  $\alpha_1$   $\alpha_2$   $\beta$   $\gamma$

IgG

IgA

IgM

Ig $\kappa$

Ig $\lambda$



Immunofixation - monoclonal IgG $\lambda$

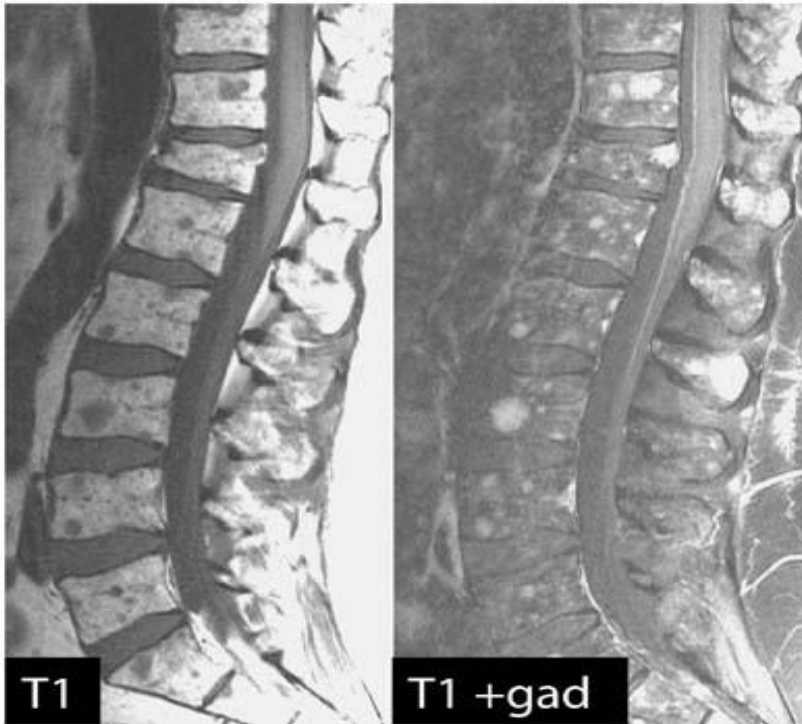
B



A



B



C

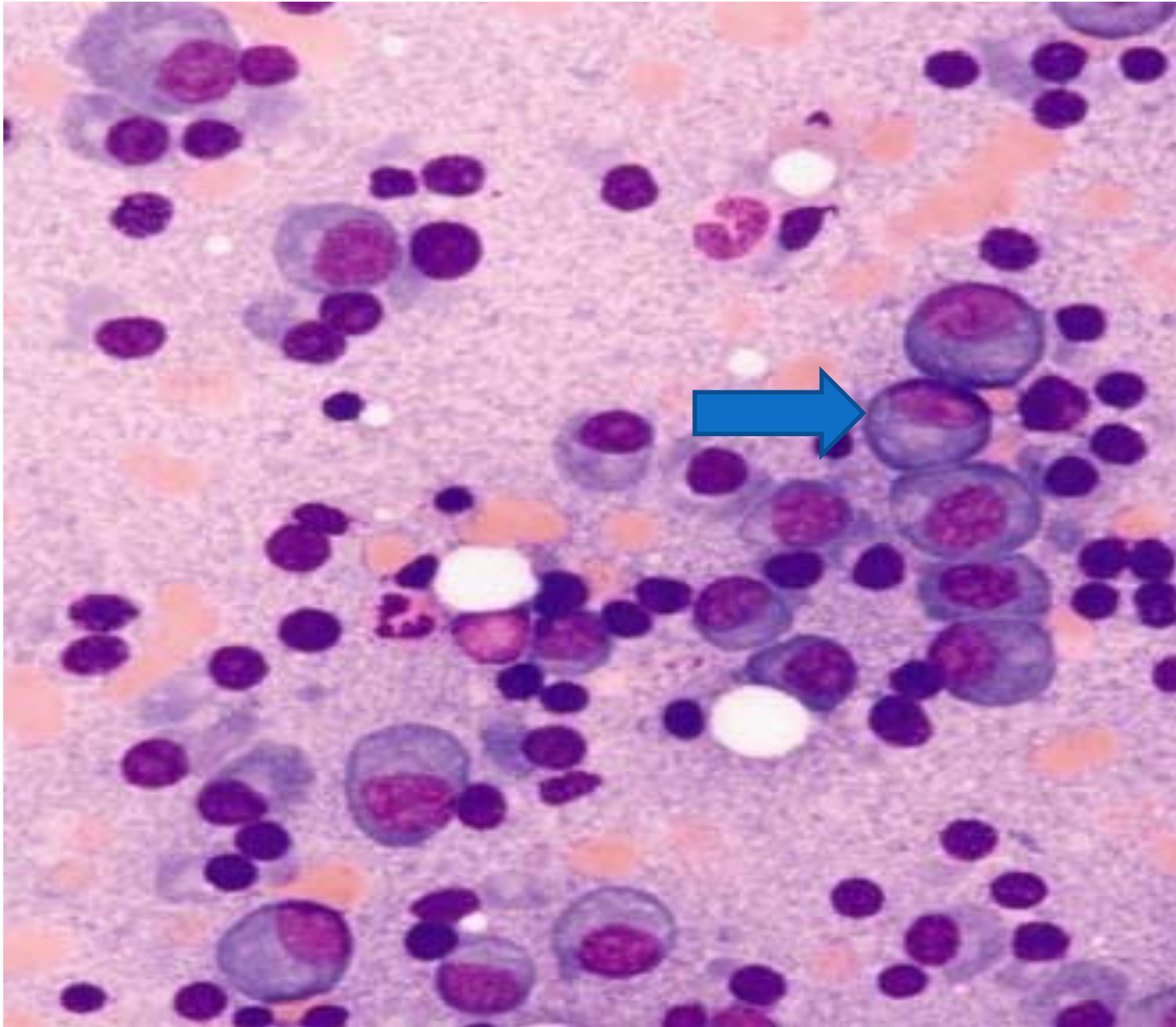
T1

T1 + gad



D

# Bone marrow smear



## **C. Tests to estimate tumour burden and Prognosis**

1. Fluorescence in situ hybridisation (FISH) analysis
2. Quantification of monoclonal protein in serum and urine
3. Albumin,  $\beta$ -2 microglobulin
4. Skeletal survey
5. PCLI ( Plasma cell labeling index)
6. Serum LDH

## **D. Tests to assess myeloma-related organ /tissue impairment (ROTI)**

1. FBC
2. Serum urea and creatinine
3. Creatinine clearance (measured or calculated)
4. Calcium Albumin
5. Plasma viscosity
6. Tissue biopsy (or fat pad aspirate) for amyloid (if suspected)
7. Quantification of non-isotypic immunoglobulins
8. Skeletal survey



## **E. Special tests indicated in some Patients**

1. SFLC(Serum free light chain ) assay in oligo-secretory, light chain only and non-secretory disease.
2. Magnetic resonance imaging (MRI).
3. Computerised tomography (CT) scan.

# Diagnostic criteria for MGUS, asymptomatic myeloma and symptomatic myeloma

*(adapted from International Myeloma Working Group, 2003)*

MGUS (monoclonal gammopathy of undetermined significance)	Asymptomatic myeloma	Symptomatic myeloma
M-protein in serum <30 g/l	M-protein in serum >30 g/l	M-protein in serum and/or urine**
Bone marrow clonal plasma cells <10 % and low level of plasma cell infiltration in a trephine biopsy (if done)	and/or Bone marrow clonal plasma cells >10 %	Bone marrow (clonal) plasma cells or biopsy proven plasmacytoma
No related organ or tissue impairment ((no end organ damage including bone lesions)	No related organ or tissue impairment ((no end organ damage including bone lesions) or symptoms	Myeloma-related organ or tissue impairment (including bone lesions)

## Myeloma-related organ or tissue impairment (ROTI)

*(adapted from International Myeloma Working Group, 2003)*

Clinical effects due to myeloma	Definition
Increased calcium levels	Corrected serum calcium >0.25mmol/l above the upper limit of normal or >2.75mmol/l
Renal insufficiency	Creatinine >173mmol/l
Anaemia	Haemoglobin 2 g/dl below the lower limit of normal or haemoglobin <10 g/dl
Bone lesions	Lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)
Other	Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> 2 episodes in 12 months)

