Onco-Nephrology

Hematological malignancies and the Kidney

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Assistant Professor of Medical Sciences

	Worldwide			Low- and Middle-income			High-income		
	Rank	Deaths	%	Rank	Deaths	%	Rank	Deaths	%
Cardiovascular diseases	1	17,513	31%	1	13,075	30%	1	4,438	38%
Malignant neoplasms	2	8,204	15%	3	5,310	12%	2	2,894	25%
Infectious and parasitic diseases	3	6,431	12%	2	6,128	14%	7	303	3%
Respiratory diseases	4	4,040	7%	4	3,395	8%	3	645	6%
Unintentional injuries	5	3,716	7%	5	3,212	7%	5	504	4%
Respiratory infections	6	3,060	5%	6	2,664	6%	6	396	3%
Digestive diseases	7	2,263	4%	7	1,748	4%	4	515	4%
Diabetes mellitus	8	1,497	3%	8	1,243	3%	9	254	2%
Intentional injuries	9	1,428	3%	9	1,185	3%	10	243	2%
Genitourinary diseases	10	1,195	2%	10	935	2%	8	260	2%
Nutritional deficiencies	11	559	1%	11	534	1%	14	25	0%
Congenital anomalies	12	556	1%	12	515	1%	13	42	0%
Maternal conditions	13	296	1%	13	293	1%	16	3	0%
Musculoskeletal diseases	14	216	0%	14	158	0%	12	58	1%
Other neoplasms	15	193	0%	15	116	0%	11	77	1%
All causes		55,843			44,172			11,671	

- Increase in the number of cancer survivors

1. Cancer associated kidney complications
2. Cancer treatment for patients with CKD

- The coexistence of CKD with cancer reduces the likelihood that cancer patients will receive optimal anti-cancer therapy and supportive care

Cancer-related injury

Tumor infiltration of the kidneys

Obstructive nephropathy related to retroperitoneal lymphadenopathy

Lysozymuria (CMML or AML) with direct tubular injury

Hemophagocytic lymphohistiocytosis with acute interstitial disease

Vascular occlusion associated with DIC and hyperleukocytosis (rare)

Hypercalcemia with hemodynamic acute kidney injury and acute nephrocalcinosis

Glomerular diseases (minimal change disease, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, membranous nephropathy, amyloidosis, immunotactoid glomerulonephritis, fibrillary glomerulonephritis, crescentic glomerulonephritis)†

Therapy-related injury

Nephrotoxicity (including thrombotic microangiopathy, acute tubular injury, tubulointerstitial nephritis, and glomerular disease)

Tumor lysis syndrome with acute uric acid nephropathy (may occur spontaneously)

Intratubular obstruction from medications (e.g., methotrexate)

Other types of injuries

Volume depletion

Sepsis and septic shock

Nephrotoxicity of radiocontrast agents

Nephrotoxicity of common medications, such as NSAIDs, ACE inhibitors, ARBs, and antibiotics

Tumor Lysis Syndrome

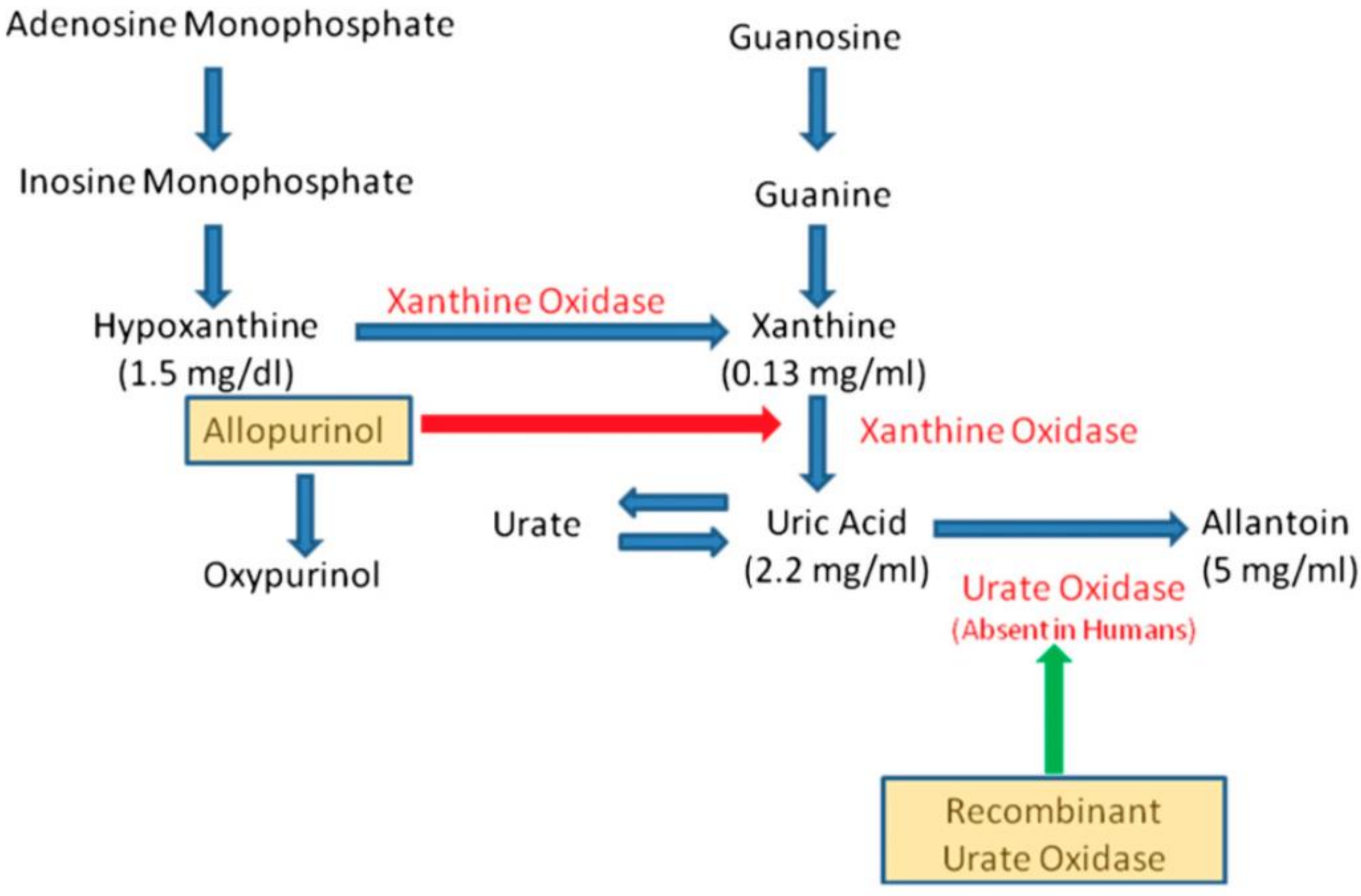
Malignancy (Reference)	Incidence (%)	Risk
Hematologic		
Burkitt lymphoma (33)	14.9	High
B cell ALL (33)	26.4	High
diffuse large-B cell lymphoma (87)	6	Intermediate
ALL	5.2–23	May vary by WBC count, with >100,000 cells/mm^3 being highest risk
AML: WBC count >75,000 cells/mm^3 (37)	18	High
AML: WBC count 25,000–75,000 cells/mm^3 (37)	6	Intermediate
AML: WBC count <25,000 cells/mm^3 (37)	1	Low
chronic lymhocytic leukemia (88)	0.33	Low (higher with WBC >100,000 cells/mm^3)
chronic myeloid leukemia (89)	Case reports only	Low
multiple myeloma (90)	1	Low
Nonhematologic		
solid tumors (35)	Unknown	Low

Cairo-Bishop classification of tumor lysis syndrome in adults

Laboratory TLS	Clinical TLS
Uric acid: ≥8.0 mg/dl	AKI (defined as creatinine >1.5× the upper limit of normal for patient age and sex)
Potassium: ≥6.0 mEq/dl	Cardiac arrhythmia
Phosphorus: ≥4.6 mg/dl	Seizure, tetany, or other symptomatic hypocalcemia
Calcium: ≤7.0 mg/dl	

Patients must meet more than two of four laboratory criteria in the same 24-hour period within 3 days before to 7 days after chemotherapy initiation. A >25% increase from "baseline" laboratory values is also acceptable (13). Other causes of AKI (*e.g.*, nephrotoxin exposure, obstruction) should be excluded. TLS, tumor lysis syndrome.

