MYELOMA

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MGUS

- Monoclonal gammopathy of undetermined significance (MGUS)
- M components are identified in the blood of patients having no signs or symptoms.
- M proteins can be identified in the serum of 1% of asymptomatic healthy persons older than 50 years of age and in 3% of individuals older than 70 years of age.
- Approximately 1% of patients with MGUS progress to an overt plasma cell dyscrasia (usually multiple myeloma) per year.

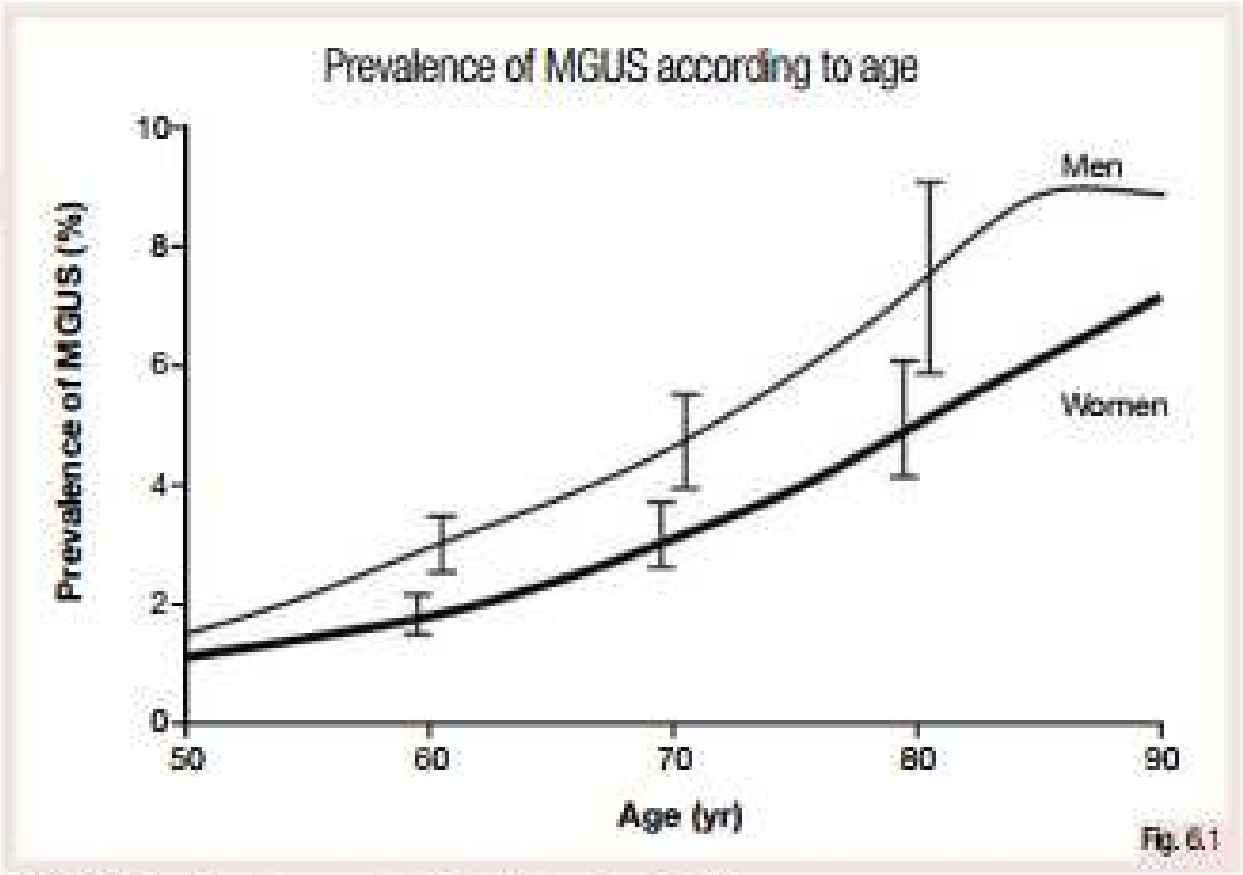
MGUS

- 26% stable
- 19% progress but require no therapy
- 24% progress to multiple myeloma, amyloidosis, macroglobulemia, or lymphoma
- 23% die from other causes (over 10 years)
- IgG most common M protein
- May see Factor Xa deficiency with amyloidosis

	MGUS	SMM	MM
Serum or urine M protein level	<30 g/L AND	IgG or IgA ≥30 g/L or urinary M protein ≥500 mg per 24 h AND/OR	
Bone marrow plasma cells	<10% AND	≥10% and <60% AND	≥10% OR biopsy proven plasmacytoma AND
CRAB criteria and/or biomarkers of malignancy	Absence	Absence	≥1 criteria

Fig. 6.2

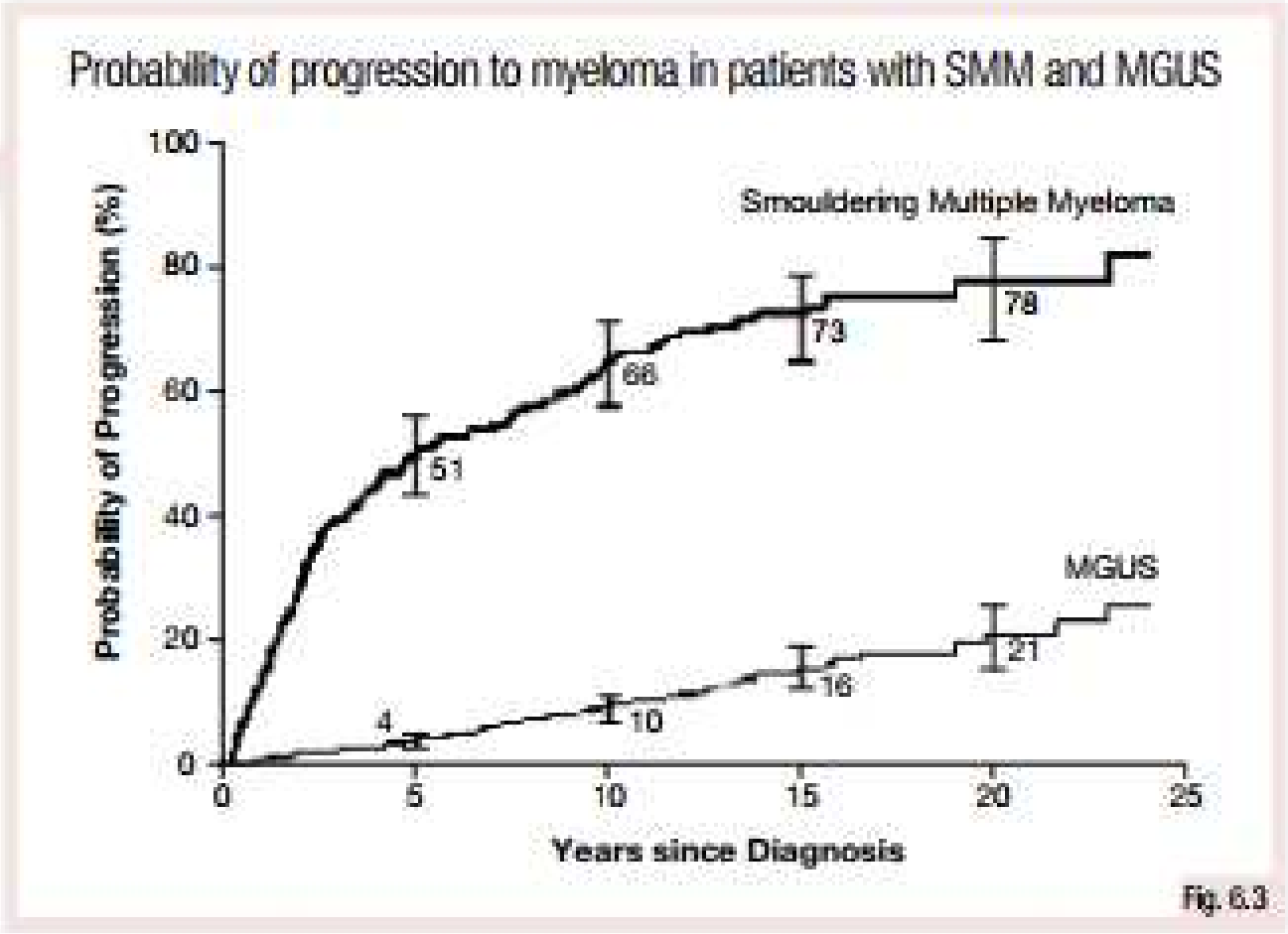
CRAB, HyperCalcaemia, Renal insufficiency, Anaemia and Bone lesions; IgA, immunoglobulin A; IgG, immunoglobulin G; M, monoclonal; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smouldering multiple myeloma.



MGUS, Monoclonal gammopathy of undetermined significance.

Smoldering myeloma

- >3g/dL M protein and/or >10% plasma cells in marrow distinguish MGUS from smoldering myeloma.
- Approximately 15% of patients with smoldering myeloma progress to an overt plasma cell dyscrasia per year.



MGUS, Monoclonal gammopathy of undetermined significance; SMM, smouldering multiple myeloma.

Disease initiating events

- Two types of disease-initiating events (DIEs) have been identified in the molecular pathogenesis of multiple myeloma:
- 1. Hyperdiploidy (HD), involving ≥2 trisomies.
- Likely to contain a range of low penetrance oncogenes, which leads to their selection. The hyperdiploid group tends to have a favorable prognosis and respond well to immunomodulatory drugs.

Disease initiating events

- 2. The primary translocations result from aberrant class-switch recombination, abnormal V(D)J rearrangement, or receptor revision.
- The end result is to place various oncogene sunder the influence of the strong enhancer region of the immunoglobulin genes (IgH).
- t(4;14): FGFR3/MMSET; t(6;14): CCND3, t(11;14): CCND1; t(14;16): MAF; and t(14;20): MAFB.
- DIEs share one common aberration: (in)direct overexpression of ≥1 cyclin D (CCND) gene(s).