# 1. Durie-Salmon Staging System

- **Stage I** All of the following:
  - Hemoglobin >100 g/L
  - Serum calcium <12 mg/dl
  - On radiograph, normal bone structure (scale 0)<sup>a</sup> or solitary bone plasmacytoma only
  - Low M-component production rates
  - IgG <50 g/L
  - IgA <30 g/L
  - Urine light-chain M component on electrophoresis <4 g/24 hours <0.6 (low)
- **Stage II** Fitting neither stage I nor III 0.6–1.2 (intermediate)
- **Stage III** One or more of the following:
  - Hemoglobin <85 g/L
  - Serum calcium >12 mg/dl
  - Advanced lytic bone lesions
  - High M-component rates
  - High M-component rates
  - IgG >70 g/L
  - IgA >50 g/L
  - Urine light-chain M component on electrophoresis >12 g/24 h >1.2 (high)
- **Subclassification** A: Serum creatinine <2 mg/dl  
B: Serum creatinine ≥2 mg/dl
- <sup>a</sup>Scale of bone lesions: normal bones, 0; osteoporosis, 1; lytic bone lesions, 2; and extensive skeletal destruction and major fractures, 3.  
From Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975;36:842–854. By permission of the American Cancer Society.

## 2. International Staging System (ISS) for multiple myeloma

*(adapted from Greipp et al, 2005)*

Stage	Criteria	Median survival in months
I	$\beta$ -2 microglobulin < 3.5 mg/l albumin > 3.5 g/dl	62 months
II	Neither I or III*	45 months
III	B-2 microglobulin > 5.5 mg/l	29 months

## 3.Cytogenetics

1. High risk (25%): Del 17p, t(4;14), t (14;16), Del 13, hypodiploidy
  2. Standard risk (75%): All other including Hyperdiploid, t(11;14),t (6;14)
- FISH studies to all patients at diagnosis as they provide important prognostic information.

