Renal Involvement in Hematological Disorders

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Disclousures

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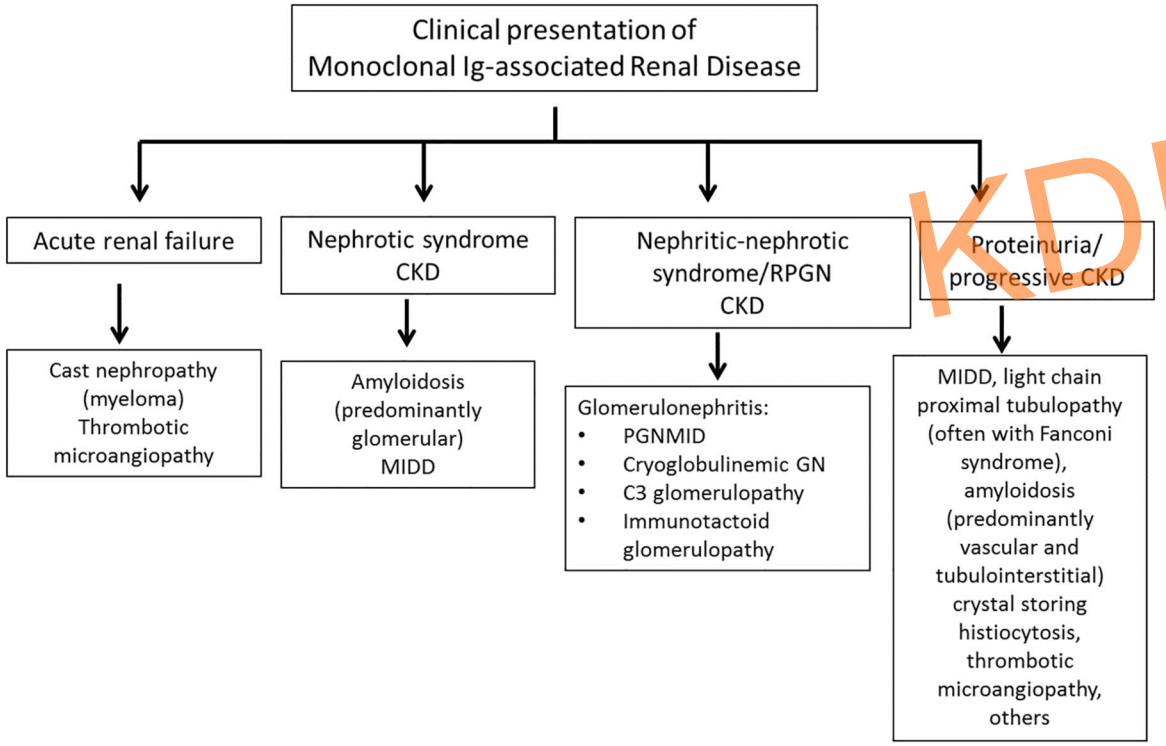
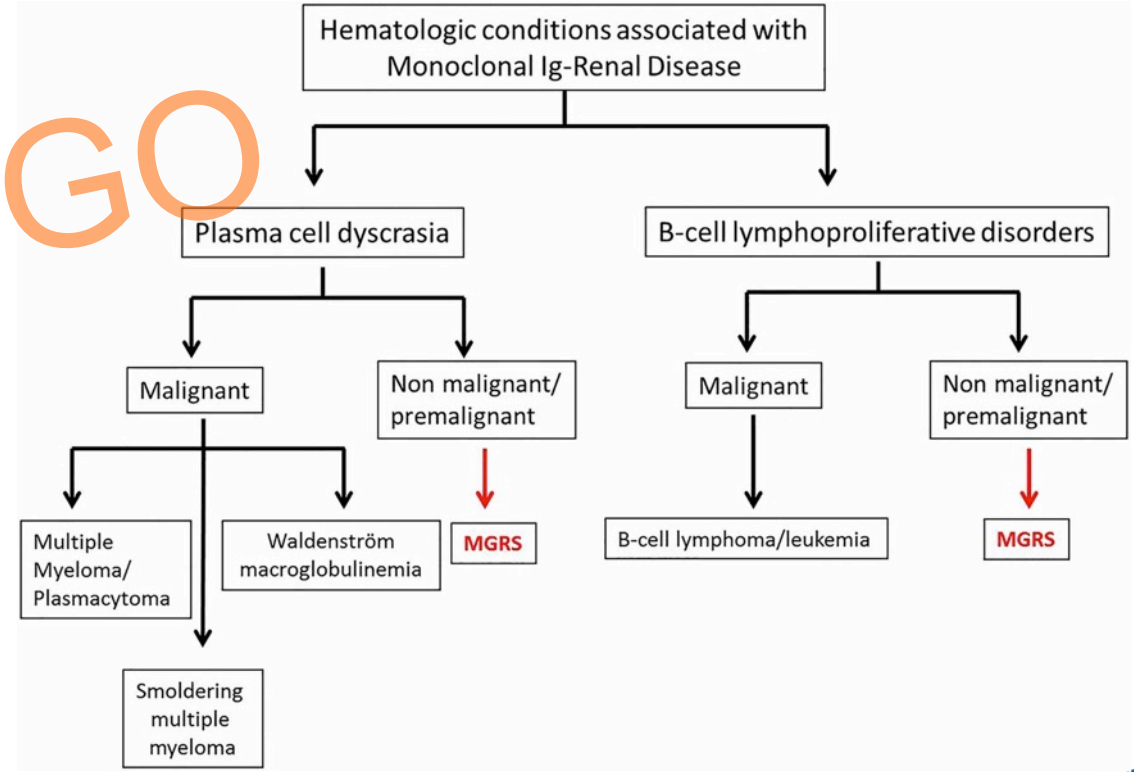
AGENDA