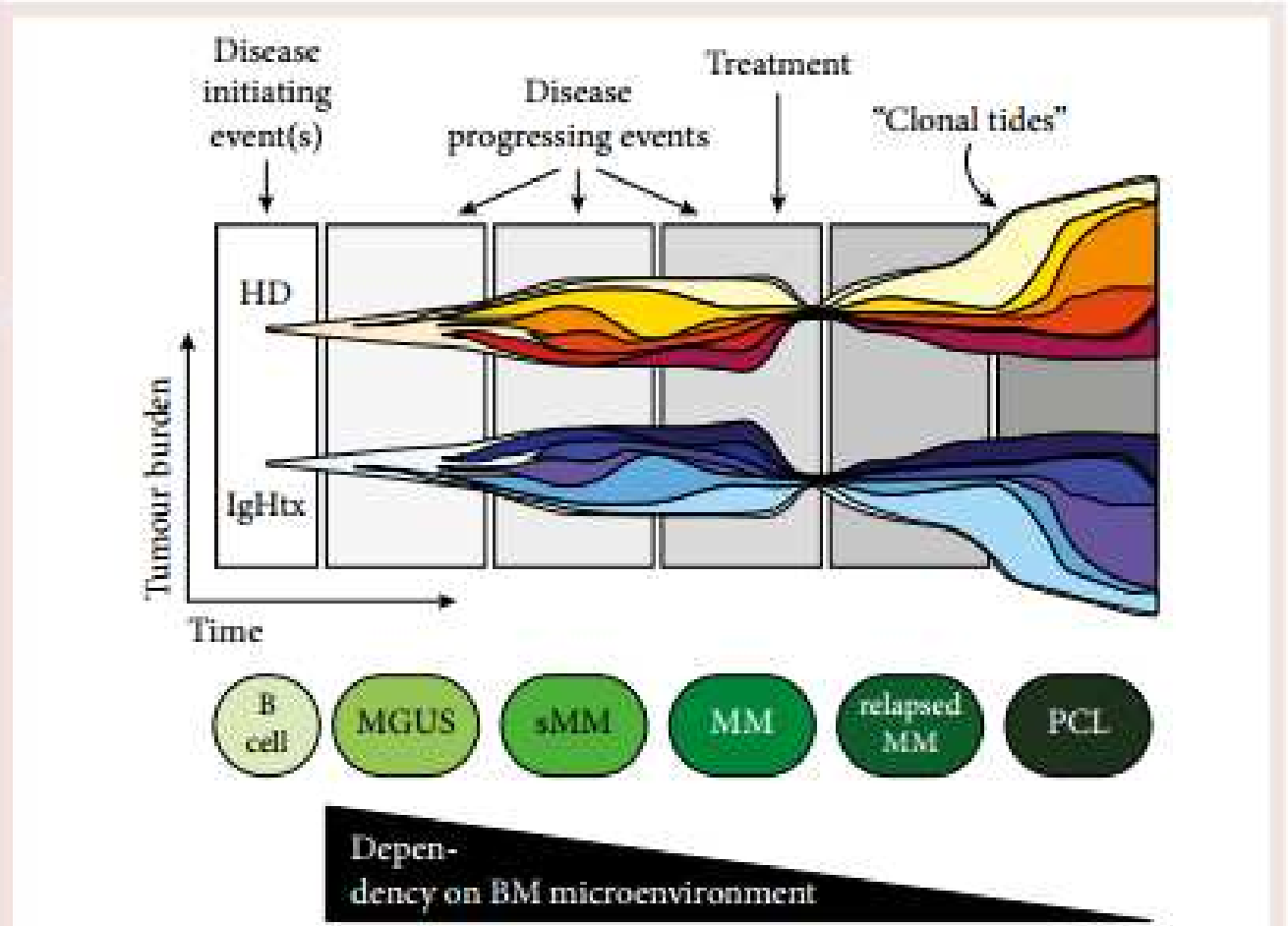


Fig. 12.1

BM, Bone marrow; HD, hyperdiploidy; IgHtx, IgH translocations; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; PCL, plasma cell leukaemia; sMM, smouldering multiple myeloma.

Myeloma evolution

- The multiple myeloma cell of origin is unknown, but may be a pro-B cell or germinal center B cell, as primary IgHtxs seem to have occurred during VDJ/class switch recombination or somatic hypermutation.
- Disease progression in multiple myeloma is characterized by a decreased bone marrow (BM) microenvironment dependency, caused by deletions and mutations that result in intrinsic activation of the NFκB pathway.

Myeloma evolution

- As the multiple myeloma genome evolves, disease-progressing events (DPEs) such as del(17p), del(1q), 1q gain and t(8;14) (involving MYC) are being selected.
- The MAPK/ERK, DNA damage response, NFκB, RNA processing, plasma cell differentiation, cell cycle control and MYC pathways are recurrently disrupted in multiple myeloma.

Highly proliferative tumor biology:

Enriched for DIEs t(4;14), t(14;16), and t(14;20), and DPEs 1q gain, del(17p) and del(13p)

Fig. 12.4

Myeloma evolution

- Two mutational etiologies have been identified in multiple myeloma: (a) an aging signature, and (b) an APOBEC signature.
- Multiple myeloma can show large intra-tumor heterogeneity, as is evidenced by the ‘waxing and waning’ of subclones during disease progression.
- The evolutionary pattern can be linear and/or branching.

Prognostic factors (non-exhaustive)	
Related to patient	Age
	Comorbidities
Related to tumour burden	Anaemia
	Thrombopaenia
	β2-microglobulin serum level
Intrinsic cellular	Genetic
	Proliferation index
Mixed	Hypoalbuminaemia
	Renal insufficiency
	Response to treatment

Cytogenetic abnormality	Frequency	Prognosis
Trisomy 3	35%	Good
Trisomy 5	37%	Good
Translocation *t(4;14)*	15%	Poor
Translocation *t(14;16)*	3%	Poor
1q gain	8%	Poor
Deletion *1p32*	8%	Poor
Trisomy 21	23%	Poor
Deletion *17p*	8%	Poor

Fig. 6.8

Prognostic factor		Criteria	OS at 5 years	PFS at 5 years
ISS stage	I	β2-microglobulin <3.5 mg/dL and albumin ≥3.5 g/dL	77%	49%
	II	No ISS stage I or III	62%	36%
	III	β2-microglobulin ≥5.5 mg/dL	47%	30%
CA by iFISH	Standard risk	No high-risk CA	69%	45%
	High risk	Presence of *del(17p)* and/or translocation *t(4;14)* and/or translocation *t(14;16)*	50%	24%
LDH	Normal	LDH < upper limit of normal	68%	42%
	High	LDH > upper limit of normal	47%	31%
R-ISS stage	I	ISS stage I and standard risk CA and normal LDH	82%	55%
	II	No R-ISS stage I or III	62%	36%
	III	ISS stage III and either high-risk CA or high LDH	40%	24%

Fig. 6.9

CA, Chromosomal abnormalities; iFISH, interphase fluorescent *in situ* hybridisation; ISS, International Staging System; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; R-ISS, Revised International Staging System.

Solitary plasmacytomas

- About 3% to 5% of plasma cell neoplasms present as a solitary lesion of either bone or soft tissue.
- The bony lesions tend to occur in the same locations as in multiple myeloma.
- Progress to multiple myeloma within 7-10 years

Solitary plasmacytomas

- Extraosseous lesions are often located in the lungs, oronasopharynx, or nasal sinuses.
- Modest elevations of M proteins in the blood or urine may be found in a minority of patients.
- Rarely progress to multiple myeloma.
- Extraosseous lesions can be cured by excision.

Multiple myeloma

- Second most common hematologic malignancy.
- 50-60 years of age (median)
- Blacks twice as likely to be affected than whites
- Men 50% more likely to be affected than women
- Risk factors include radiation, benzene, formaldehyde, epichlorohdrin

Multiple myeloma

- Bone pain is present in 80% of patients.
- Focal lesions involve:
- Vertebral column, 66%
- Ribs, 44%
- Skull, 41%
- Pelvis, 28%
- Femur, 24%
- Clavicle, 10%
- Scapula, 10%.

Clinical/laboratory features	Proportion of patients with abnormality (%)
Anaemia	72
Bone lesions	80
Renal failure	19
Hypercalcaemia	13
M protein on serum electrophoresis	82
M protein on serum immunofixation	93
M protein on serum plus urine immunofixation (or sFLC assay)	97
≥10% clonal BMPCs	96

BMPC, Bone marrow plasma cell; M, monoclonal; sFLC, serum free light chain.

Fig. 8.5

Definition of multiple myeloma	
Clonal BMPCs ≥10% AND one or more of the following myeloma-defining events:	
CRAB criteria	Hypercalcaemia
	Renal insufficiency
	Anaemia
	Bone lesions
OR	
Biomarkers of malignancy	Clonal BMPCs ≥60%
	sFLC ratio ≥100
	>1 focal lesion on MRI

BMPC, Bone marrow plasma cell; MRI, magnetic resonance imaging; sFLC, serum free light chain.

Fig. 6.6

Multiple myeloma

- Focal lesions generally begin in the medullary cavity, erode cancellous bone, and progressively destroy the bony cortex
- Often lead to pathologic fractures.
- 70% of patients will develop pathologic fractures at some point in the course of disease.
- Any cancer patient with significant back pain should undergo MRI to evaluate for cord compression.

Multiple myeloma

- Fatigue, normocytic normochromic anemia, and hypercalcemia are common clinical features.
- Renal insufficiency noted in 25% of patients at diagnosis.
- Acquired Fanconi syndrome with glycosuria, phosphaturia, and aminoaciduria can occur.
- Hyperviscosity symptoms may occur with IgA and IgG3 subtypes.
- Infections common.

POEMS (POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, MONOCLONAL PROTEIN, SKIN CHANGES)

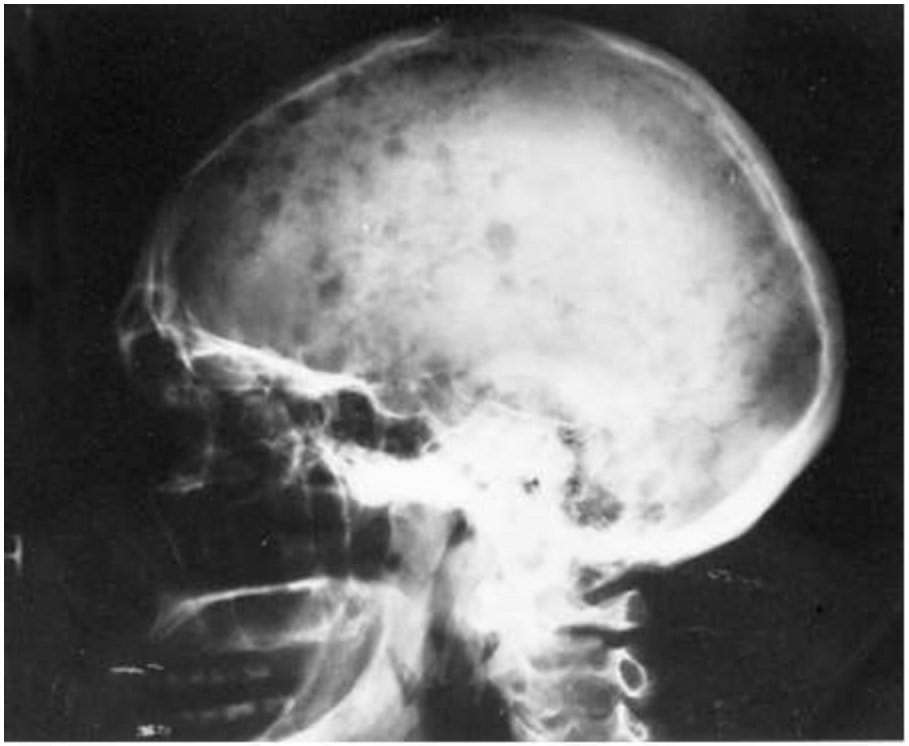
Table 1 Criteria for the Diagnosis of POEMS Syndrome[a]

Mandatory major criteria	**1. Polyneuropathy (typical demyelinating)**
	2. Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria (one required)	**3. Castleman's disease[b]**
	4. Sclerotic bone lesions
	5. Vascular endothelial growth factor elevation
Minor criteria	**6. Organomegaly (splenomegaly, hepatomegaly, lymphadenopathy)**
	7. Extravascular volume overload (edema, pleural effusion, or ascites)
	8. Endocrinopathy (adrenal, thyroid,c pituitary, gonadal, parathyroid, pancreatic)
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)
	10. Papilledema
	11. Thrombocytosis/polycythemia[d]
Other signs and symptoms	**Clubbing, weight loss, hyperhidrosis, pulmonary hypertension, restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B_{12} levels**

[a] The diagnosis of POEMS syndrome is confirmed when both of the mandatory major criteria, one of the other three major criteria, and one of the six minor criteria are present.
[b] There is a Castleman's disease variant of POEMS that occurs **without** evidence of a clonal plasma cell disorder that is not accounted for in this table. This entity should be considered separately.
[c] Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.
[d] Approximately 50% of patients will have bone marrow changes that distinguish it from a typical MGUS or myeloma bone marrow. Anemia and/or thrombocytopenia are distinctively unusual in this syndrome unless Castleman's disease is present.