# Management Objective

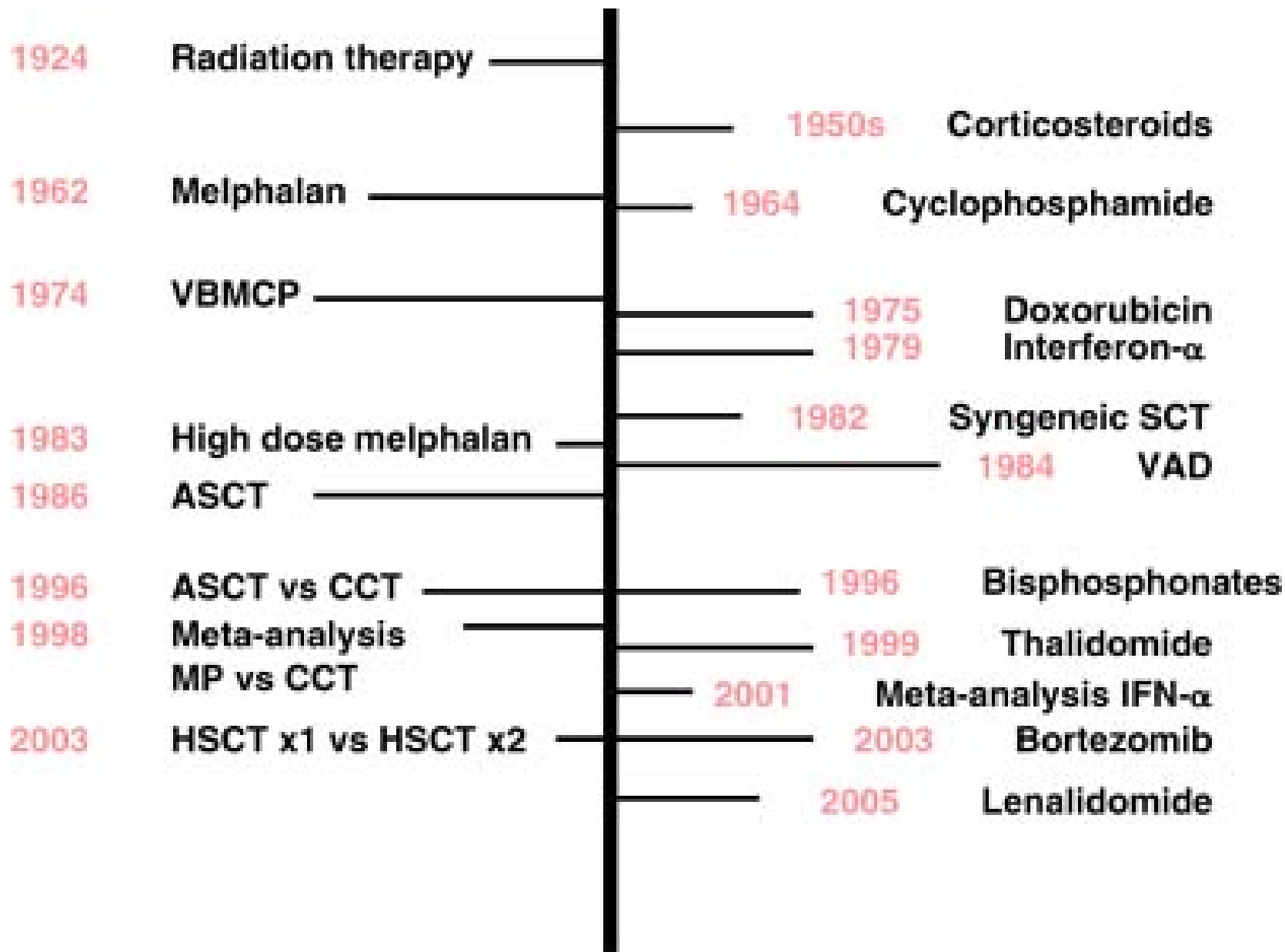
1. Control disease.
2. Maximise quality of life.
3. Prolong survival.

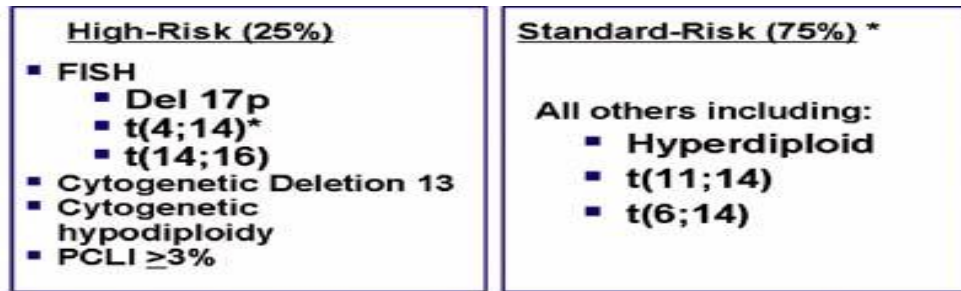
# Management Plan

1. Management of common medical emergencies in myeloma patients.
2. Management of Potential transplant candidate
3. Management of Non- transplant candidate
4. Management of treatment related complications