Characteristic	Risk Factor
Tumor burden	Bulky lymphatic disease (>10 cm)
	Elevated lactate dehydrogenase (2× upper limit of normal)
	Elevated white blood cell count (>25,000 cells/mm^3)
Renal function	Baseline creatinine > 1.4 mg/dl (37)
Baseline uric acid	>7.5 mg/dl
Chemosensitivity	Variable


Adenosine Monophosphate
Guanosine
Inosine Monophosphate
Guanine
Hypoxanthine
(1.5 mg/dl)
Xanthine Oxidase
Xanthine
(0.13 mg/ml)
Allopurinol
Xanthine Oxidase
Oxypurinol
Urate
Uric Acid
(2.2 mg/ml)
Allantoin
(5 mg/ml)
Urate Oxidase
(Absent in Humans)
Recombinant
Urate Oxidase

Measure: potassium, phosphorous, calcium, uric acid
Assess kidney function: creatinine, urine output

≤1 Abnormal value

≥ 2 Abnormal values

No TLS

Assess tumor burden:
LDH, Disease type,
size of mass, WBC, bone marrow

Small or resected

Medium size
LDH ≤ 5 x Nl

Large Mass
LDH ≥ 5 x Nl
Hyperleukocytosis
Packed marrow

Assess Lysis Risk:
Nephropathy
Dehydration
Acidosis
Hypotension
Nephrotoxins

TLS Risk

Laboratory TLS
No symptoms/signs

Clinical TLS
Azotemia
Hypocalcemia
Hyperuricemia
Dysrhythmia

Negligible

Low

Hydration
Allopurinol
Daily lab

Intermediate

Hydration
Allopurinol/Rasburicase
Inpatient monitoring
Lab every 8–12 hrs

High

Hydration
Rasburicase
Cardiac monitoring
Lab every 6–8 hrs

Established TLS
Hydration
Rasburicase
Cardiac monitoring
Intensive care
Lab every 4–6 hrs
Possible dialysis

Hematologic Malignancy Induced Paraneoplastic Glomerulopathies

Hematologic Cancer
Minimal change disease (Hodgkin lymphoma, thymoma)
Membranoproliferative glomerulonephritis (chronic lymphocytic leukemia, non-Hodgkin lymphoma)
Membranous nephropathy (chronic lymphocytic leukemia, non-Hodgkin lymphoma)
Crescentic glomerulonephritis (chronic lymphocytic leukemia, Hodgkin and non-Hodgkin lymphoma)
IgA nephropathy (non-Hodgkin lymphoma)
Focal segmental glomerulosclerosis (Hodgkin lymphoma)
AA amyloidosis (Hodgkin and non-Hodgkin lymphoma)

- Autopsy studies suggest that renal involvement occurs in about 90% of patients with lymphoma

- Patients who present with AKI have predominantly bilateral interstitial infiltration of the kidneys by lymphoma cells

- Increased interstitial pressure leading to a reduced intra-renal blood flow with subsequent renal tubular injury

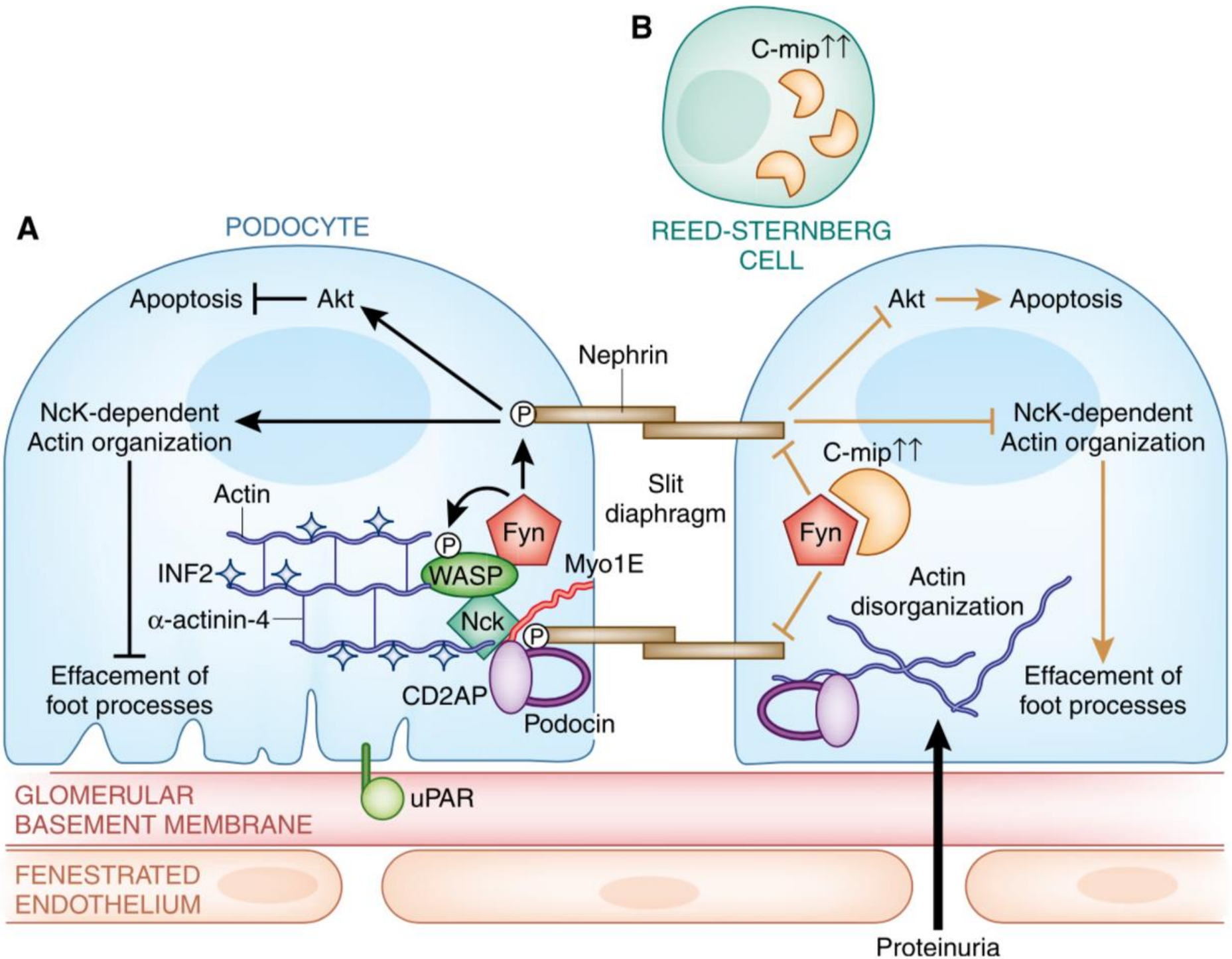
- In the presence of proteinuria, the local release of permeability factors and cytokines by lymphomatous cells is probably the main pathophysiological mechanism

- Minimal change disease is the most frequent paraneoplastic manifestation of classic Hodgkin lymphoma

- High frequency of steroid resistance (50%) and cyclosporine resistance

- Effective treatment of classic Hodgkin lymphoma generally induces simultaneous remission of nephrotic syndrome

- Nephrotic syndrome usually relapses simultaneously with the hematologic malignancy


B
C-mip↑↑
REED-STERNBERG CELL
A
PODOCYTE
Apoptosis
Akt
Nephrin
NcK-dependent Actin organization
P
Actin
Fyn
P
WASP
INF2
Myo1E
α-actinin-4
Nck
P
CD2AP
Podocin
Effacement of foot processes
Slit diaphragm
Akt
Apoptosis
NcK-dependent Actin organization
C-mip↑↑
Fyn
Actin disorganization
Effacement of foot processes
GLOMERULAR BASEMENT MEMBRANE
uPAR
FENESTRATED ENDOTHELIUM
Proteinuria

- The prevalence of nephrotic syndrome in patients with CLL is 1%–2%

- They often reveal CLL with a simultaneous diagnosis of both diseases in about 50% of patients

- Improvement of GN is mainly due to control of hematologic disease

- The link between CLL and GN is the dysproteinemia produced by the B cell clone

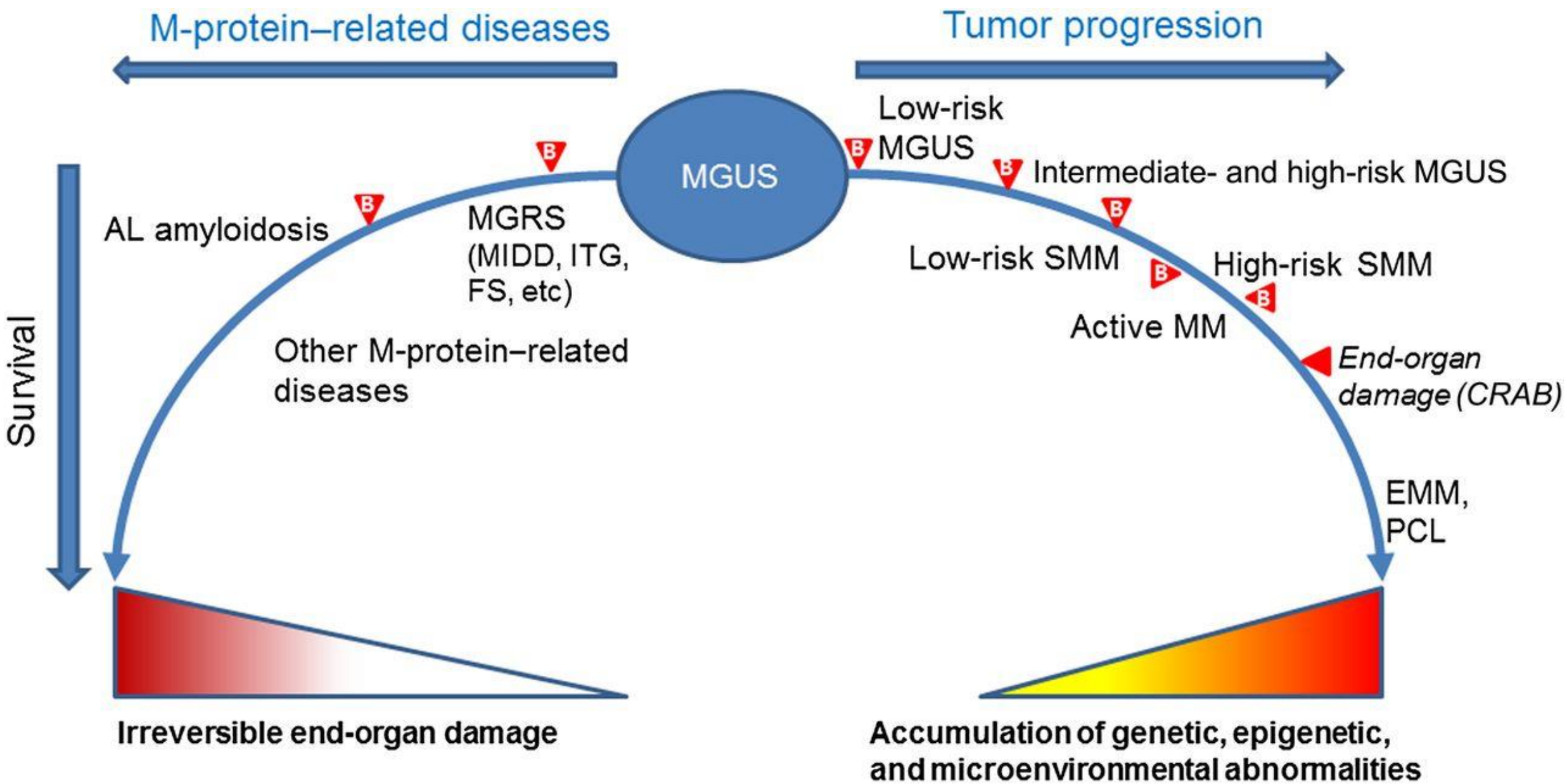
- Glomerulopathies have occasionally been reported in patients with MPN