60% 5year survival

Multiple myeloma



Radiographic image of the skull showing the "punched out" osteolytic lesions characteristic of multiple myeloma.

Fig. 106-4 Accessed 02/01/2010

Molecular alterations

- Antigen driven somatic mutation in complementarity-determining regions of the variable gene segment of B-cells.
- Somatic hypermutation of Ig genes (post-germinal memory B-cell).
- 5 recurrent translocations involving heavy chain locus on chromosome 14 have been identifed.
- t(11;14), CD20 + lymphoplasmacytic

Molecular alterations

- Cyclin D1 (11q13) and D3 (6p21) are other translocation partners as are MUM1/IRF4 transcription factor (6p25) and FGFR3 (4p16).
- t(4;16) is a deletion of 17 base pairs that is found in 5% of myelomas
- Involves c-MAF transcription factor (16p23).
- t(4;4) seen in 15% of myelomas
- Poor prognosis
- 1p21, 1p15 abnormal in 40-50%
- 14q+ (20-25%)
- T(11,14) (12-30%)
- 11q abnormality associated with poor prognosis

Molecular aberrations

- Amplification of 1q (amp1q)
- > 4 copies
- Present in 10% of newly diagnosed cases and is tightly linked to high-risk disease.
- Amp1q arises via multiple cycles of break-fusion-bridge leading to the amplification of a transcriptional unit at 1q21 comprising a number of key genes including CKS1B, MCL1, and ANP32E.
- The basis of amplification of 1q may be due to hypoxia and the expression of KDM4A.

Molecular aberrations

- Loss of 1p32 is associated with high-risk disease and the deletion of the cyclin-dependent kinase inhibitor CDKN2C.
- Loss of this cell cycle inhibitor deregulates the G1/S cell cycle checkpoint.
- Another important region of deletion is located at 1p12, which contains FAM46C, which is also frequently mutated.

Molecular aberrations

- Deletions of 17p are seen in about 5% of patients at diagnosis, but is more frequent at relapse and in high-risk disease.
- Monallelic TP53 loss is not prognostic.
- Biallelic inactivation, by copy number loss and/or mutation, is a very poor prognostic feature and is associated with high-risk disease.

Molecular aberrations

- Deletions of chromosome 13 are a feature of approximately 40% of myeloma cases.
- A secondary event.
- Biallelic deletions associated with poor prognosis
- RB1 and DIS3 may be inactivated.
- Mutations in KRAS, NRAS, and, BRAF account for 50% of all cases at presentation.
- These numbers increase at relapse.
- Elevation of Activin-A is also a sign of poor prognosis

Multiple myeloma

- IL-6 produced by stromal cells, osteoclasts
- IL-1β stimulates stromal cells
- Non-transmembrane gp80 (IL-6sr) bound to IL-6 stimulates gp130
- gp130 forms part of IL-6, G-CSF receptor
- Occupation initiates signal transduction in myeloma cell as activation leads to Jak kinase activity (interferon stimulates), ras protein activation leading to mitogen activated protein kinase activity and that of transcription factors such as NF-kB and IL-6
- G-CSF also stimulates gp130 and mobilizes myeloma cells
- High levels of IL-6sr associated with poor prognosis
- IL-6 inhibits apoptosis

Multiple myeloma

- Decreased production of the natural RANKL inhibitor osteoprotegerin coupled with increased secretion of the osteoclast activating factors such as RANKL and MIP-1 leads to bone damage.
- Proliferation sustained by IL-6.
- β-2 microglobulin a good marker for disease activity.

Multiple myeloma

- Neo-angiogenesis along with mesenchymal stem cell derived pericyte abnormalities may directly affect the endosteal and perivascular niches
- Lead to vascular leak and alteration in the immune content of the bone marrow.

Multiple myeloma

- The changes in the microenvironment can be mediated directly by:
- Integrins, such as ITGB7
- Secreted factors that generate paracrine loops
- Upregulating cytokines via the stromal cells such as interleukin (IL)-6.
- In addition, secreted exosomes with their cargo of miRNA may be important.

Multiple myeloma

- CD40 important in activation and transduction of B-cell
- B cell maturation antigen (BCMA) is a member of the TNF superfamily.
- Preferentially expressed on mature B-cells
- CD44, CD56, LFA-1 adhesion molecules important in homing to marrow
- VLA-4 bind to VCAM-1 and stromal cells; Syndecan-1 to Collagen I and VLA-4 to fibronectin and the basement membrane

Pathologic diagnosis

- Minimal diagnostic criteria:
- >10% plasma cells in the bone marrow (or histologic proof of a plasmacytoma)
- AND
- M protein in the serum (>3gm/dL) or urine or lytic bone lesions.
- Serum protein electrophoresis with immunofixation necessary to demonstrate subtype.
- Circulating monoclonal protein is IgG (50%), IgA (20%), light chain only (Bence-Jones proteinemia, 20%), IgD (2%), biclonal (1%).

DEFINITIONS OF SMOLDERING AND MULTIPLE MYELOMA

Smoldering Myeloma (Asymptomatic)[a]

- Serum monoclonal protein ≥3 g/dL

or

- Bence-Jones protein ≥500 mg/24 h

and/or

- Clonal bone marrow plasma cells 10%–59%

and

- Absence of myeloma-defining events or amyloidosis
  - If skeletal survey negative, assess for bone disease with whole-body MRI, FDG PET/CT, or low-dose CT scan

Multiple Myeloma (Symptomatic)[a,b]

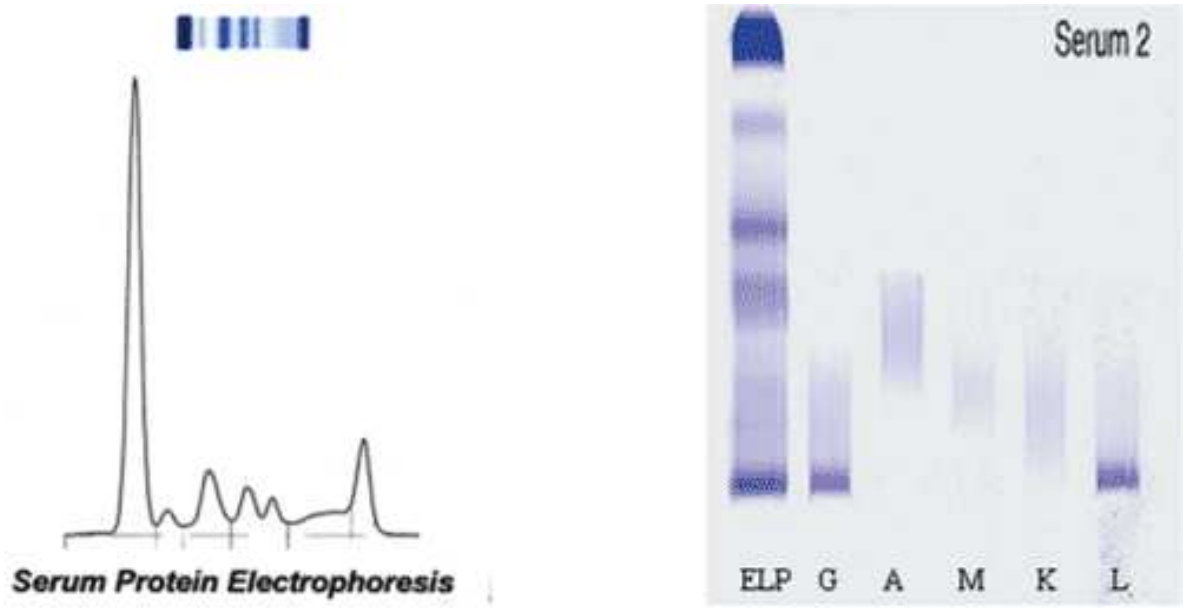
Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma

and

Any one or more of the following myeloma-defining events:

- 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 >2 mg/dL) [>177 µmol/L] or creatinine clearance <40 mL/min
- Anemia (hemoglobin <10 g/dL or hemoglobin >2 g/dL below the lower limit of normal)
- One or more osteolytic bone lesions on skeletal radiography, CT, or FDG PET/CT
- Clonal bone marrow plasma cells ≥60%
- Involved:uninvolved serum FLC ratio ≥100 and involved FLC concentration 10 mg/dL or higher
- >1 focal lesions on MRI studies ≥5 mm

Immunoelectrophoresis



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig.8-8 Accessed 02/01/2010

Serum protein electrophoresis demonstrates an M protein peak (*left*). Immunofixation electrophoresis confirms it to be monoclonal IgG lambda type.