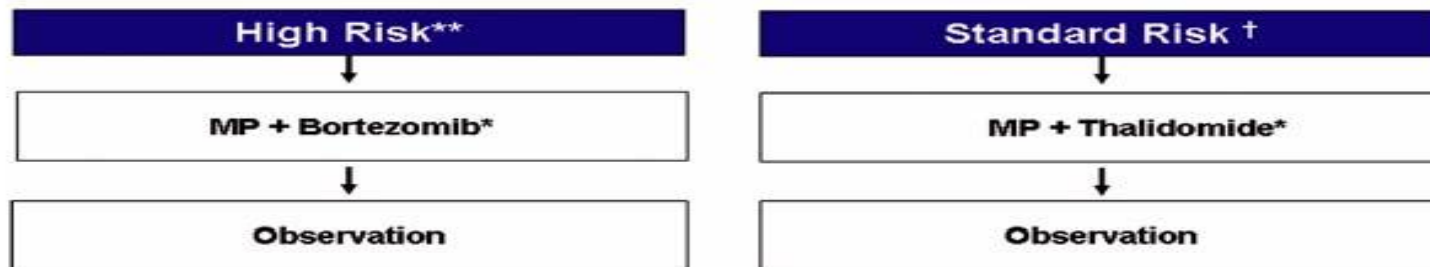
# Landmark of therapeutic innovation





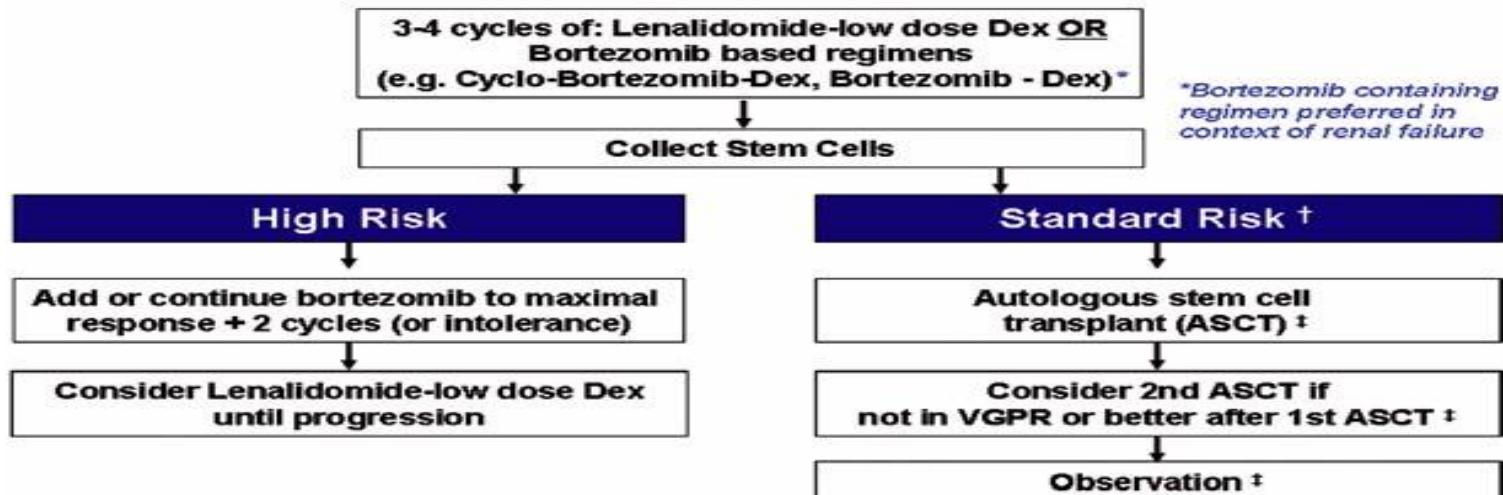
A \*Patients with t(4;14), b2M<4 mg/l and Hb≥10g/dl may have intermediate risk disease

### Transplant Ineligible



\* In patients in whom administration of thalidomide or bortezomib is of concern, consider MP or Rd

### Transplant Eligible



† If transplant deferred continue induction as tolerated

B † For patients not in VGPR or better after ASCT, consider Thalidomide to maximum response as tolerated

# Management of common medical emergencies in myeloma patients

## 1. Hyperviscosity

- Particularly those of IgA and IgG3 type.
  
- Symptoms include –
  - a) Blurred vision
  - b) Headaches
  - c) Mucosal bleeding and
  - d) Dyspnoea due to heart failure.
  
- Fundoscopy - retinal vein distension, haemorrhages and papilloedema.

## Hyperviscosity Recommendations :

1. Saline fluid replacement
2. Plasmapheresis
3. Isovolaemic venesection
4. Effective treatment of the underlying disease

## 2. Hypercalcaemia

Up to 30% of patients present with hypercalcaemia.

Symptoms-

1. Central nervous system dysfunction (confusion, coma and obtundation)
2. Muscle weakness
3. Pancreatitis
4. Constipation
5. Thirst, Polyuria
6. Acute renal insufficiency.