- Most patients (73%) had primary myelofibrosis

- Less common than PV, ET, and CML

- Not considered a pure paraneoplastic disease because of the presence of hematopoietic cell infiltration

Plasma Cell Dyscrasias


M-protein–related diseases
Tumor progression
Survival
MGUS
AL amyloidosis
MGRS
(MIDD, ITG,
FS, etc)
Other M-protein–related
diseases
Low-risk
MGUS
Intermediate- and high-risk MGUS
Low-risk SMM
High-risk SMM
Active MM
End-organ
damage (CRAB)
EMM,
PCL
Irreversible end-organ damage
Accumulation of genetic, epigenetic,
and microenvironmental abnormalities

M-protein

Immunofixation

Non-IgM

IgM

Bone marrow biopsy [type of clonal cell]

Bone marrow biopsy [type of clonal cell]

Lymphocytes or Lymphoplasmacytic

Plasma cells

Lymphocytes or Lymphoplasmacytic

Symptomatic

Asymptomatic

Symptomatic

Differential Diagnosis
- CLL
- LPL

Amyloidosis
- Restrictive Cardiomyopathy
- Non-selective proteinuria
- Peripheral neuropathy
- Autonomic dysfunction
- Hepatomegaly

POEMS
- Polyneuropathy
- Organomegaly
- Endocrinopathy
- M-protein (Almost always Lambda light chain restricted)
- Skin lesions

LCDD
MGUS-neuropathies
Solitary plasmacytoma

Multiple Myeloma

C-Hypercalcemia
R -Renal failure
A -Anemia
B -Bone disease

MGUS
M-spike < 3g/dl
BM Clonal cell < 10%

SMM/SWM
M-spike ≥ 3g/dl
BM Clonal cell ≥ 10%

Waldenström Macrogobulinemia
- Anemia
- Thrombocytopenia
- Bulky lymphadenopathy
- Splenomegaly
- Hyperviscosity syndrome
- Bleeding (epistaxis)

Differential Diagnosis
- CLL
- Other B-cell lymphoproliferative disorders

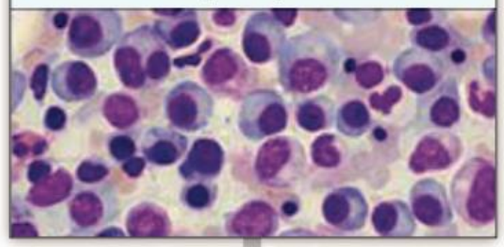
- Most patients with MM initially present with varying degrees of AKI

- Renal failure often anticipates the diagnosis of myeloma in half of patients and develops in most of the remaining patients within 1 month of the diagnosis of MM

- Of the 50% of patients with MM who experience renal impairment, 10% will require dialysis

Glomerular manifestations

Multiple myeloma



Overproduction

Kappa or lambda light chains | or | Heavy immunoglobulin chains

Urine albumin >2 g/day

Urine albumin ≤2 g/day

Deposition of light chains or monoclonal immunoglobulins, leading to glomerulopathy and proteinuria (urine albumin typically >2 g/day)

Glomerulopathy

AL amyloidosis

AH amyloidosis

Monoclonal immunoglobulin deposition disease (light-chain, heavy-chain, or both)

Proliferative GN with monoclonal IgG deposits

Monoclonal cryoglobulinemia

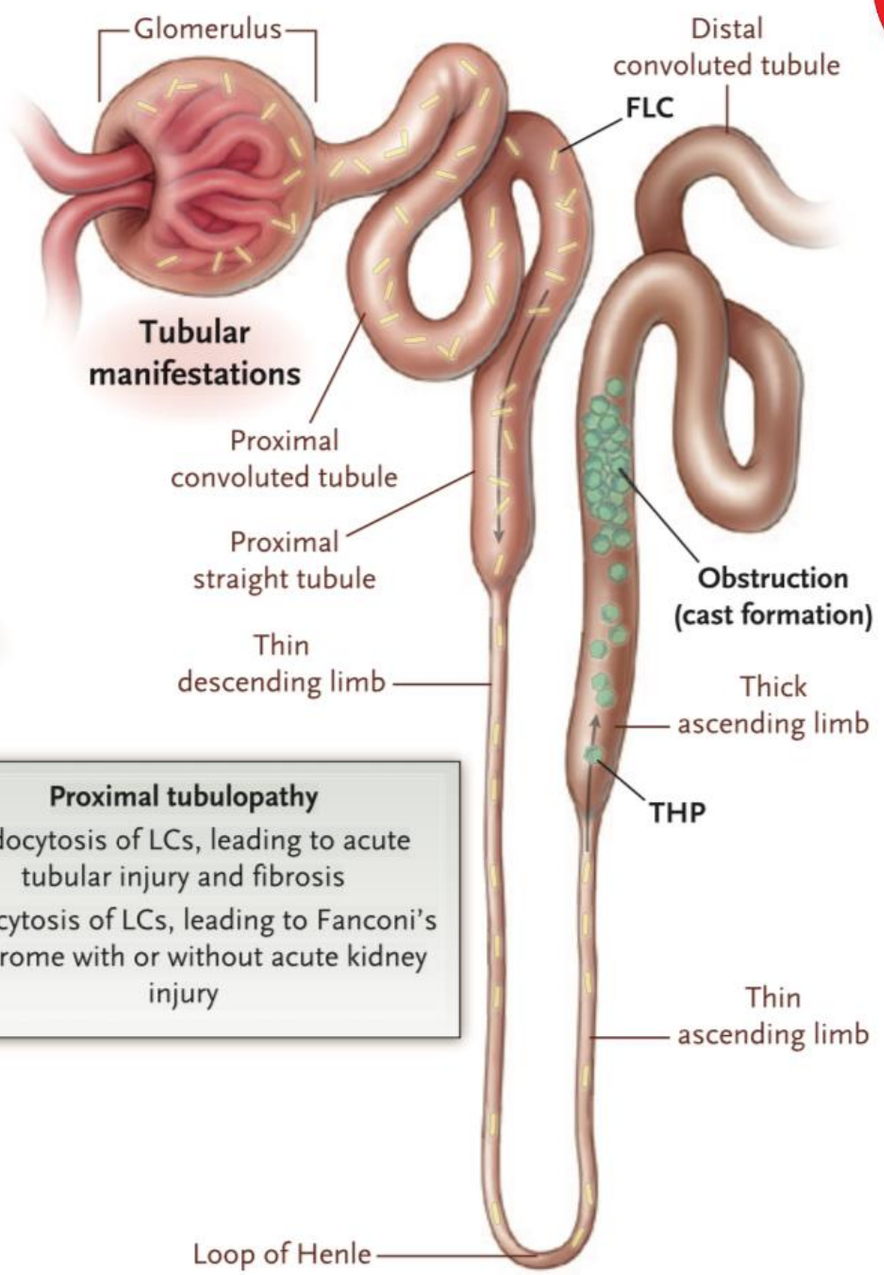
Membranoproliferative GN

C3 glomerulopathy

Fibrillary GN

Immunotactoid glomerulopathy

Tubular manifestations



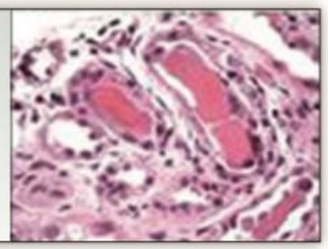
Proximal tubulopathy

Endocytosis of LCs, leading to acute tubular injury and fibrosis

Endocytosis of LCs, leading to Fanconi's syndrome with or without acute kidney injury

Cast nephropathy

LCs bind with THP, forming insoluble casts that obstruct tubular lumen and elicit local inflammation, leading to acute kidney injury with or without chronic kidney disease



Current therapy for cast nephropathy includes :

- Adequate hydration
- Correction of hypercalcemia
- Chemotherapy to reduce the free light-chain level rapidly