Multiple myeloma

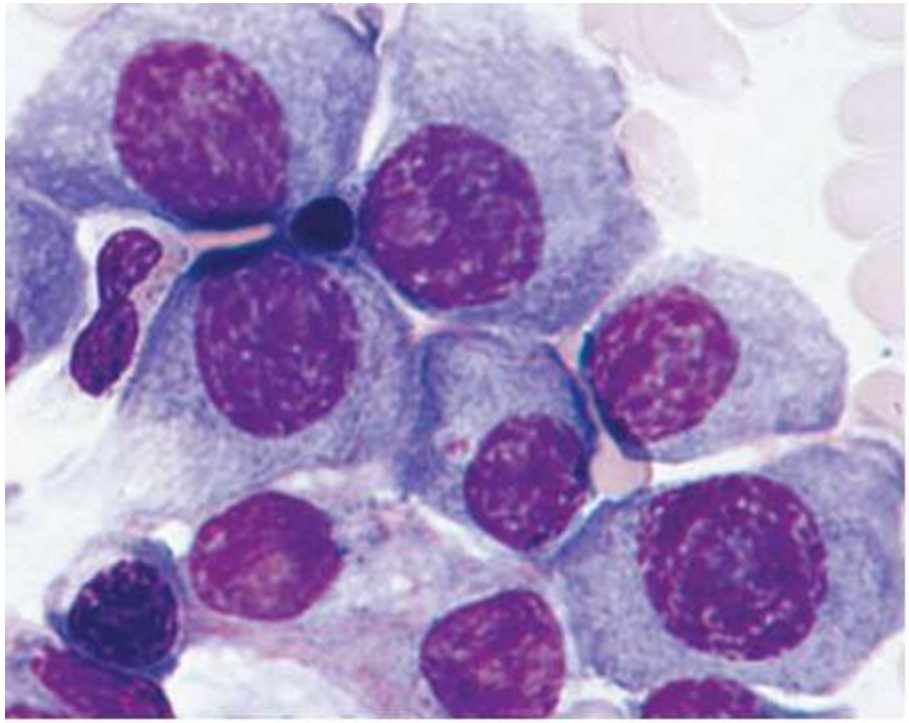


Fig. e11-56 Accessed 02/01/2010

STAGING SYSTEMS FOR MULTIPLE MYELOMA[a]

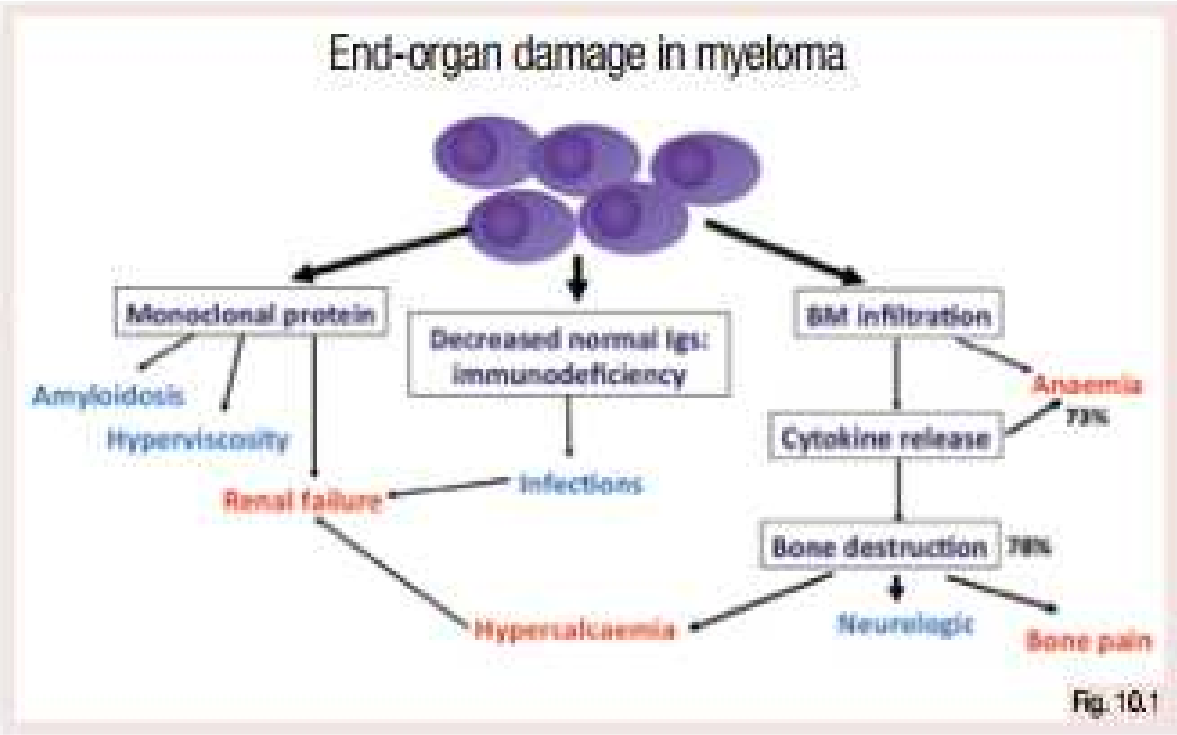
Stage	International Staging System (ISS)	Revised-ISS (R-ISS)
I	Serum beta-2 microglobulin <3.5 mg/L, Serum albumin ≥3.5 g/dL	ISS stage I and standard-risk chromosomal abnormalities by FISH[b] and Serum LDH ≤ the upper limit of normal
II	Not ISS stage I or III	Not R-ISS stage I or III
III	Serum beta-2 microglobulin ≥5.5 mg/L	ISS stage III and either high-risk chromosomal abnormalities by FISH[b] or Serum LDH > the upper limit of normal

Durie-Salmon staging

Stage	Criteria
I Low risk (All present)	Hemoglobin >10 g/dL
	Serum calcium 12 mg/dL (normal)
	Normal bone or solitary plasmacytoma on x-ray
	Low production rates of M component:
	IgG <5 g/dL or igA <3g/dL
	Urine light chain M component <4 g/24h
II Intermediate risk	Not fitting stage I or III
III High risk (One or more present)	Hemoglobin <8.5 g/dL
	Serum calcium >12 mg/dL
	Multiple lytic bone lesions on x-ray
	High production rates of M component:
A if serum creatinine <2.0 mg/dL	IgG <7 g/dL of IgA <5 g/dL
B if serum creatinine >2.0 mg/dL	Urine light chain M component <12 g/24h

Complications of myeloma

- Immunoglobulin (Bence-Jones protein) deposition leads to nodular mesangial expansion granular deposits of immunoglobulin.
- Macrophages and giant cells may be seen.
- Immunoglobulin demonstrated on gomerular tufts and renal tubules with immunofluorescent staining.
- Kappa light chain principally involved.
- No deposits on electron microscopy.
- Complication of dehydration, hypercalcemia.



BM, Bone marrow; Ig, immunoglobulin.

Myeloma-defining events

Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcaemia: 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)
- Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
- Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or fluorodeoxyglucose (FDG)-positron emission tomography (PET)-CT

Any one or more of these biomarkers of malignancy:

- Clonal plasma cell bone marrow infiltration ≥60%
- Involved: uninvolved serum free-light chain ratio ≥100
- >1 focal lesion on magnetic resonance imaging studies

Fig. 10.2

Plasma cell leukemia

- Plasma cells >20% in peripheral blood
- or >2,000 cells/L
- Marrow over 90% myeloma cells
- Higher counts associated with poorer outcomes
- Extramedullary disease
- Rare bone lesion
- Paraprotein complications
- Mean age of presentation 61 years of age
- 25% 1year survival
- IgG, light chain disease, non-secretory in descending order of incidence

Plasma cell leukemia

- t(11;14), t(14;16), and t(4;14)
- Other deletions 1p, 6q, 8p, 13q, 14q, and 16q
- TP53 and DIS3 mutations are more common in PCL than in MM
- NRAS, KRAS, and BRAF less common in PCL than in MM
- Autologous stem cell transplant, bortozemib, and lelanomide

Systemic amyloidosis

- May be asymptomatic.
- Symptoms depend on magnitude and site of deposits.
- Pressure atrophy of adjacent cells results
- Types:
- Light chain (AL)
- Reactive (AA)
- Hemodyalisis related ($A\beta_2M$)

Systemic amyloidosis

- Deposition of mis-folded proteins as insoluble fibrillary aggregates in extracelluar space in normal organs and tissues.
- Soluble in their normal folded configuration
- Pleated sheets in a zig-zag configuration
- Cross-β-pleated sheet of continuous non-branching fibrils oriented parallel to fibril axis comprise approximately 95% of the amyloid material.
- Serum amyloid P component and other glycoproteins bound, form 5% of amyloid material

Systemic amyloidosis

- Measurement of NT-proBNP (N-terminal pro-brain natriuretic peptide [and, if indicated, of cardiac troponin-T]) and urine for protein – would detect >90% of such cases very early, potentially improving outcomes.

Overview of systemic amyloidosis

Type of systemic amyloidosis	Amyloid protein	Underlying cause	Age of onset	Organs most commonly affected	Additional information
Light-chain amyloidosis	• Light chains of immunoglobulins → AL amyloid protein	• Plasma cell dyscrasias (e.g., multiple myeloma)	• > 40 years	• Heart • Kidney • Tongue • Autonomic nervous system • Gastrointestinal tract	• Most common form of amyloidosis in the western world • **Rapidly progressive clinical course**
Reactive amyloidosis	• Serum amyloid-associated protein (SAA) → AA amyloid protein	• Chronic inflammatory conditions (e.g., IBD, rheumatoid arthritis, SLE) • Chronic infectious diseases (e.g., tuberculosis, osteomyelitis) • Certain tumors (e.g., renal cell carcinoma, lymphomas)	• Any age	• Kidney • Adrenal glands • Liver and spleen • Gastrointestinal tract	• Most common form of amyloidosis in the developing world • The progression of the disease can be slowed by controlling the underlying condition.
Hemodialysis-associated amyloidosis	• β2-microglobulin → Aβ2M amyloid protein	• Long-term hemodialysis	• ~ 10 years after starting hemodialysis	• Joints and tendons	• Almost all individual on long-term hemodialysis will develop amyloidosis at some point

DEFINITION OF ORGAN INVOLVEMENT BASED ON AMYLOIDOSIS CONSENSUS CRITERIA[1]

Organ Involvement	
Kidney	**24-h urine protein >0.5 g/d, predominantly albumin**
Heart	**Echo: mean wall thickness >12 mm, no other cardiac cause or an elevated NT-proBNP (>332 ng/L) in the absence of renal failure or atrial fibrillation**
Liver	**Total liver span >15 cm in the absence of heart failure or alkaline phosphatase >1.5 times institutional upper limit of normal**
Nerve	**Peripheral: clinical; symmetric lower extremity sensorimotor peripheral neuropathy** **Autonomic: gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration**
Gastrointestinal tract	**Direct biopsy verification with symptoms**
Lung	**Direct biopsy verification with symptoms** **Interstitial radiographic pattern**
Soft tissue	**Tongue enlargement, clinical** **Arthropathy** **Claudication, presumed vascular amyloid** **Skin** **Myopathy by biopsy or pseudohypertrophy** **Lymph node (may be localized)** **Carpal tunnel syndrome**

Revised Consensus Criteria for amyloidosis involvement from XII International Symposium on Amyloidosis:

Gertz M and Merlini G. Definition of organ involvement and response to treatment in AL amyloidosis: an updated consensus opinion [abstract]. Amyloid 2010 17(Suppl 1):48-49. (Abstract CP-B).