1. Renal involvement in hematological disorders. Introduction
2. Monoclonal gammopathy of renal significance (MGRS)
3. Renal involvment in Multiple Myeloma (MM) and amyloidosis
4. Kidney Complications of HSCT
5. Chronic lymphocytic leukemia (CLL)
6. Kidney Involvement in Waldenström macroglobulinemia

Renal disease in monoclonal gammopathies

The clinical spectrum of diseases associated with monoclonal gammopathies is wide and they are most commonly the consequence of renal deposition of monoclonal immunoglobulin or its components.





Sethi S et al. Jasn 2018; 29 (7):1810-1823

MGRS

Updated definition of MGRS

The term MGRS applies specifically to any B cell or plasma cell clonal lymphoproliferation with both of the following characteristics:

- **One or more kidney lesions that are related to the produced monoclonal immunoglobulin**
- **the underlying B cell or plasma cell clone does not cause tumour complications or meet any current haematological criteria for specific therapy**

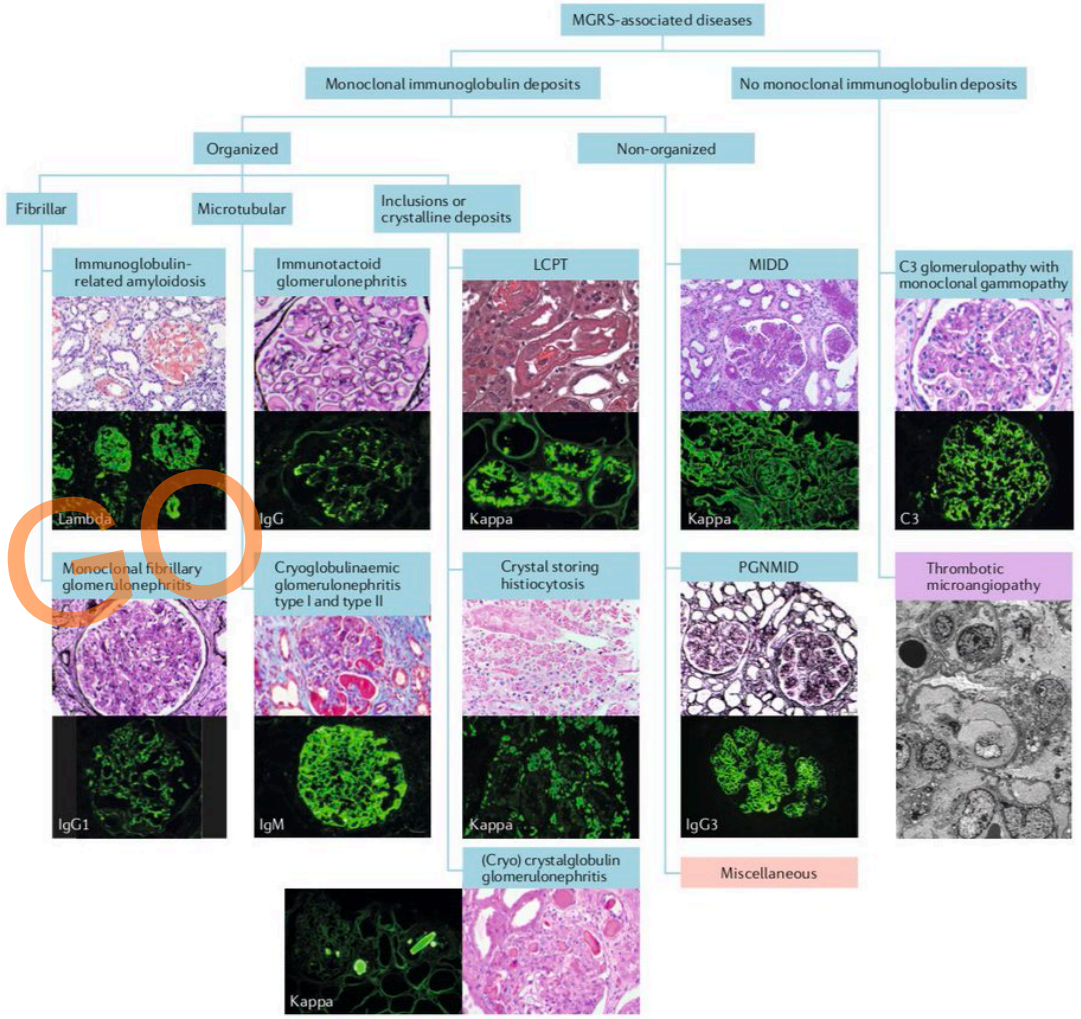


Fig. 2 | **Categorization of MGRS-associated renal lesions.** Monoclonal gammopathy of renal significance (MGRS)-associated renal lesions (blue boxes) are initially separated by the presence or absence of monoclonal immunoglobulin deposits in kidney biopsy samples. They are further subcategorized by the ultrastructural characteristics of the deposits into organized and non-organized. Organized deposits are further subdivided into fibrillar, microtubular and inclusions or crystalline categories. Images of typical histological sections stained with haematoxylin and eosin (H&E), periodic acid–Schiff or Masson