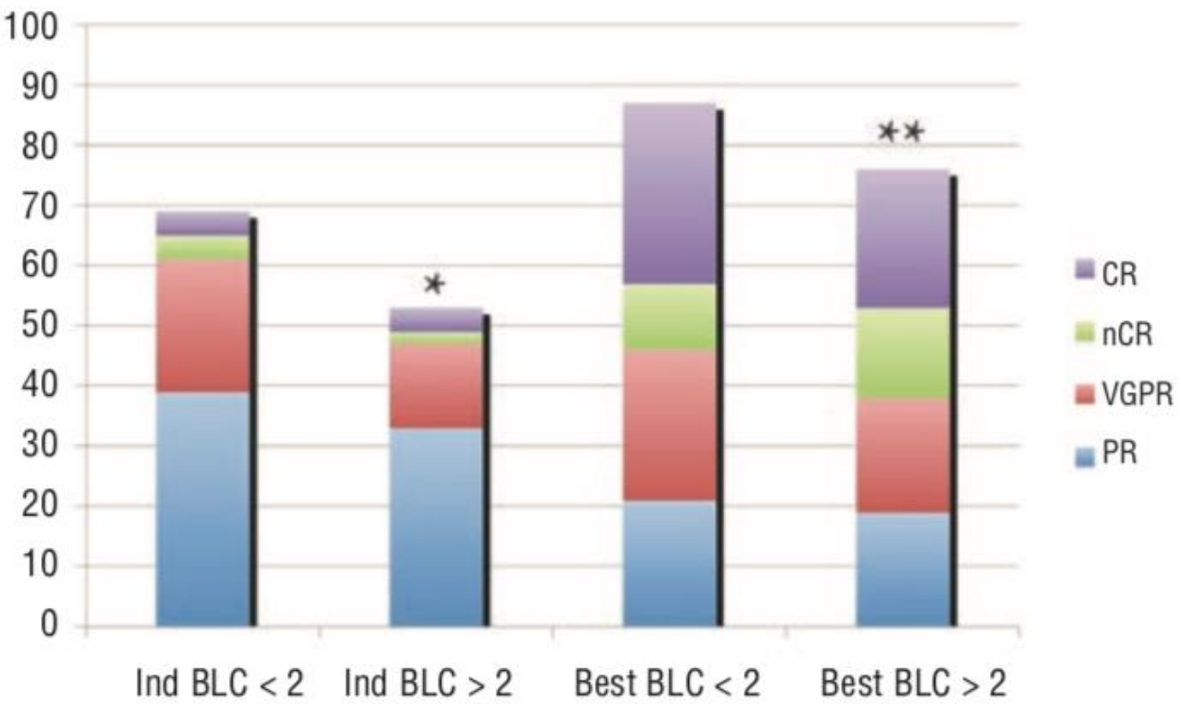
- Agents such as thalidomide, lenalidomide, pomalidomide, bortezomib, and carfilzomib rapidly lower FLC concentrations

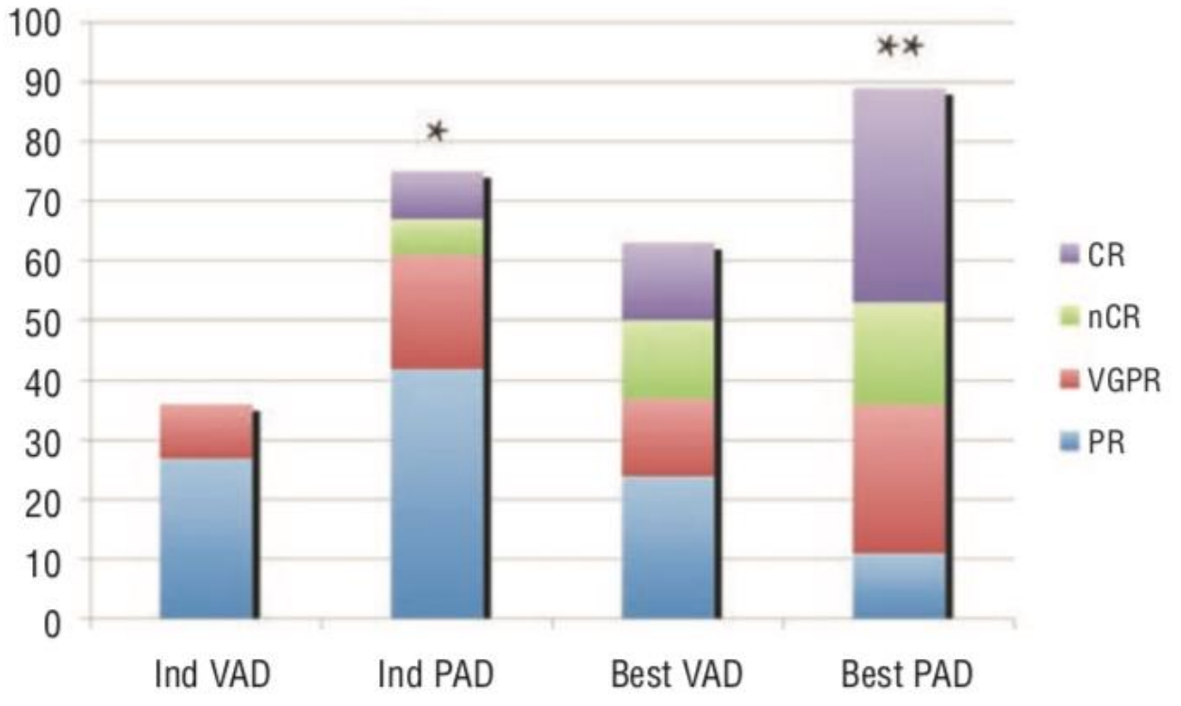
- Effective chemotherapeutic regimens for patients with myeloma who present with AKI generally include the proteasome inhibitor bortezomib

- Does not require dosage adjustments for AKI

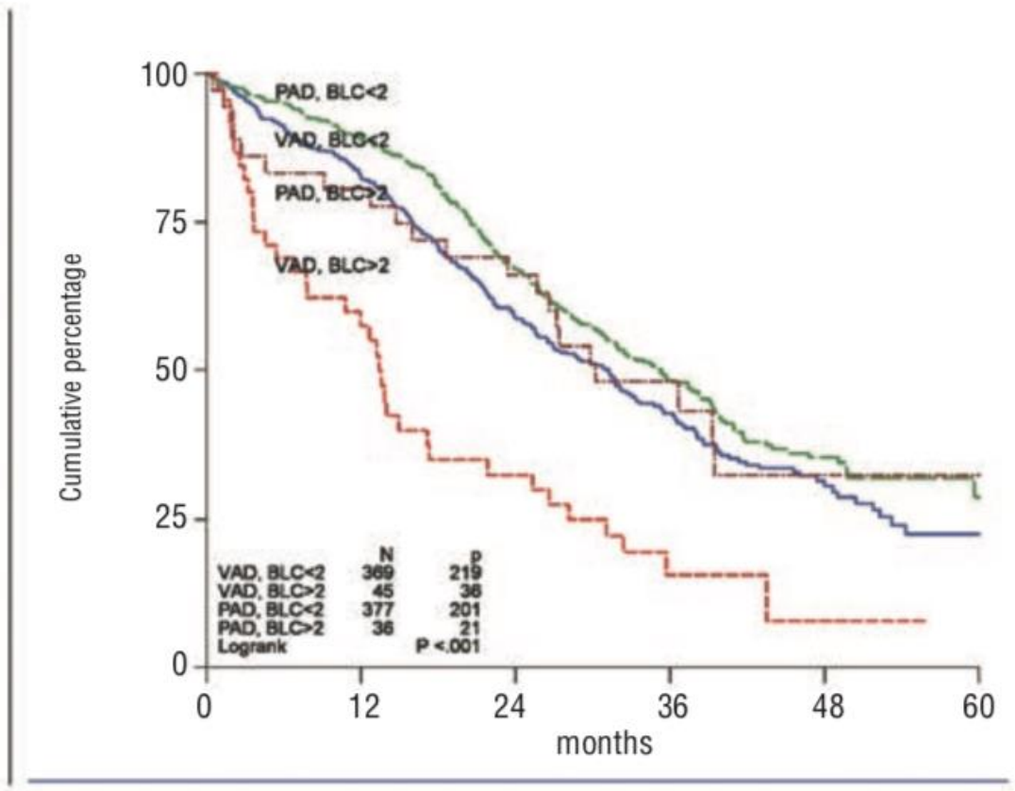
Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/GMMG-HD4 trial

Christof Scheid,[1] Pieter Sonneveld,[2] Ingo G.H. Schmidt-Wolf,[3] Bronno van der Holt,[2] Laila el Jarari,[2] Uta Bertsch,[4] Hans Salwender,[3] Sonja Zweegman,[2] Igor Wolfgang Blau,[3] Edo Vellenga,[2] Katja Weisel,[3] Michael Pfreundschuh[3], Kon-Siong Jie,[2] Kai Neben,[4] Helgi van de Velde,[5] Ulrich Duehrsen,[3] M. Ron Schaafsma,[2] Walter Lindemann,[3] Marie José Kersten,[2] Norma Peter,[3] Mathias Hänel,[3] Sandra Croockewit,[2] Hans Martin,[3] Shulamiet Wittebol,[2] Gerard MJ Bos,[2] Marinus van Marwijk-Kooy,[2] Pierre Wijermans,[2] Hartmut Goldschmidt,[4] and Henk M. Lokhorst[2]