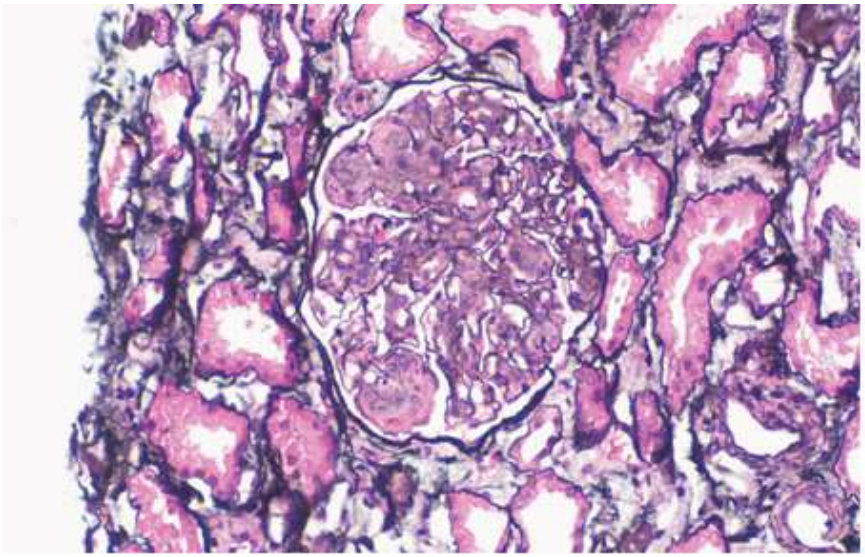
PROGNOSTIC STAGING SYSTEM FOR LIGHT CHAIN AMYLOIDOSIS

Prognostic Variables	Value	Assigned Prognostic Variable Score
cTnT	≥0.025 ng/mL (or hs-cTnT ≥40 pg/mL)	1
NT-ProBNP	≥1,800 pg/mL	1
FLC-diff	≥18 mg/dL	1

REVISED STAGING SYSTEM BASED ON THE ABOVE THREE PROGNOSTIC SCORES[1]

Total Prognostic Score	Stage
0	Stage I
1	Stage II
2	Stage III
3	Stage IV

Light chain deposition disease



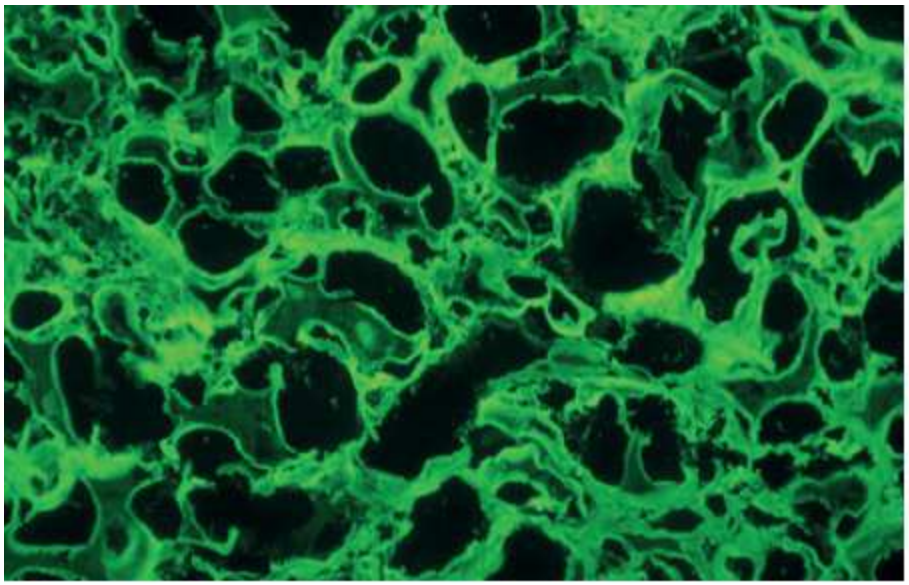
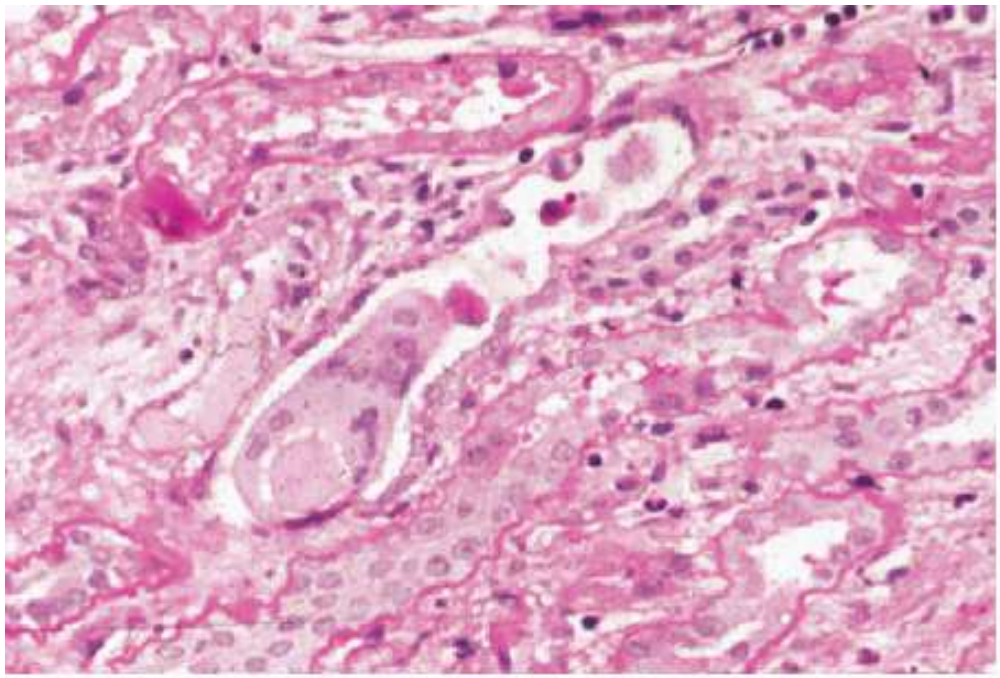


Fig. e9-14 Accessed 03/17/2010

There is mesangial expansion, often nodular by light microscopy (left). Immunofluorescence shows monoclonal staining of tubules and glomerular tufts (right). More commonly kappa light chain is involved. (ABF/Vanderbilt Collection.)

Light chain cast nephropathy

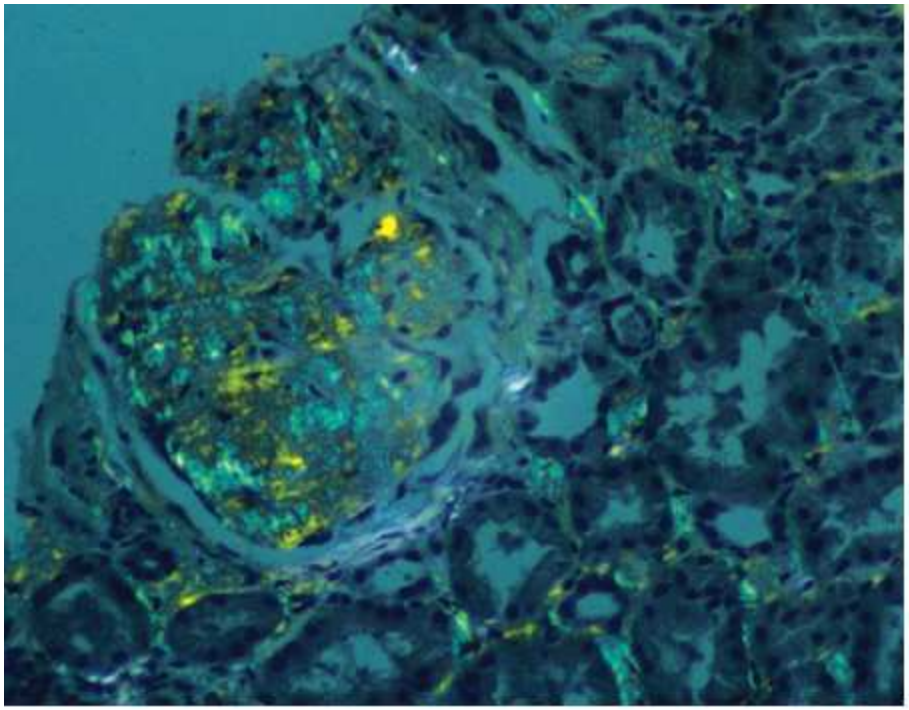


Monoclonal light chains precipitate in tubules and result in a syncytial giant cell reaction surrounding the cast, and a surrounding chronic interstitial nephritis with tubulointerstitial fibrosis. Worsened in dehydration.

(ABF/Vanderbilt Collection.)

Fig. e9-15 Accessed 03/17/2010

Amyloidosis



Amyloidosis shows amorphous, acellular expansion of the mesangium, with material often also infiltrating glomerular basement membranes, vessels, and in the interstitium, with apple-green birefringence by polarized Congo red stain. The deposits are composed of randomly organized 9- to 11-nm fibrils by electron microscopy.

(ABF/Vanderbilt Collection.)

Fig. e9-13 Accessed 03/17/2010

Treatment strategy

- Solitary plasmacytoma is treated with radiation therapy to involved site (if in bone)
- 40-50Gy in 1.8-2.0 Gy/fraction
- OR surgical removal (extraosseus).
- Close follow-up essential because of the risk of overt myeloma.

Treatment strategy

- If the patient is asymptomatic, the disease is referred to as smoldering multiple myeloma.
- Observed.
- Stage I patients (as well as those with smoldering disease) can be observed until progression to higher stage.
- For smoldering disease, the mean time to progression is 2 years.
- Upfront transplant is best treatment option.

Treatment strategy

- Proteasome inhibitor (bortezomib), immunomodulatory drug (lelanidomide), dexamethasone, with/without anti-CD38 antibody as induction therapy in high risk myeloma
- Similar outcomes with or without anti-CD38 antibody
- Bortezomib, a NFκB inhibitor
- Del 13 responds best.
- Bortezomib also eliminates t(4;14), t(14;16) and del 17p as prognostic factors

Treatment strategy

- Lenalidomide and dexamethasone administered prior to collection of stem cells for autologous stem cell transplantation.
- Then, melphalan followed by stem cell therapy
- All suitable patients are transplanted.
- Two transplants within 12 months (tandem)
- Maintenance therapy with lenalidomide.

Treatment strategy

- Proteasome inhibitor and/or immunomodulatory drug maintenance following autologous stem cell transplant.
- CD38-directed monoclonal antibodies (daratumumab and ixasomib)
- Elotuzumab targets SLAMF7
- Relapse drug options based on earlier response

Treatment strategy

- Used in frail patients or those with poor functional status:
- Bortezomib/dexamethasone
- Lenalidomide/dexamethasone
- Pomalidomide/dexamethasone
- Single-agent daratumumab
- Most relapse on lenalidomide.
- Bortezomib/pomalidomide/dexamethasone preferable.