trichrome stain and Congo red (top) are paired with immunofluorescence studies of frozen tissue sections (bottom) to reveal the specific immunoglobulin species. Pink box: the miscellaneous category represents polyclonal glomerulopathies that sometimes present with monoclonal immunoglobulin deposits, such as monotypic membranous nephropathy and monotypic anti-glomerular basement membrane disease. Purple box: thrombotic microangiopathy currently has a provisional status as an MGRS-associated lesion pending further evidence. Because this lesion has no immunoglobulin deposits and is best identified by electron microscopy, the immunofluorescence and H&E stained sections were replaced by an electron micrograph. LCPT, light-chain proximal tubulopathy; MIDD, monoclonal immunoglobulin

The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. **Leung N et al.** Nat Rev Nephrol. 2018 Dec 3. doi: 10.1038/s41581-018-0077-4.

MGUS and MGRS

- Monoclonal gammopathy of renal significance (MGRS) is a new nosological group of entities defined in 2012[1]
- MGRS describes a group of hematological disorders associated with kidney disease that fail to meet the standard definitions for MM or lymphoma
- MGRS do not meet criteria for MM, WM, CLL or malignant lymphoma but can be associated with high morbidity due to renal lesions induced by a monoclonal immunoglobulin (MIg)

How to differentiate MGRS from MGUS?

Diagnostic	MGUS	MGRS
Clonal BM plasma cell	< 10%	< 10%
Serum M-spike	< 3 g/dl M protein	< 3 g/dl M protein and
CRAB	Absent	Absent
Renal Disease (not cast nephrophaty)	Not attributable to the monoclonal gammopathy	Attributable to the monoclonal gammopathy