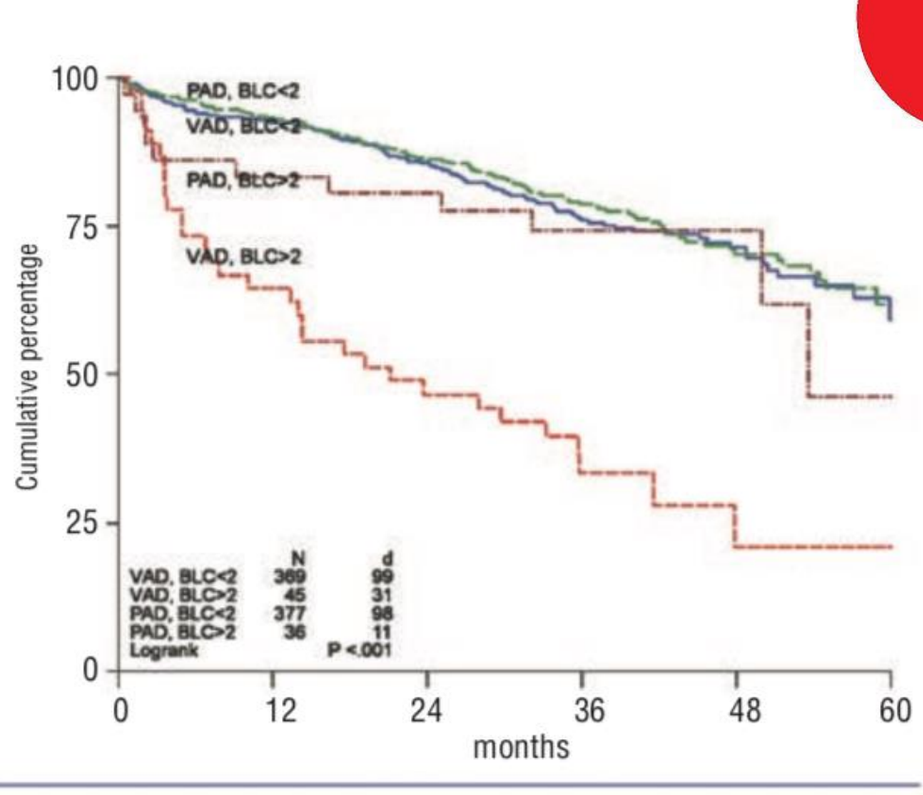




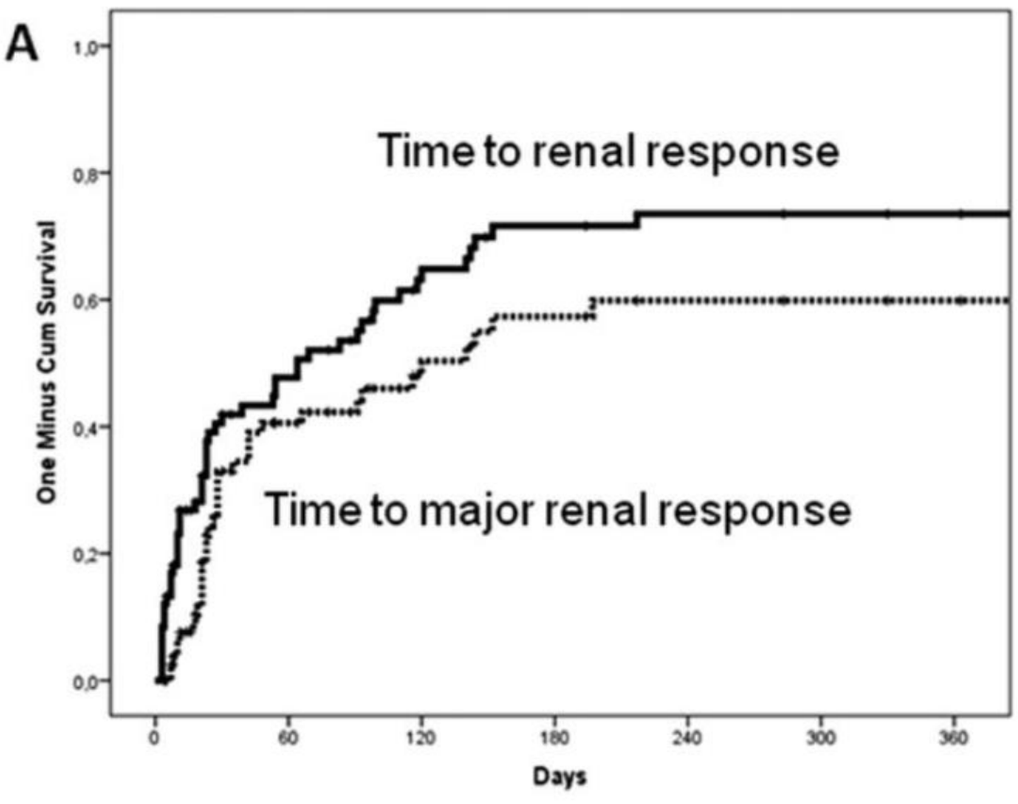
A


100
75
50
25
0
Cumulative percentage
PAD, BLC<2
VAD, BLC<2
PAD, BLC>2
VAD, BLC>2
N p
VAD, BLC<2 369 219
VAD, BLC>2 45 38
PAD, BLC<2 377 201
PAD, BLC>2 36 21
Logrank P <.001
0 12 24 36 48 60
months

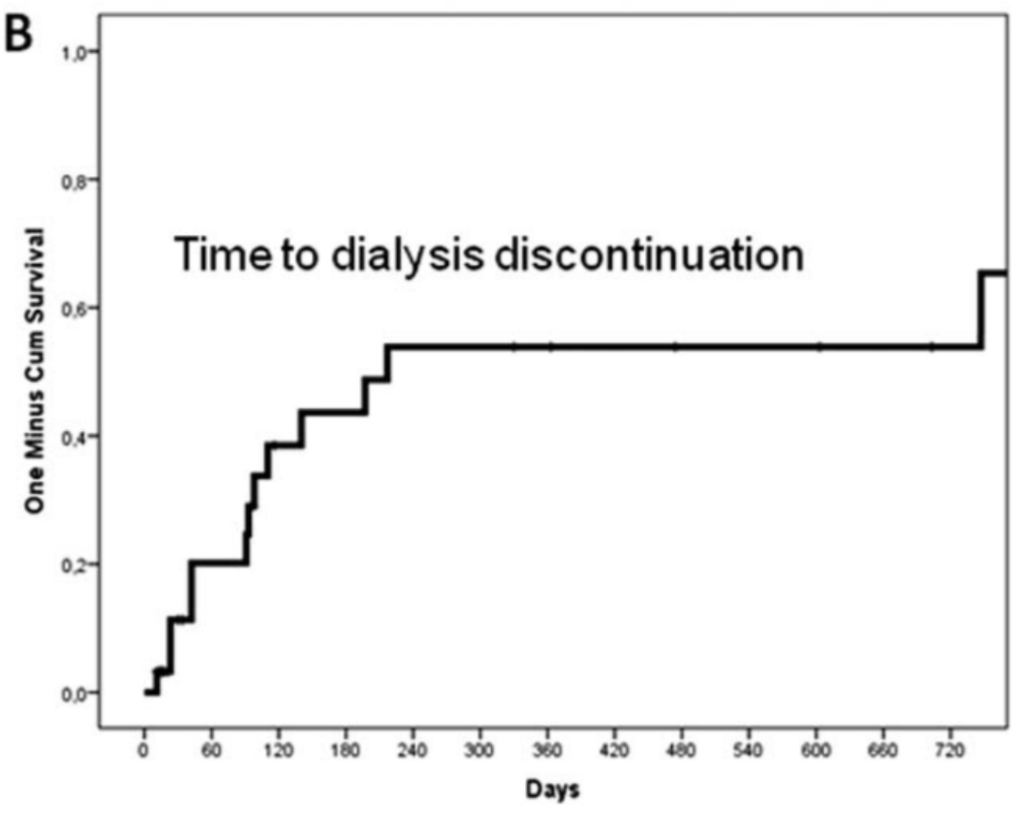
B


100
75
50
25
0
Cumulative percentage
PAD, BLC<2
VAD, BLC<2
PAD, BLC>2
VAD, BLC>2
N d
VAD, BLC<2 369 99
VAD, BLC>2 45 31
PAD, BLC<2 377 98
PAD, BLC>2 36 11
Logrank P <.001
0 12 24 36 48 60
months

A


1,0
0,8
0,6
0,4
0,2
0,0
One Minus Cum Survival
Time to renal response
Time to major renal response
0 60 120 180 240 300 360
Days