Treatment strategy

- Median survival 4 years without transplant.
- If 17p deletion, consider adding selinexor (inhibitor of the nuclear export protein XPO1; as a result of inhibition, cargo is trapped in the nucleus, resulting in cell cycle arrest and apoptosis.)
- Daratmtumab and bortezomib in refractory disease
- In treatment failures, CAR-T therapy probably the better choice

Treatment strategy

- Bortezomib with cyclophosphamide and dexamethasone is the treatment regimen of choice in systemic amyloidosis therapy

Frailty index

Multivariate analysis (final Cox regression model)			
	HR for OS (95% CI)	P	Score
Age, years			
≤75	1	–	0
76–80	1.13 (0.76–1.69)	0.549	1
>80	2.40 (1.56–3.71)	<0.001	2
ADL			
>4	1	–	0
≤4	1.67 (1.08–2.56)	0.020	1
IADL			
>5	1	–	0
≤5	1.43 (0.96–2.14)	0.078	1
CCI			
≤1	1	–	0
≥2	1.37 (0.92–2.05)	0.125	1

ADL, Activities of Daily Living; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; IADL, Instrumental Activities of Daily Living; OS, overall survival.

Fig. 8.10

The IMWG Frailty Index is based on age, Charlson Comorbidity Index (CCI) and (Instrumental) Activities of Daily Living ([I]ADL). Definitions are as follows: fit score 0, unfit/intermediate fit score 1 and frail score 2 or higher.

Overall survival (a) and discontinuation rate (b) in fit, unfit and frail patients.

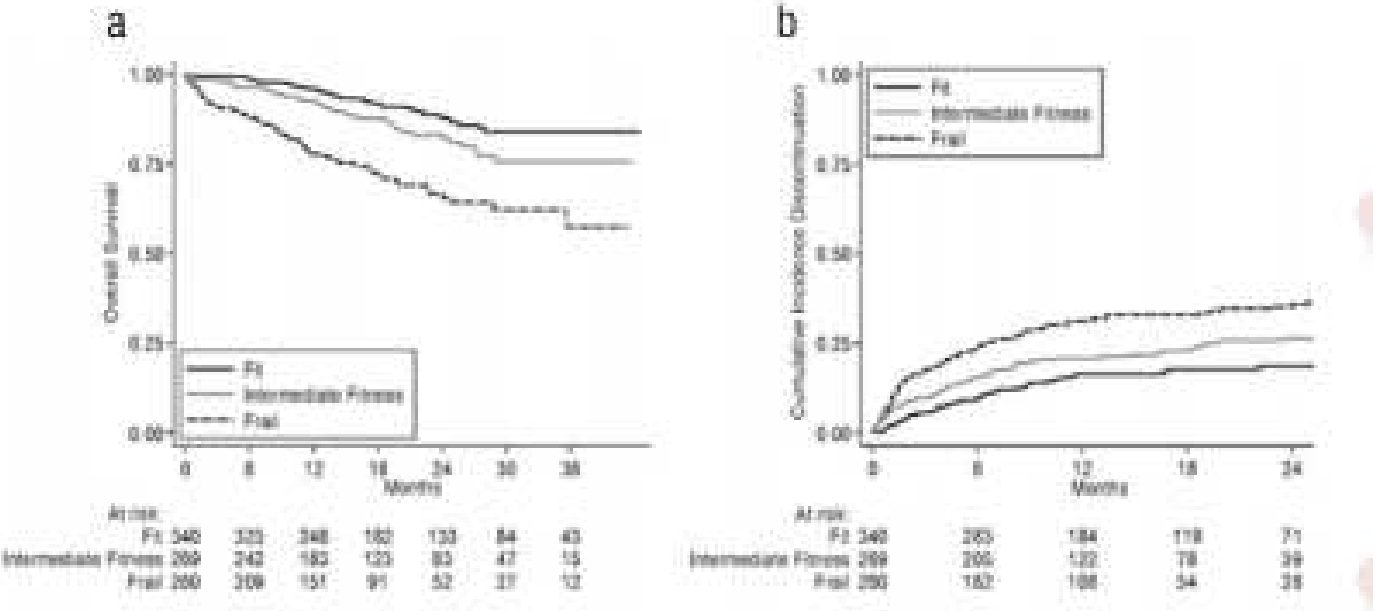
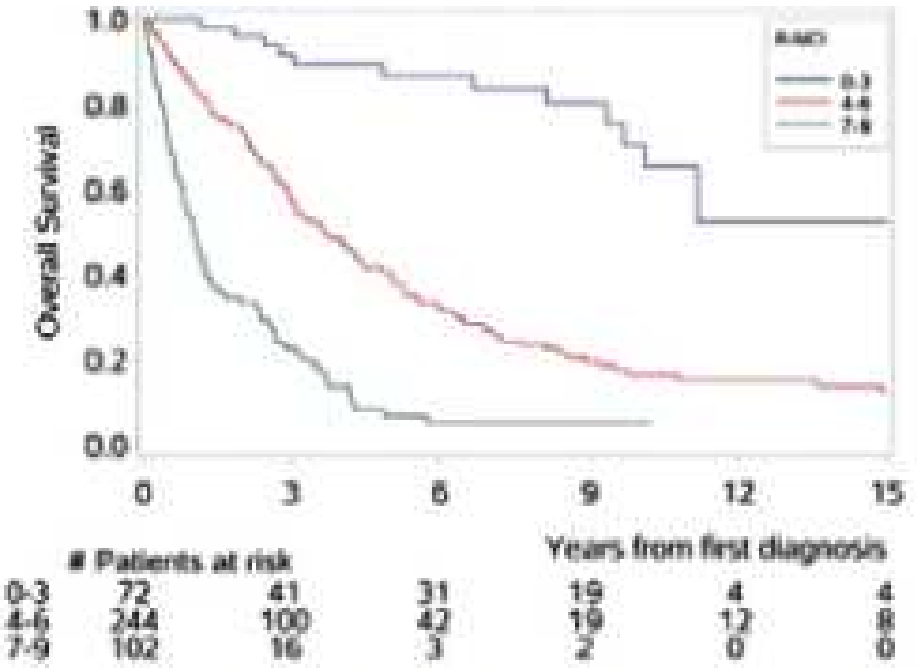


Fig. 8.11

Overall survival according to R-MCI based frailty assessment in patients who did not receive an SCT



# Patients at risk						
0-3	72	41	31	19	4	4
4-6	244	100	42	19	12	8
7-9	102	16	3	2	0	0

Fig. 8.12

R-MCI, Revised-Myeloma Comorbidity Index; SCT, stem cell transplantation.

MYELOMA THERAPY[a-d]

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES

Preferred Regimens
- Bortezomib/lenalidomide/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone[e]

Other Recommended Regimens
- Carfilzomib/lenalidomide/dexamethasone
- Daratumumab[f]/lenalidomide/bortezomib/dexamethasone
- Ixazomib/lenalidomide/dexamethasone (category 2B)

Useful In Certain Circumstances
- Bortezomib/doxorubicin/dexamethasone
- Carfilzomib/cyclosphosphamide/dexamethasone[g]
- Ixazomib/cyclophosphamide/dexamethasone[g]
- Bortezomib/thalidomide/dexamethasone (category 1)
- Cyclophosphamide/lenalidomide/dexamethasone
- Daratumumab[f]/cyclophosphamide/bortezomib/dexamethasone
- Daratumumab[f]/bortezomib/thalidomide/dexamethasone
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib[h] (VTD-PACE)

MAINTENANCE THERAPY

Preferred Regimens
- Lenalidomide[i] (category 1)

Other Recommended Regimens
- Ixazomib (category 1)
- Bortezomib

Useful In Certain Circumstances
- Bortezomib/lenalidomide

MYELOMA THERAPY[a-d]

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1)[j] • Daratumumab[f]/lenalidomide/dexamethasone (category 1) • Lenalidomide/low-dose dexamethasone (category 1)[k] • Bortezomib/cyclophosphamide/dexamethasone[e]
Other Recommended Regimens • Carfilzomib/lenalidomide/dexamethasone • Ixazomib/lenalidomide/dexamethasone • Daratumumab[f]/bortezomib/melphalan/prednisone (category 1) • Daratumumab[f]/cyclophosphamide/bortezomib/dexamethasone
Useful In Certain Circumstances • Bortezomib/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone[g]

MAINTENANCE THERAPY
Preferred Regimens • Lenalidomide (category 1)
Other Recommended Regimens • Bortezomib
Useful In Certain Circumstances • Bortezomib/lenalidomide

MYELOMA THERAPY[a-d]

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[l,m]

Preferred Regimens

- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone (category 1)[n]
- Daratumumab[f]/bortezomib/dexamethasone (category 1)
- Daratumumab[f]/carfilzomib/dexamethasone (category 1)
- Daratumumab[f]/lenalidomide/dexamethasone (category 1)
- Isatuximab-irfc/pomalidomide/dexamethasone (category 1)[o]
- Ixazomib/lenalidomide/dexamethasone (category 1)[n]
- Ixazomib/pomalidomide[p]/dexamethasone
- Pomalidomide[p]/bortezomib/dexamethasone (category 1)

Other Recommended Regimens

- Belantamab mafodotin-blmf[q]
- Bendamustine/bortezomib/dexamethasone
- Bendamustine/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone
- Carfilzomib/cyclophosphamide/dexamethasone
- Carfilzomib (twice weekly)/dexamethasone (category 1)
- Cyclophosphamide/lenalidomide/dexamethasone
- Daratumumab[f]/cyclophosphamide/bortezomib/dexamethasone
- Daratumumab[f]/pomalidomide[r]/dexamethasone
- Elotuzumab/bortezomib/dexamethasone
- Elotuzumab[s]/lenalidomide/dexamethasone (category 1)[n]
- Elotuzumab/pomalidomide/dexamethasone[r]
- Ixazomib/cyclophosphamide/dexamethasone
- Panobinostat[u]/bortezomib/dexamethasone (category 1)
- Pomalidomide[p]/cyclophosphamide/dexamethasone
- Pomalidomide[p]/carfilzomib/dexamethasone

Useful In Certain Circumstances

- Bendamustine
- Bortezomib/dexamethasone (category 1)
- Carfilzomib/cyclophosphamide/thalidomide/dexamethasone
- Carfilzomib (weekly)/dexamethasone
- Daratumumab[f,v]
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[h]
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)[h] ± bortezomib (VTD-PACE)[h]
- High-dose cyclophosphamide
- Ixazomib/dexamethasone
- Lenalidomide/dexamethasone[t] (category 1)
- Panobinostat[u]/carfilzomib
- Panobinostat[u]/lenalidomide/dexamethasone
- Pomalidomide[p]/dexamethasone[t] (category 1)
- Selinexor/dexamethasone[w]
- Venetoclax/dexamethasone only for t(11;14) patients

SYSTEMIC LIGHT CHAIN AMYLOIDOSIS THERAPY
(Order of regimens is alphabetical and does not indicate preference)