MGUS is not equivalent to MGRS

1. Leung N et al. Blood 2012;120:4292-5

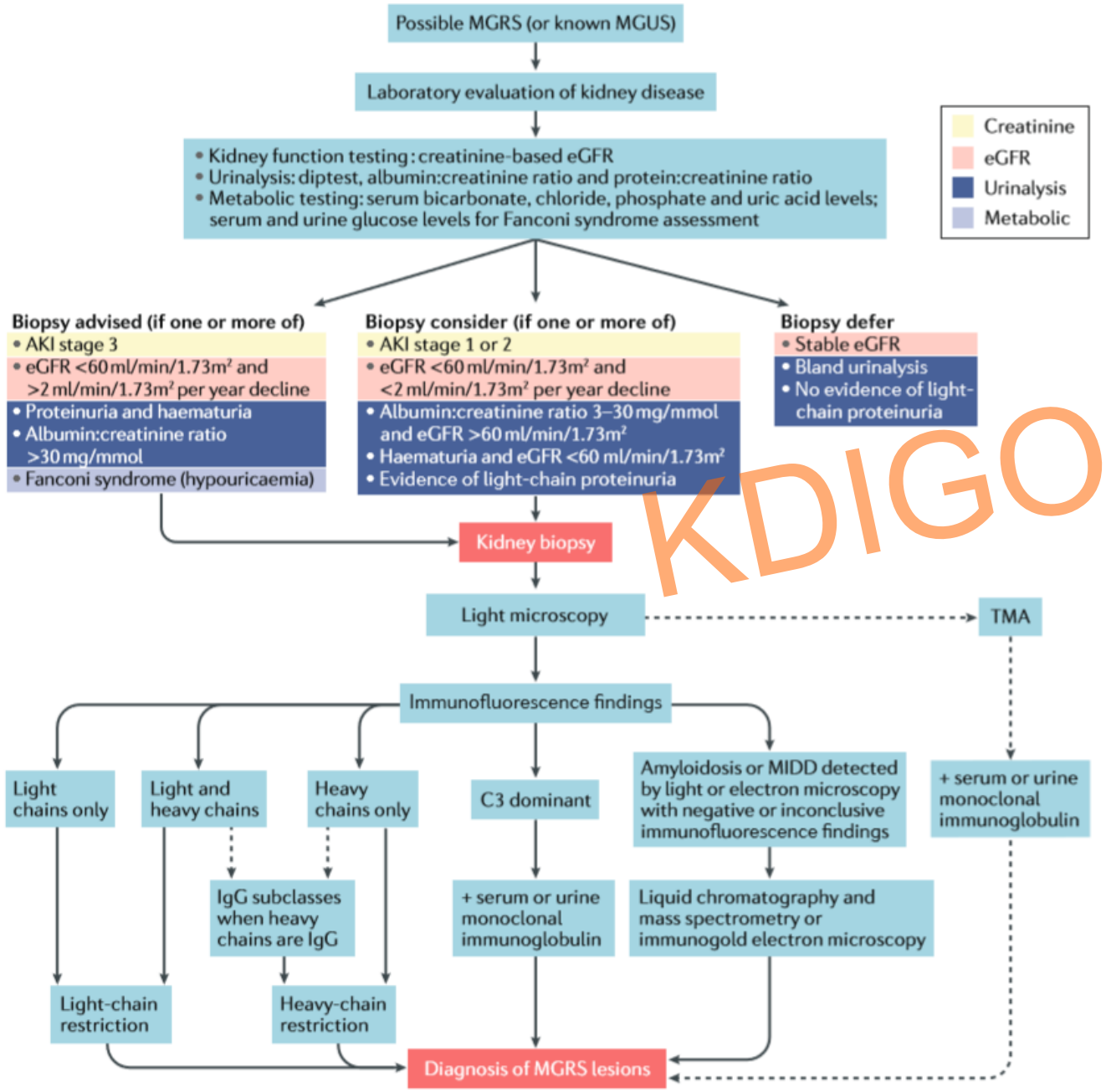
MGRS. Pathomechanism

- MGRS represents a group of kidney disorders caused by a monoclonal immunoglobulin that is secreted by a nonmalignant or premalignant B cell or plasma cell clone
- Renal damage is the result of monoclonal Ig deposit or its activity as autoantibodies, which can compromise any nephronal area
- MGRS does not include kidney diseases produced by high-grade lymphoproliferative disorders as well as those whose pathogenesis are independent of monoclonal Ig (such as drug toxicity or metabolic disorders) [1]