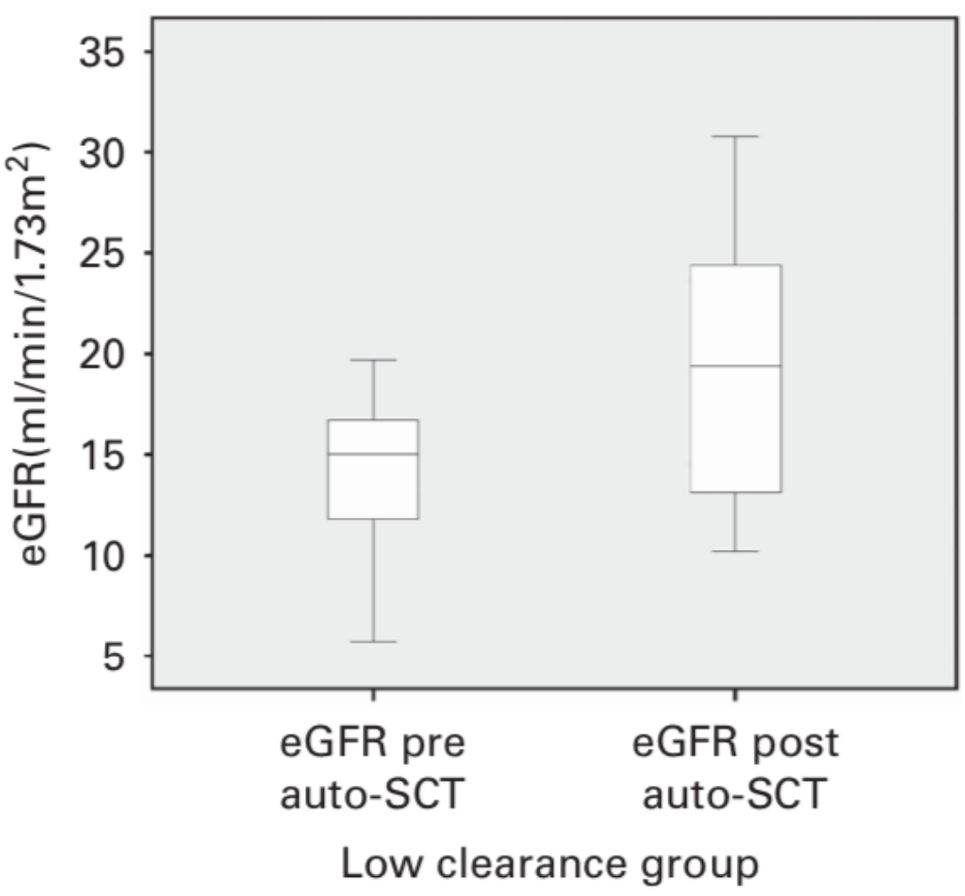
B

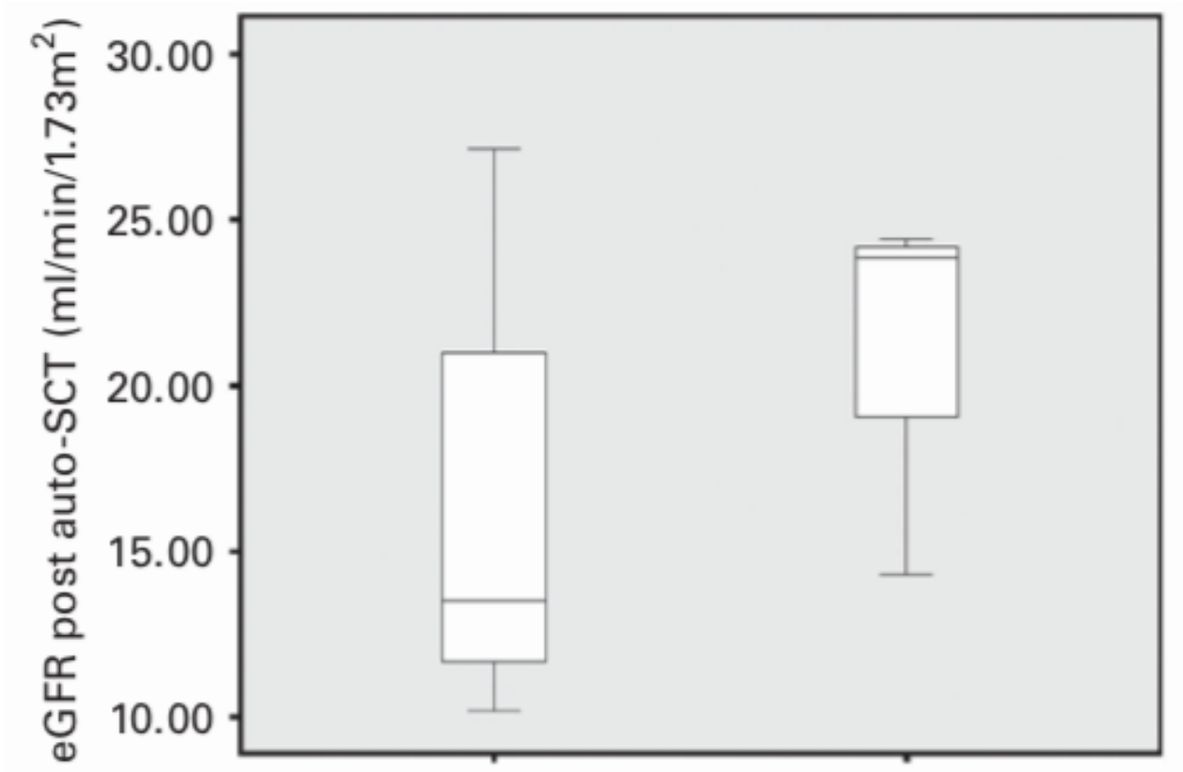

1,0
0,8
0,6
0,4
0,2
0,0
One Minus Cum Survival
Time to dialysis discontinuation
0 60 120 180 240 300 360 420 480 540 600 660 720
Days

ORIGINAL ARTICLE

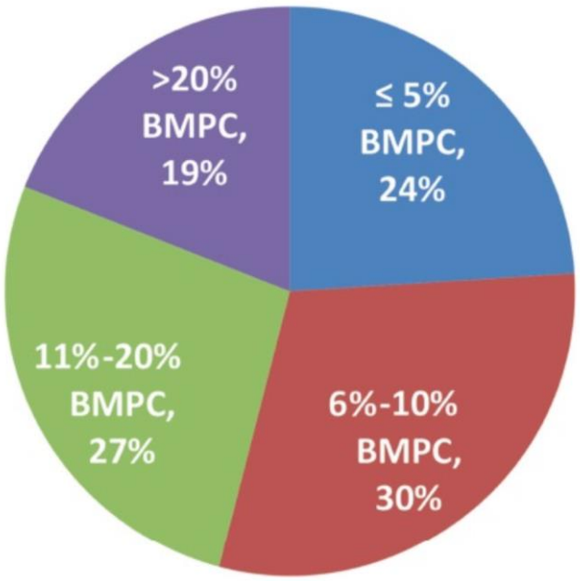
Long-term outcome of patients with mutiple myeloma-related advanced renal failure following auto-SCT

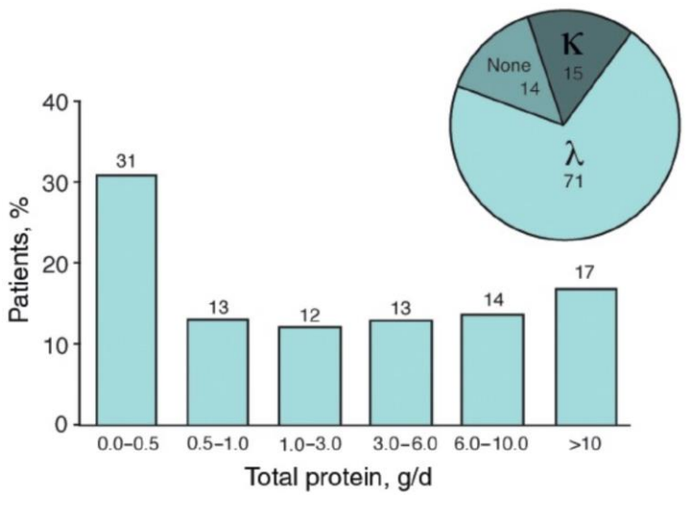
SV Glavey[1], MA Gertz[2], A Dispenzieri[2], S Kumar[2], F Buadi[2], M Lacy[2], SR Hayman[2], D Dingli[2], A McCurdy[2], WJ Hogan[2], DA Gastineau[2] and N Leung[2,3]





AL Amyloidosis





All four criteria must be met:

- Presence of an amyloid-related systemic syndrome (such as renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement)
- Positive amyloid staining by Congo red in any tissue (e.g., fat aspirate, bone marrow, or organ biopsy)
- Evidence that amyloid is light chain related established by direct examination of the amyloid (possibly using mass spectrometry (MS)-based proteomic analysis, or immunoelectron microscopy; note that immunohistochemistry results to type amyloid may be unreliable), and
- Evidence of a monoclonal plasma cell proliferative disorder (serum or urine M protein, abnormal free light chain ratio, or clonal plasma cells in the bone marrow).

Note: Approximately 2–3% of patients with AL amyloidosis will not meet the requirement for evidence of a monoclonal plasma cell disorder listed above; the diagnosis of AL amyloidosis must be made with caution in these patients.

Critical clinical syndromes commonly associated with amyloidosis should trigger screening :