➤ Shortening of the Q-T interval on ECG

## *Hypercalcaemia Recommendations :*

1. Mild hypercalcaemia - (corrected calcium 2.6-2.9 mmol/l) rehydration with oral and /or iv fluids.
2. Moderate-Severe hypercalcaemia - (corrected calcium >2.9 mmol/l) rehydration with intravenous fluids and frusemide if required.
3. Moderate to Severe hypercalcaemia should receive a bisphosphonate ( zoledronic acid).

### **3. Cord compression**

Occurs in 5% of patients with myeloma during the course of their disease.

Symptoms commonly include –

1. Sensory loss
2. Paraesthesiae
3. Limb weakness
4. Walking difficulty
5. Sphincter disturbance.

## **Cord compression Recommendations :**

1. Dexamethasone 40 mg daily for 4 days
2. Urgent MRI and neurosurgical intervention
3. Local radiotherapy for non-bony lesions within 24 hours of the diagnosis.



## **4. Early Infection**

10% of patients die of infective causes within 60 days of diagnosis .

Increased incidence of early infection due to –

1. Deficits in both humoral and cellular immunity

2. Reduced mobility and performance status due to both the disease and its treatment.

(Neutropenia is not usually a factor in early infection .)

## *Early Infection Recommendations :*

1. Access to primary care team.
2. Broad spectrum antibiotics. Intravenous antibiotics for severe systemic infection or neutropenic sepsis.
3. Avoid aminoglycosides.
4. Insufficient evidence to recommend the routine use of prophylactic antibiotics

# **Management of Potential transplant candidate**

Potential transplant Candidate



Induction



Stem cell Harvesting



Successful mobilisation of peripheral blood stem cells (PBSC)



Conditioning with High dose therapy (HDT)



Autologous stem cell transplantation (ASCT)



Maintenance

# Induction therapy

VAD( Vincristine, doxorubicin and dexamethasone)

or

single agent dexamethasone

should **no longer** be routinely used as induction therapy.

## Induction therapy (continued...)

Induction regimens should contain at least one novel agent.

Followings are superior to VAD in terms of response rates-

1. CTD ( Cyclophosphamide, Thalidomide and Dexamethasone)
2. TAD ( Thalidomide, Doxorubicin and Dexamethasone)
3. PD ( Bortezomib , Dexamethasone)
4. PAD ( Bortezomib, Doxorubicin and Dexamethasone).

❑ CTD is the most common combination used in UK.

## **Use of novel agents in high risk cytogenetic abnormalities**

15-20% of newly diagnosed patients are with cytogenetic abnormalities. One fourth of them are with high risk cytogenetic abnormalities.

Bortezomib may increase the overall and complete remission rates if used pre-ASCT in some patients of this group.

## **Stem cell harvesting**

1. Peripheral blood stem cell harvesting (PBSCH) within 4-6 cycles for all induction regimens
2. Mobilisation with cyclophosphamide and G-CSF.
3. Stem cell mobilisation within 6 to 8 weeks of completion of induction therapy



## Myeloma refractory to induction therapy

If not at least a PR after a minimum of 6 weeks treatment

or

Progresses with a 25% or greater increase in M-protein level

or

The appearance of organ dysfunction

or

Evidence of deteriorating organ function.

If still considered a candidate for high dose therapy-

1. If intolerant of thalidomide, or refractory to first-line therapy, a bortezomib-based salvage regimen.
2. Patients with  $\geq$  grade 2 peripheral neuropathy a lenalidomide-based regimen

# High dose therapy and autologous stem cell transplantation (ASCT)

1. Conditioning with High dose melphalan (200 mg/m<sup>2</sup>) prior to ASCT.
2. Indication of HDT
  - a. Newly diagnosed patients up to 65 years with adequate performance status and organ function
  - b. aged >65 years with good performance status
3. Conditioning with melphalan alone, without TBI( Total Body Irradiation). The usual dose should be reduced in older patients (over 65-70 years) and those with renal failure.
4. In severe renal impairment (creatinine clearance/GFR <30 ml/min) the dose of melphalan should be a maximum of 140 mg/m<sup>2</sup>

## **Allogeneic Stem Cell Transplantation (AlloSCT)**

- Young patients with matched sibling donors who are interested in pursuing curative therapy
- Allogeneic SCT should only be considered in selected patients up to the age of 40 years who have achieved at least a partial response to initial therapy.