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES[1,2,3]
Preferred Regimen: • Bortezomib[4]/cyclophosphamide/dexamethasone
Other Recommended Regimens: • Bortezomib[4] ± dexamethasone • Bortezomib[4]/lenalidomide[5]/dexamethasone • Bortezomib[4]/melphalan/dexamethasone • Lenalidomide[5]/cyclophosphamide/dexamethasone • Lenalidomide[5]/dexamethasone • Melphalan/dexamethasone

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES[1,3] (if not a candidate for stem cell transplant at initial diagnosis, reassess after 2 cycles of systemic therapy)
Preferred Regimen: • Bortezomib[4]/cyclophosphamide/dexamethasone • Melphalan/dexamethasone
Other Recommended Regimens: • Bortezomib[4] ± dexamethasone • Bortezomib[4]/lenalidomide[5]/dexamethasone • Bortezomib[4]/melphalan/dexamethasone • Lenalidomide[5]/cyclophosphamide/dexamethasone • Lenalidomide[5]/dexamethasone

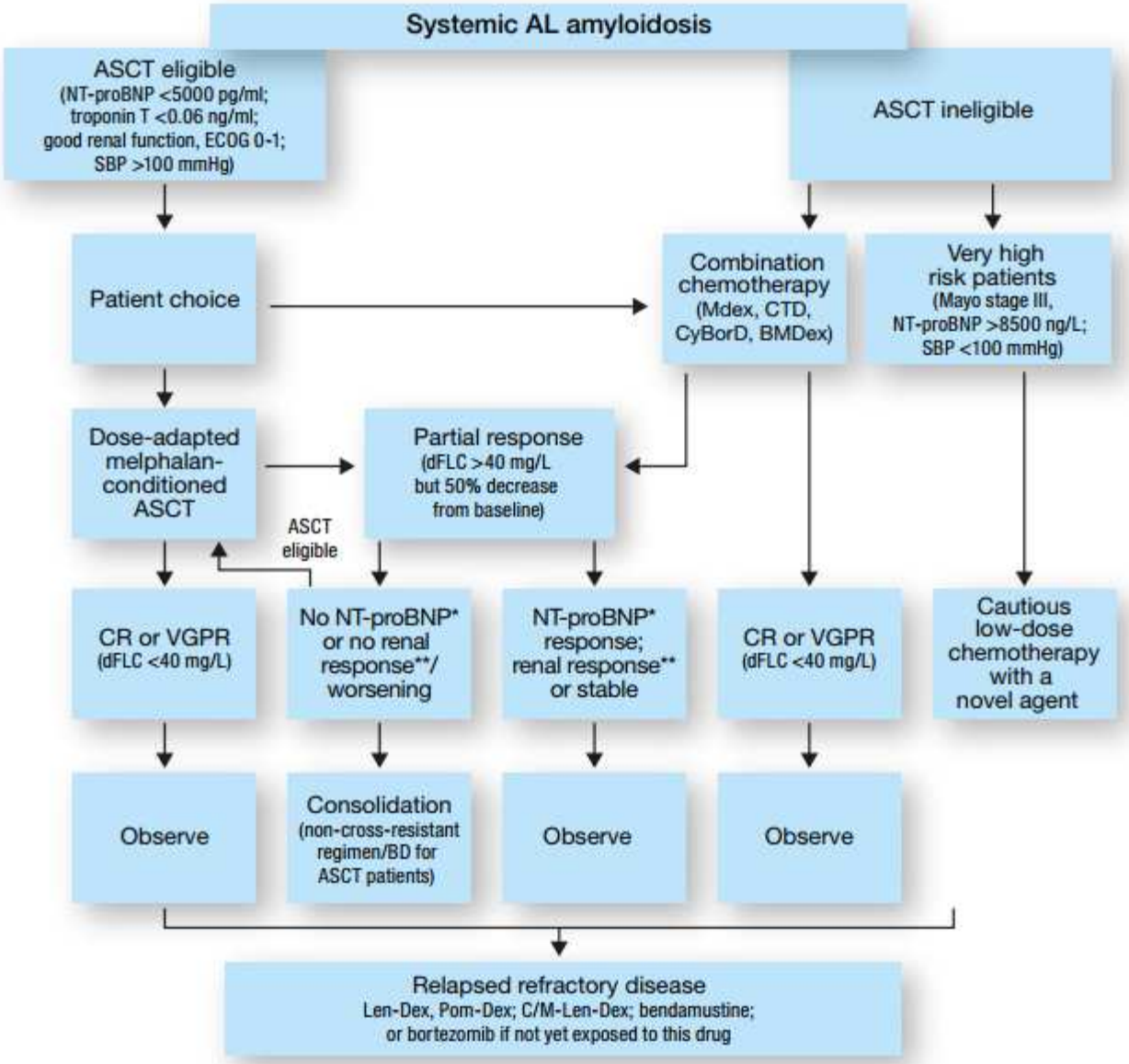


Fig. 18.7

*Reduction of 30% and 300 ng/L
** 50% decrease in proteinuria with stable or < 25% increase in serum creatinine
AL, Light-chain; ASCT, autologous stem cell transplantation; BD, bortezomib/dexamethasone; BMDex, bortezomib/melphalan/dexamethasone; C/M-Len-Dex, cyclophosphamide/melphalan/lenalidomide/dexamethasone; CR, complete response; CTD, cyclophosphamide/thalidomide/dexamethasone; CyBorD, cyclophosphamide/bortezomib/dexamethasone; dFLC, difference between involved minus uninvolved serum free light chains; ECOG, Eastern Cooperative Oncology Group; Len-Dex, lenalidomide/dexamethasone; Mdex, melphalan/dexamethasone; NT-proBNP, N-terminal pro-brain natriuretic peptide; Pom-Dex, pomalidomide/dexamethasone; SBP, systolic blood pressure; VGPR, very good partial response.

THERAPY FOR PREVIOUSLY TREATED DISEASE[1,6]
Consider repeating initial therapy, especially if relapse-free for several years • High-dose melphalan[7] with stem cell transplant • Bortezomib[4] ± dexamethasone • Bortezomib[4]/melphalan/dexamethasone • Daratumumab[8,9,10] • Ixazomib ± dexamethasone • Lenalidomide[5]/cyclophosphamide/dexamethasone • Lenalidomide[5]/dexamethasone • Melphalan/dexamethasone • Pomalidomide/dexamethasone

Adoptive T cell immunotherapeutic strategies

1. Unmodified cells:
   Marrow infiltrating lymphocytes (MILs) → Broad endogenous tumour specificity, enriched for central memory T cells → more suitable for adoptive T cell approaches

2. CAR-T cells:
   ASCT plus CTL019 → Rescue therapy in 12 patients progressing within 1 year after ASCT. Median PFS: 6 months, all patients have progressed

   CAR-T-BCMA → Rescue therapy in 6 RRMM patients after a median of 9 prior lines. 1 sCR (+7 m), 1 VGPR (+5m) and 2 MR

   BCMA Ab (conjugated with auristatin) → 24 patients after more than 4 prior lines. 25% of unconfirmed responses

Fig. 9.15

Ab, Antibody; ASCT, autologous stem cell transplantation; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; MR, minimal response; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; VGPR, very good partial response.

Measurable disease definition	
Serum M protein	≥10 g/L
Urine M protein	≥200 mg/24 h
Serum FLC assay	Involved FLC level ≥100 mg/L provided serum FLC ratio is abnormal

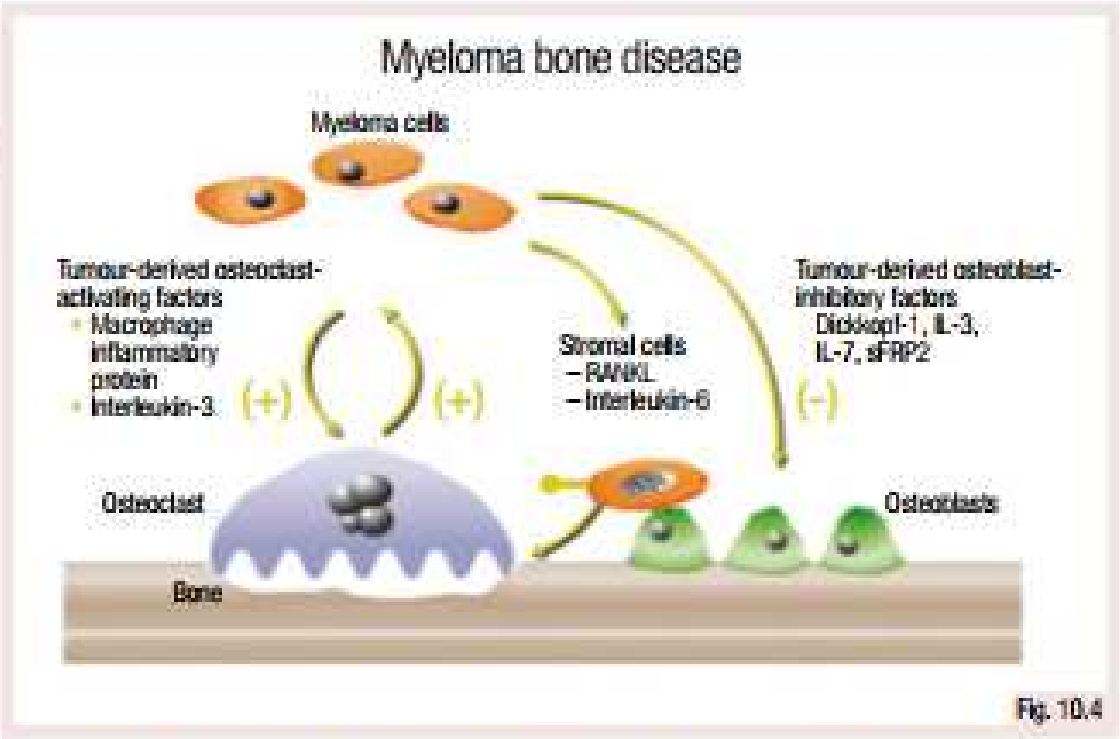
FLC, Free light chain; M, monoclonal.

Fig. 8.10

Response subcategory	Response criteria
Stringent complete response (sCR)	Complete response plus normal FLC ratio and absence of clonal cells in bone marrow
Complete response (CR)	Negative immunofixation on the serum and urine and <5% plasma cells in bone marrow
Very good partial response (VGPR)	Serum and urine M protein detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M protein plus urine M protein level <100 mg per 24 h
Partial response (PR)	≥50% reduction of serum M protein plus reduction in 24 h urinary M protein by ≥90% or to <200 mg per 24 h; if the serum and urine M protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR or PD
Progressive disease (PD)	• Increase of 25% from lowest value in serum M component (absolute increase must be ≥0.5 g/dL) and/or urine M component (absolute increase must be ≥200 mg/24 h); if the serum and urine M protein are unmeasurable, a ≥25% increase in the difference between involved and uninvolved FLC levels is required and/or • Development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas and/or • Development of hypercalcaemia

Fig. 6.11

FLC, Free light chain; M, monoclonal.