1. Gastrointestinal tract symptoms of pseudo-obstruction or steatorrhea

2. Tongue enlargement

3. Carpal tunnel syndrome

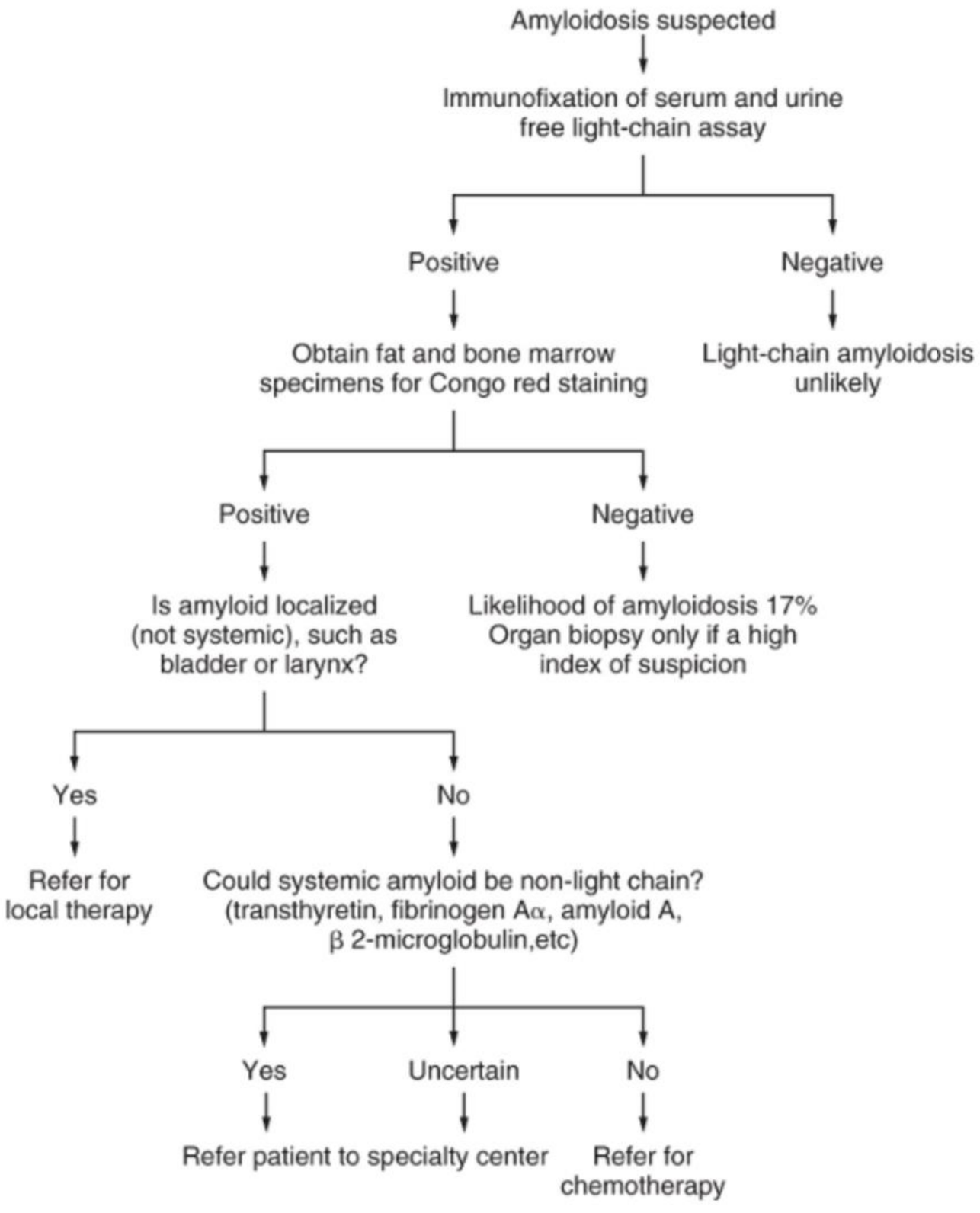
4. Hepatomegaly

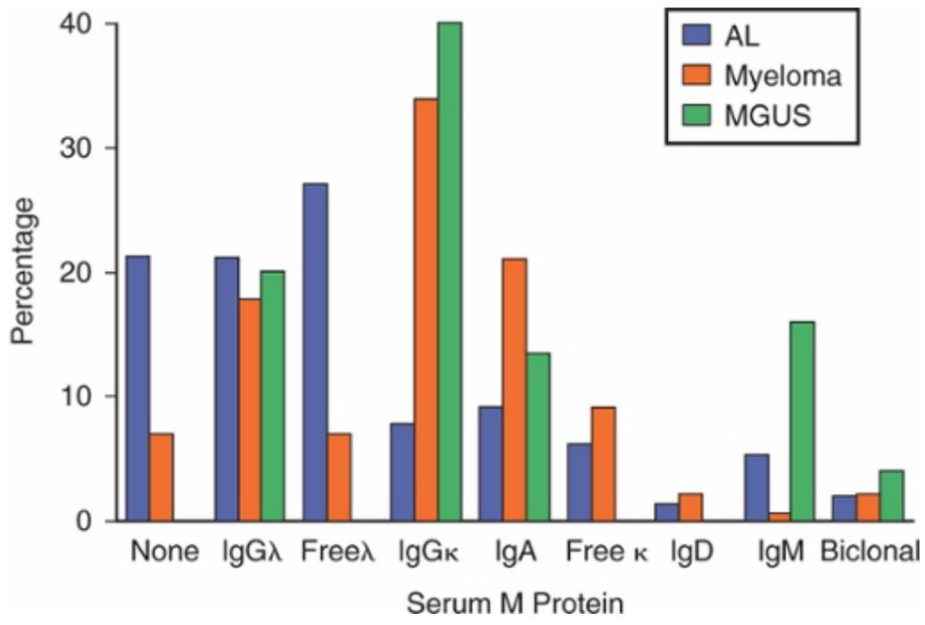
5. Peripheral neuropathy

6. Nephrotic-range proteinuria

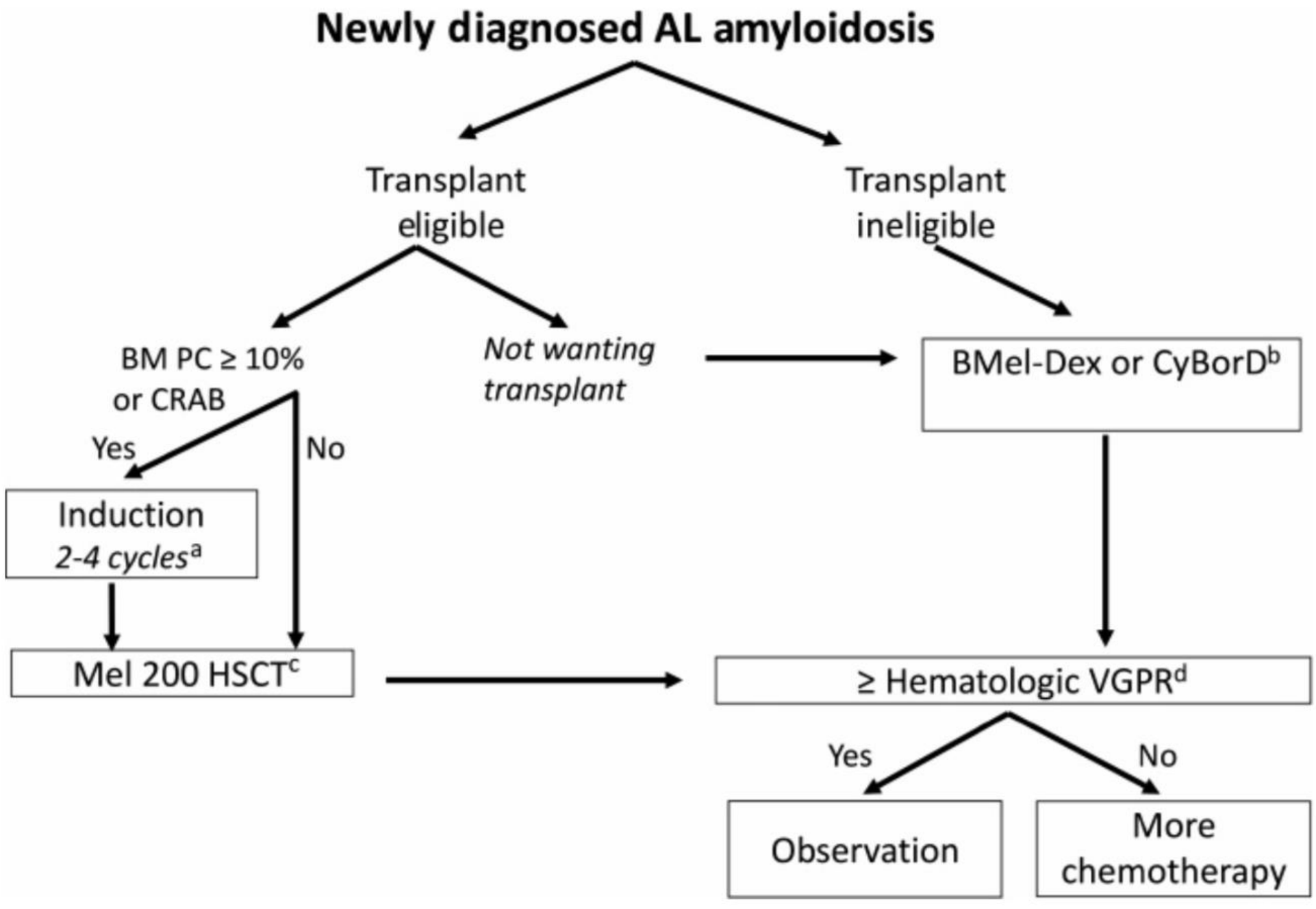
7. Infiltrative cardiomyopathy with restrictive hemodynamics