# Maintenance therapy

- No benefit has been demonstrated for the role of maintenance with chemotherapy.
- IFN or single-agent corticosteroids cannot be routinely recommended as maintenance therapy. In the allograft setting, IFN may be useful for those who have not achieved a CR (*Complete Response*).
- Single agent thalidomide therapy may improve EFS (*Event Free Survival*) and OS (*Overall Survival*) in patients who did not achieve VGPR (*Very Good Partial Response*) post high-dose therapy and in this setting maintenance therapy could be considered. Patients with deletion 13q may not benefit.

## Maintenance therapy (continued....)

- The dose of thalidomide should not exceed 150 mg
- Routine anticoagulant prophylaxis is not required
- No evidence of benefit for use of thalidomide maintenance in elderly patients who did not undergo autologous transplantation.
- The combination of steroids and thalidomide is not recommended due to increase toxicity and unclear benefit over thalidomide alone.
- Bortezomib or lenalidomide may be promising in future.

## Treatment at relapse

- Thalidomide, bortezomib and lenalidomide-based regimens as treatment modalities at first and subsequent relapse.
- Clinical effectiveness of thalidomide, bortezomib and lenalidomide is not dependent on the number of previous lines of therapy or type of therapy previously received .
- Unless contraindicated treatment with thalidomide, bortezomib or lenalidomide treatment should be delivered with dexamethasone +/- chemotherapy
- A second autologous transplant may be considered in patients who had a good response to the initial transplant procedure (> 18 months to disease progression)

# **Management of Non - transplant candidate**

# Specific treatment recommendations for older and/or less fit patients in whom HDT is not planned initial therapy

Induction therapy should consist of either a thalidomide containing regimen in combination with an alkylating agent and steroid such as

MPT (Melphalan, Prednisolone, Thalidomide)

Or

CTD (Cyclophosphamide, Thalidomide and Dexamethasone)

Or

Bortezomib in combination with Melphalan and Prednisolone



# Currently using Therapy Options in NonTransplant Candidate

- **Melphalan + Prednisone (MP)**
- **Melphalan + Prednisone + Thalidomide (MPT)**
- **Dexamethasone (Dex)**
- **Thalidomide + Dexamethasone (Thal/Dex)**
- **Lenolidomide + Dexamethasone (Rev/Dex)**
- **Bortezomib +/- Dexamethasone (Vel/Dex)**

## 1. Peripheral neuropathy

As a result of many myeloma therapies. Recommendations-

1. Graded dose reduction or drug withdrawal.
2. Symptom control along with treatment of any potentially reversible causes.
3. Diabetes mellitus may also improve tolerance of neurotoxic drugs
4. Neuropathic pain is poorly responsive to simple analgesics, NSAIDs and opioid drugs.
5. Neuromodulatory agents are recommended to treat neuropathic pain.

## **2. Venous thromboembolism**

1. Risk assessment for VTE.

2. Patients receiving thalidomide or lenalidomide: If no other VTE risk factors are present, aspirin unless contraindicated.

3. If one or more major risk factors are present, prophylaxis with low molecular weight heparin (LMWH) or adjusted therapeutic-dose warfarin.

4. Patients with previous VTE prophylaxis with adjusted therapeutic-dose warfarin or LMWH.

5. Treatment of confirmed VTE practice guidelines using adjusted dose warfarin or LMWH and appropriate monitoring.

## Conclusion:

1. Common haematological malignancy in old age with diversified systemic involvement.
2. Symptomatic multiple myeloma patients are candidate to receive treatment
3. Newer agents are promising to produce complete response
4. Autologous stem cell transplant should be attempted in fit candidate
5. Proper identification of organ dysfunction and their management should be done side by side along with decreasing tumour burden.

THANK YOU