IL, Interleukin; RANKL, receptor activator of nuclear factor kappa-B ligand.

Prevention of bone disease

Practical recommendations during BP therapy

- Calcium and vitamin D3 should be used to maintain the calcium homeostasis
- All BP-treated patients should have creatinine clearance, serum electrolytes and urinary albumin monitored

Preventive strategies to avoid osteonecrosis of the jaw

- Comprehensive dental examination to treat all dental problems before initiating BP
- Educate about dental hygiene
- Unnecessary invasive dental procedures should be avoided
- If osteonecrosis occurs, BP therapy should be discontinued until healed

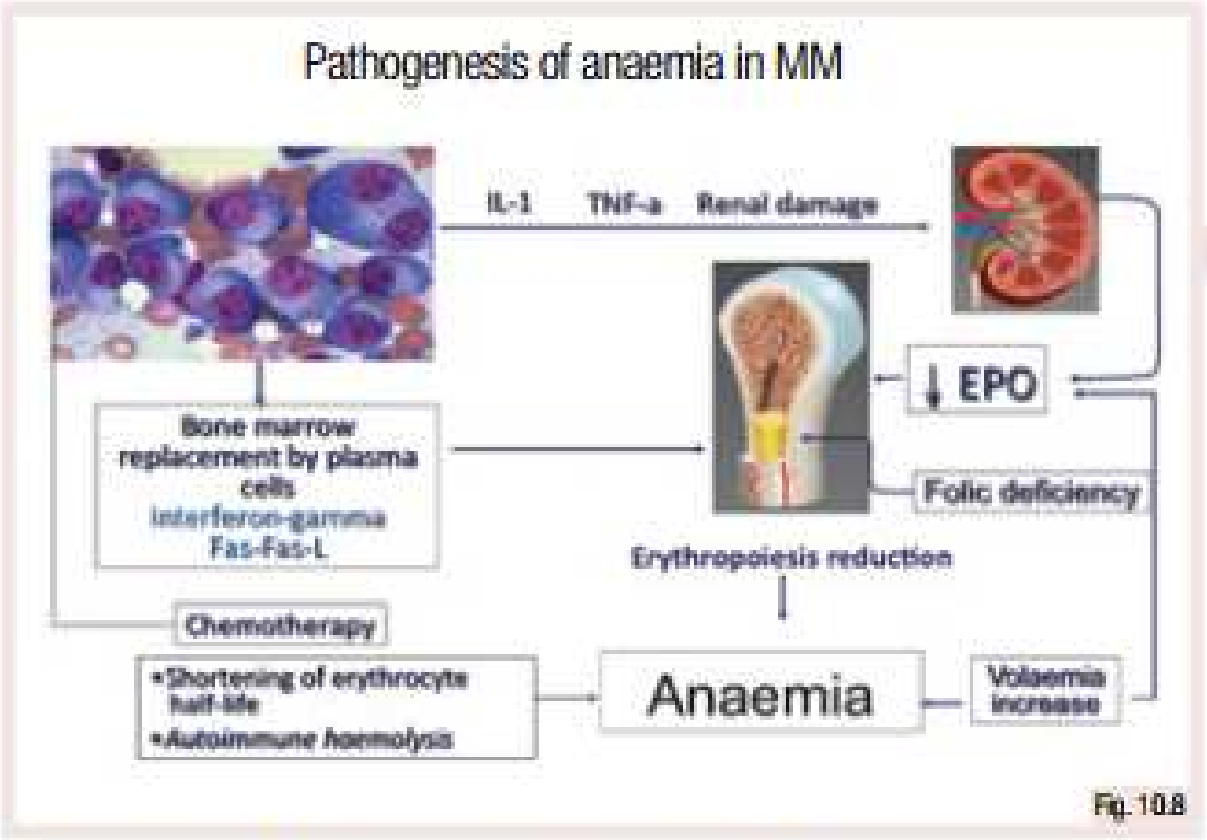
Fig. 10.6

BP, Bisphosphonate.

Treatment of bone disease
Therapeutic strategies

Procedure	Recommendations
Balloon kyphoplasty	Painful vertebral compressive fractures
Vertebroplasty	Remains debatable in the absence of prospective trials
Radiotherapy	• Solitary plasmacytoma, symptomatic spinal cord compression, extremely painful lytic lesions • Prevention of pathological fractures
Surgery	• To fix pathological fractures of the long bones • To prevent and restore axial skeleton in cases of unstable spinal fractures • For spinal cord compression with bone fragments within the spinal route

Fig. 10.7



EPO, Erythropoietin; IL, interleukin; MM, multiple myeloma; TNF, tumour necrosis factor.

Management of anaemia

Condition	Management

• Symptomatic anaemia or
• Asymptomatic anaemia with:
  ◦ cardiac disease
  ◦ chronic pulmonary disease
  ◦ cerebral vascular disease
	Transfusional support

• Persistent symptomatic anaemia, usually <10 g/dL with other causes of anaemia excluded	Use of erythropoiesis-stimulating agents (ESAs): Erythropoietin-α 40 000 UI/week ◦ Erythropoietin-β 30 000 UI/week ◦ Darbepoetin 150 μg/week or 500 μg/3 weeks

- Haemoglobin level should not increase more than 12 g/dL
- ESAs should be stopped after 6–8 weeks if adequate response is not achieved
- True or functional iron deficiency during treatment with an ESA should be treated with intravenous iron

Fig. 10.9

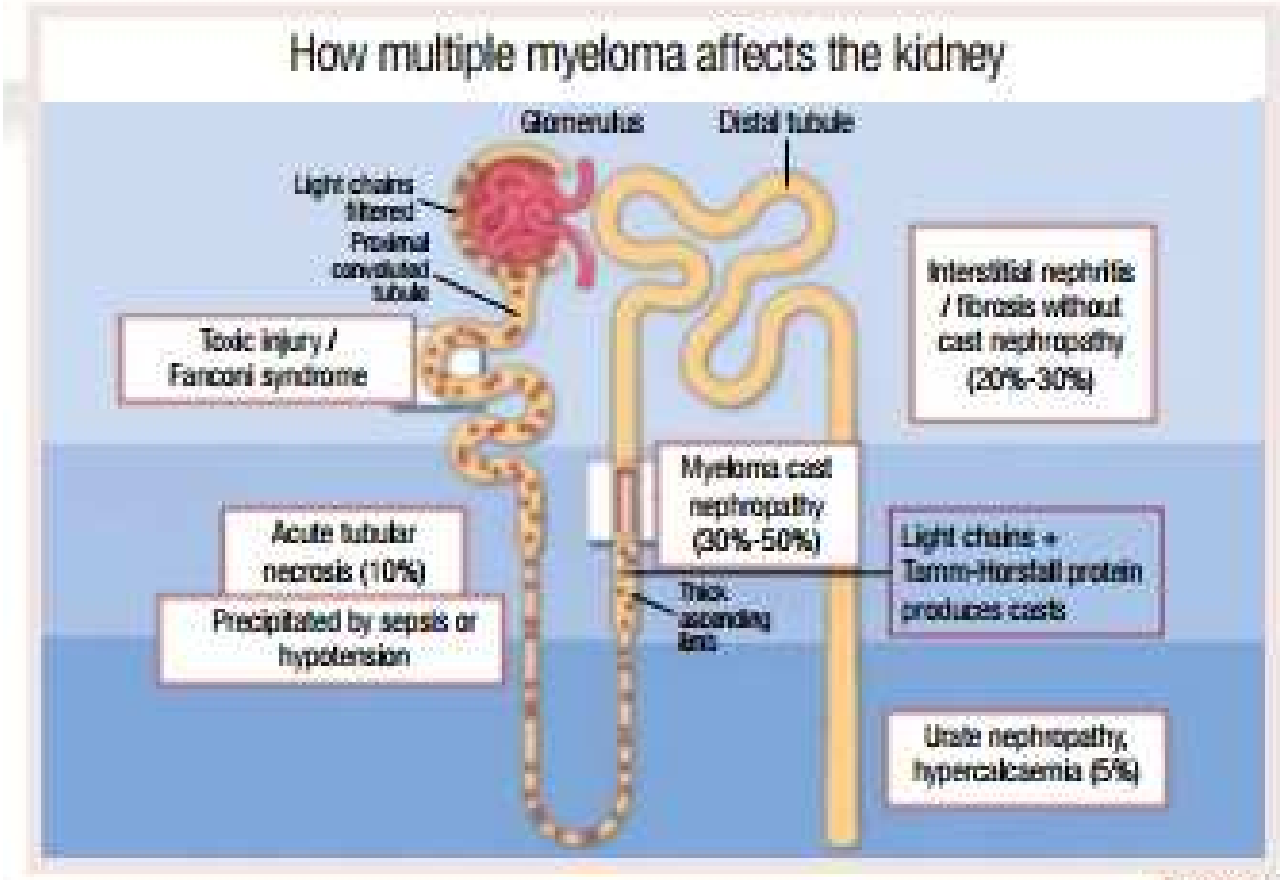

How multiple myeloma affects the kidney
Glomerulus
Distal tubule
Light chains filtered
Proximal convoluted tubule
Toxic injury / Fanconi syndrome
Interstitial nephritis / fibrosis without cast nephropathy (20%-30%)
Myeloma cast nephropathy (30%-50%)
Light chains + Tamm-Horsfall protein produces casts
Acute tubular necrosis (10%)
Precipitated by sepsis or hypotension
Thick ascending limb
Urate nephropathy, hypercalcaemia (5%)

Fig. 10.10

Renal insufficiency diagnosis and management in MM

Myeloma-related renal insufficiency includes the presence of:

- Serum creatinine ≥2 mg/dL, or
- Estimated glomerular filtration rate (eGFR) <40 mL/minute

The patient has to present proteinuria, which consists mainly of light chains

Management:

- Effective therapy
- Adequate hydration
- Urine alkalinisation
- Treatment of hypercalcaemia if present
- Plasma exchange remains controversial
- Dialysis is required (conventional versus high cut-off dialysers is controversial)

MM, Multiple myeloma.

Fig. 10.11

Management of hypercalcaemia in MM

- Definition: Ionic calcium >11 mg/dL (mild <12 mg/dL; moderate 12–14 mg/dL; severe >14 mg/dL)
- Pathogenesis: Local resorption of bone induced by release of cytokines and production of humoural osteoclast activators
- Symptoms: Dehydration, lethargy and psychosis, malaise, fatigue, headaches, constipation, …
- Approaches to management:
  - Increase urinary calcium excretion: Isotonic saline with or without loop diuretics
  - Diminish bone resorption: bisphosphonates
  - Decrease intestinal calcium absorption: corticosteroids
  - Dialysis if required
  - Active treatment of myeloma

Fig. 10.13

MM, Multiple myeloma.