8. Atypical multiple myeloma



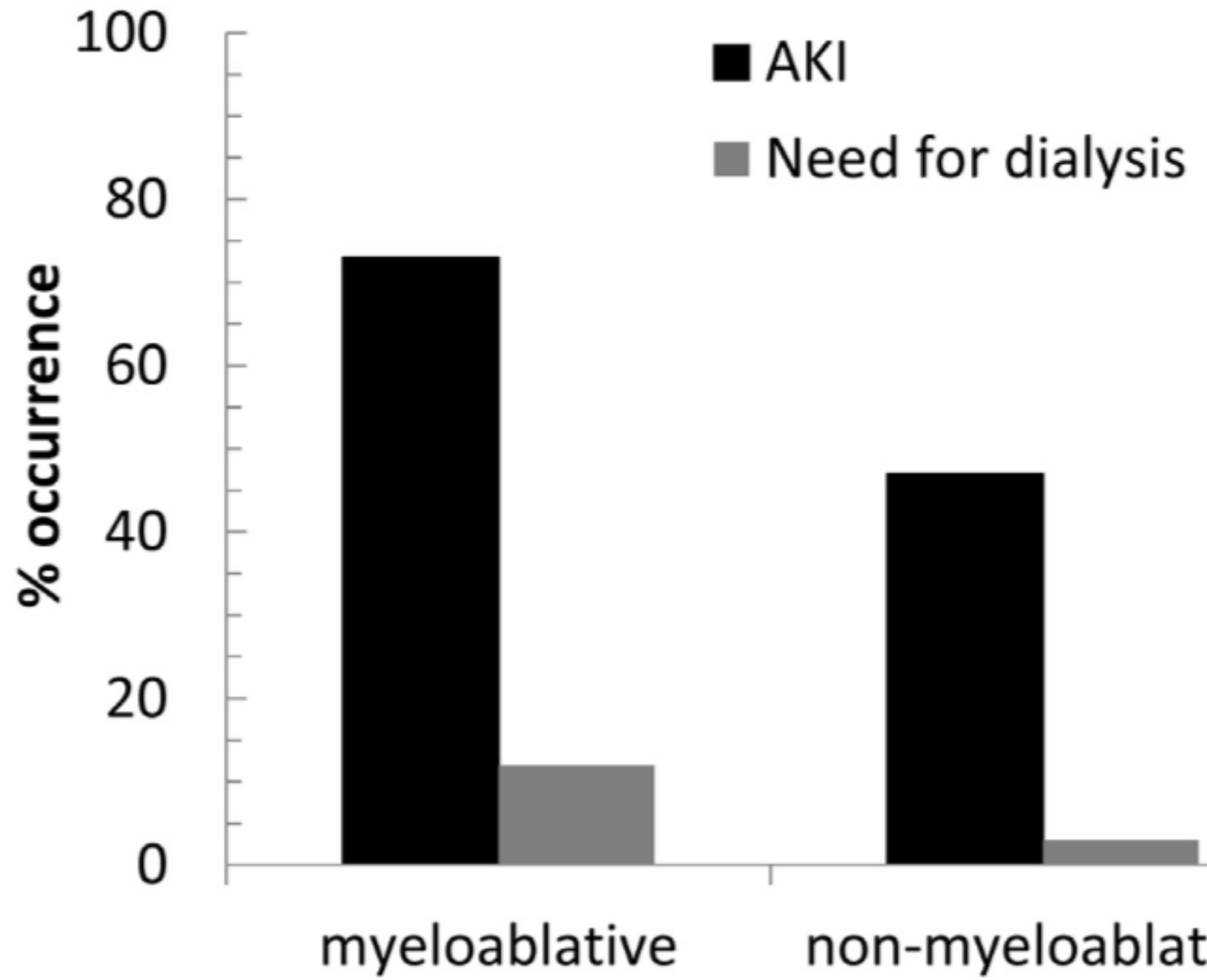


Biopsy Finding		
Fat	Marrow	Patients (%)
+	+	55
+	–	22
–	+	10
–	–	13

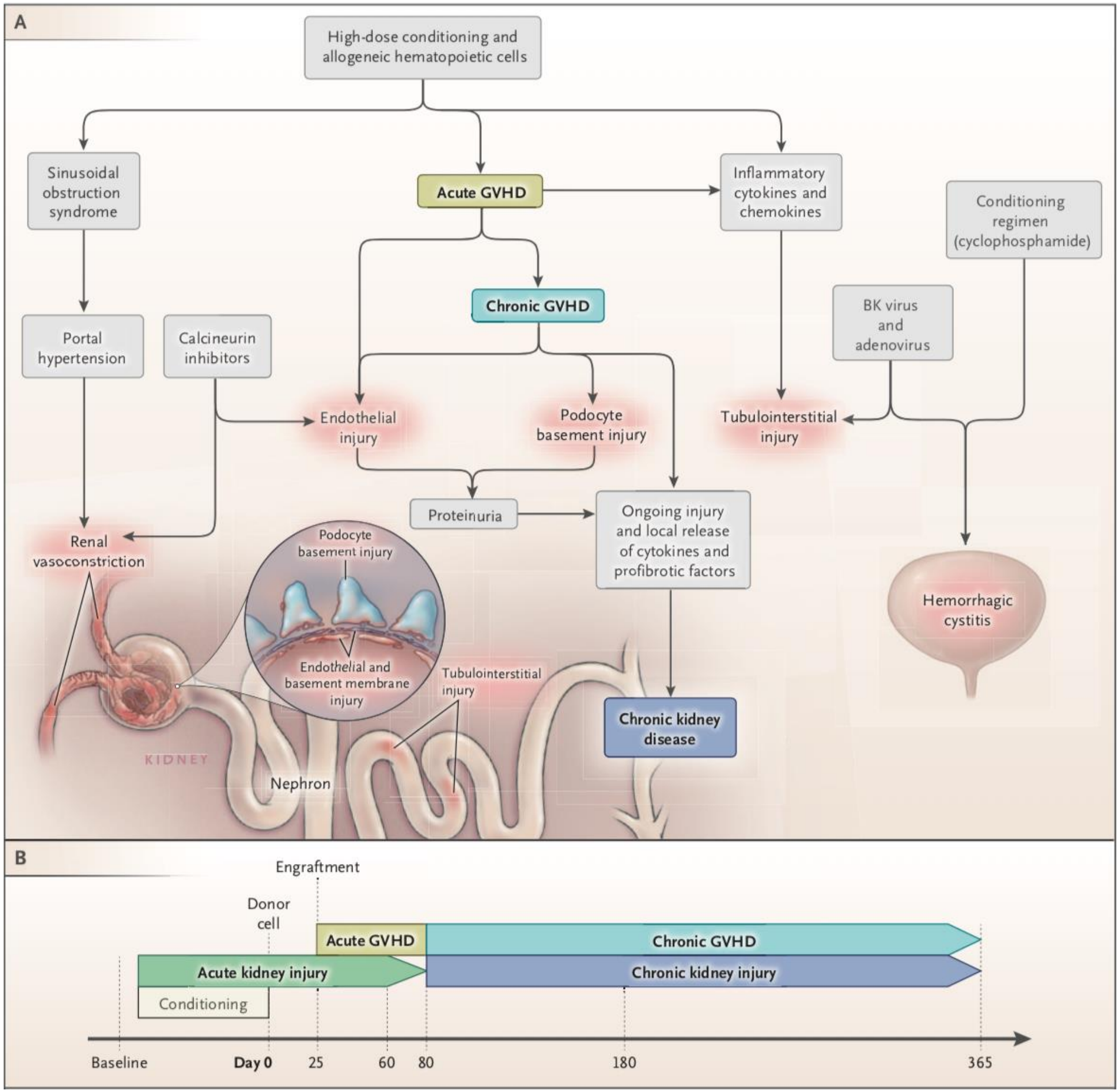

Newly diagnosed AL amyloidosis
Transplant eligible
Transplant ineligible
BM PC ≥ 10% or CRAB
Yes
No
Not wanting transplant
BMel-Dex or CyBorD[b]
Induction 2-4 cycles[a]
Mel 200 HSCT[c]
≥ Hematologic VGPR[d]
Yes
No
Observation
More chemotherapy

Renal Complications of Hematopoietic-Cell Transplantation

RIFLE	
Risk	Increase in serum Cr ≥1.5 × baseline or decrease in GFR ≥25%
Injury	Increase in serum Cr ≥2.0 × baseline or decrease in GFR ≥50%
Failure	Increase in serum Cr ≥3.0 × baseline or decrease in GFR ≥75% or an absolute serum Cr ≥4.0mg/dL (354 μmol/L) with an acute rise of at least 0.5 mg/dL (44 μmol/L)
Loss	Persistent AKI >4 weeks
ESKD	ESKD >3 months
AKIN	
Stage 1	Increase in serum Cr ≥0.3 mg/dL (26.5 μmol/L) or increase to 150–199% (1.5–1.9-fold) from baseline
Stage 2	Increase in serum Cr to 200–299% (>2.0–2.9 fold) from baseline
Stage 3	Increase in serum Cr to ≥300% (≥3-fold) from baseline or serum Cr ≥4.0 mg/dL (354 μmol/L) with an acute rise of at least 0.5 mg/dL (44 μmol/L).
Grading	
Grade 0	Decrease in GFR <25% of baseline
Grade 1	Increase in serum Cr <2-fold from baseline with a decrease in GFR >25% but <50% of baseline
Grade 2	Increase in serum Cr ≥2-fold from baseline but not requiring dialysis
Grade 3	Increase in serum Cr ≥2-fold from baseline and need for dialysis


100
80
60
40
20
0
% occurrence
AKI
Need for dialysis
myeloablative
non-myeloablative

Acute kidney injury	Chronic kidney disease
Prerenal (hemodynamic): - N/V and diarrhea associated with acute gastrointestinal GVHD - Drug-induced nausea and vomiting Acute tubular injury: - Sepsis and septic shock - Sinusoidal obstruction syndrome - Marrow infusion syndrome - Tumor lysis syndrome Thrombotic microangiopathy: - Acute graft versus host disease - Calcineurin inhibitors - Total body irradiation Drug-induced AKI: - Amphotericin, aminoglycosides, vancomycin, non-steroidal anti-inflammatory drugs, calcineurin inhibitors, acyclovir, quinolones, sulfonamides, other nephrotoxins Drug-induced ATIN: - B-lactam antibiotics, quinolones, sulfonamides, vancomycin, anti-viral agents, non-steroidal anti-inflammatory drugs, proton pump inhibitors, other drugs Infection-related ATIN: - BK virus nephropathy - Adenovirus nephropathy	Thrombotic microangiopathy: - Calcineurin inhibitors - Chronic GVHD - Total body irradiation Arteriolonephrosclerosis: - Hypertension-related kidney injury - Radiation-induced kidney injury Membranous nephropathy, minimal change disease: - Chronic GVHD Infection-related CTIN: - BK virus nephropathy - CMV nephropathy - Adenovirus nephropathy


A
High-dose conditioning and allogeneic hematopoietic cells
Sinusoidal obstruction syndrome
Acute GVHD
Inflammatory cytokines and chemokines
Conditioning regimen (cyclophosphamide)
Chronic GVHD
BK virus and adenovirus
Portal hypertension
Calcineurin inhibitors
Endothelial injury
Podocyte basement injury
Tubulointerstitial injury
Proteinuria
Ongoing injury and local release of cytokines and profibrotic factors
Renal vasoconstriction
Podocyte basement injury
Endothelial and basement membrane injury
Tubulointerstitial injury
Hemorrhagic cystitis
Chronic kidney disease
KIDNEY
Nephron
B
Engraftment
Donor cell
Acute GVHD
Chronic GVHD
Acute kidney injury
Chronic kidney injury
Conditioning
Baseline
Day 0
25
60
80
180
365

Risk factors for chronic kidney disease include :

- Previous acute kidney injury
- Acute and chronic GVHD
- Age of 45 years or older at the time of transplantation
- A baseline GFR below 90 ml per minute per 1.73 m^2
- Hypertension
- Survival more than 1 year after transplantation
- Exposure to high-dose total-body irradiation

Take Home Messages

- Kidney injury is a frequent and increasing complication of cancer
- There is a bidirectional relationship between cancer and kidney disease
- AKI in patients with cancer is associated with increased morbidity and mortality
- In cancer patients, a multi-disciplinary approach and early intervention may reduce the incidence of AKI and its life-threatening consequences
- Onco-Nephrology is a growing area of nephrology that requires clinicians to have a better understanding of the renal complications of cancer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