The spectrum of renal pathology in B-cell clonal disorders

Type of deposits	Renal condition	Clone
Whole immunoglobulin	ALH amyloidosis	PC, BC, CLL
LHCDD	PC, BC, LPL	
	Cryoglobulinemia	LPL, PC, CLL, BC
	PGNMID	PC, BC, CLL
	Immunotactoid GN	CLL, PC
	Fibrillary GN with MG	PC, CLL
	(Cryo) crystalglobulinemia	PC
	Crystal storage histiocytosis	PC, LPL
Light chain	AL amyloidosis	PC, LPL, CLL, BC
	LCDD	PC, LPL, BC
	Light chain tubulopathy (Fanconi syndrome)	PC, LPL, CLL
	Light chain cast nephropathy	PC, LPL, CLL
Heavy chain	AH amyloidosis	PC
	HCDD	PC
Hidden Ig	C3 glomerulopathy	PC
None	TMA (POEMS)	PC
Atypical	Anti-GBM	PC
	Membranous with MG	PC

Ciocchini M. et all. Int Urol Nephro 2017; 49 (Suppl 1)



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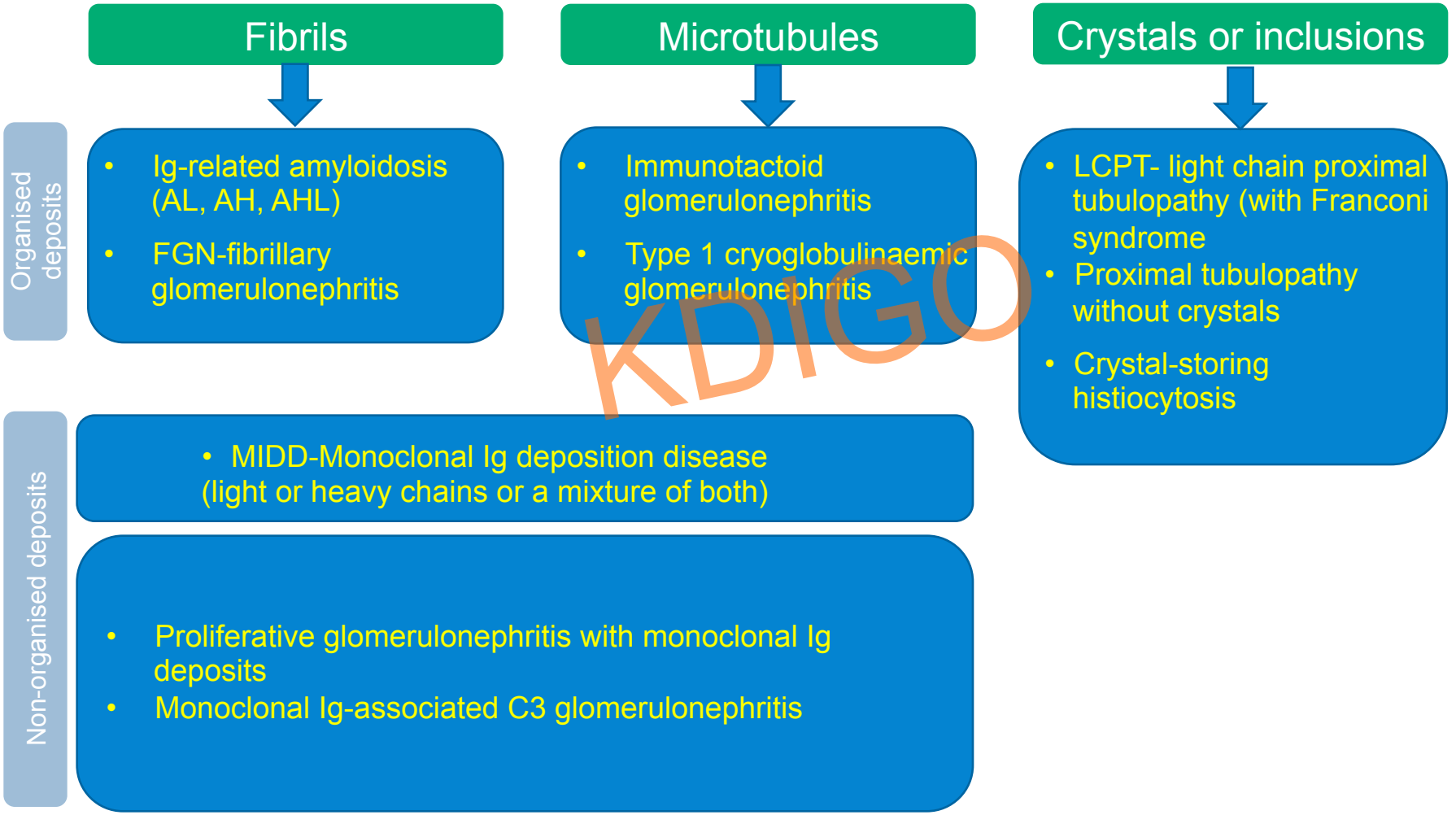
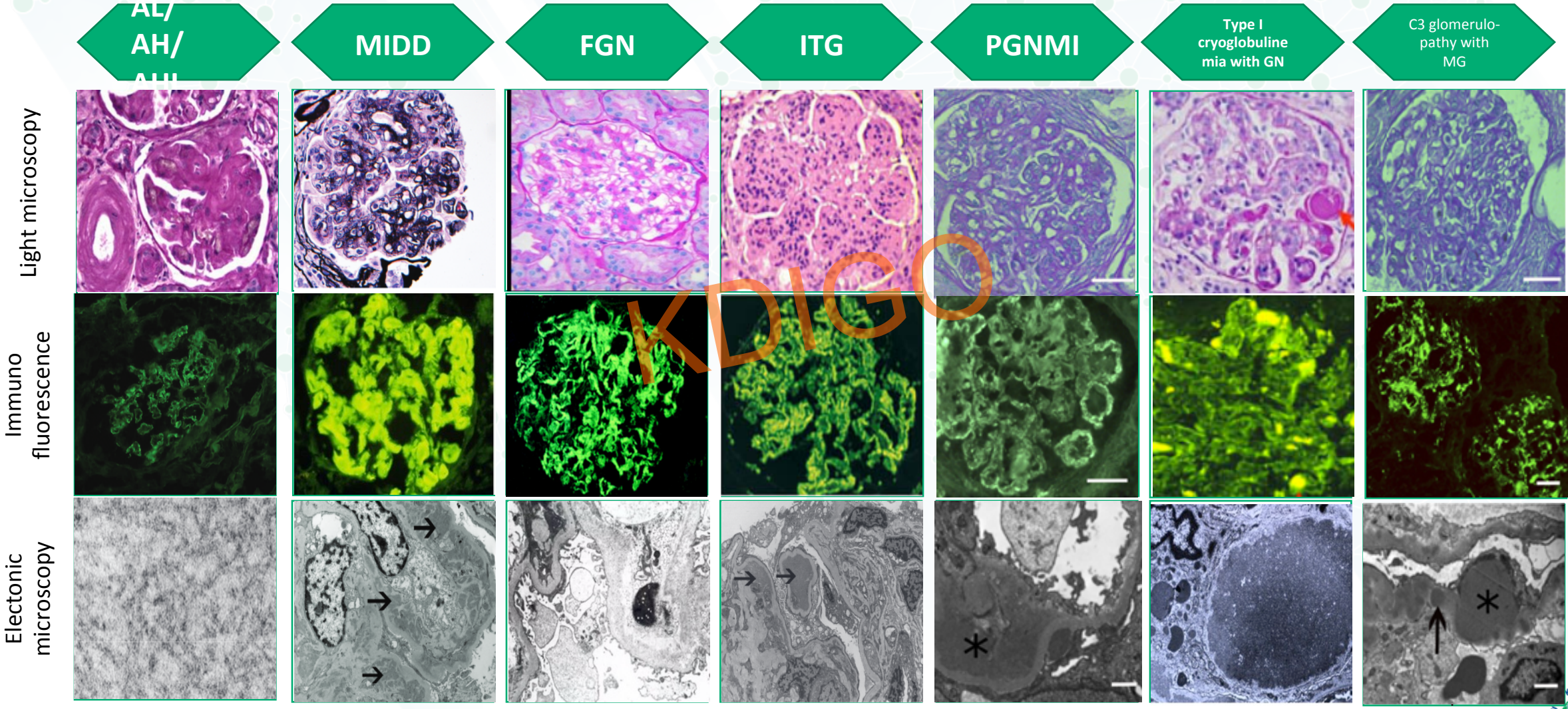
MGRS-associated renal lesions



Bridoux et al. Kidney Int 2015; 87(4):698-711

MGRS. Pathological characteristics



https://unckidneycenter.org/kidneyhealthlibrary

MGRS. Treatment options

- A multi-disciplinary collaboration between nephrologist, pathologist and hematologist is a priority in the treatment of MGRS

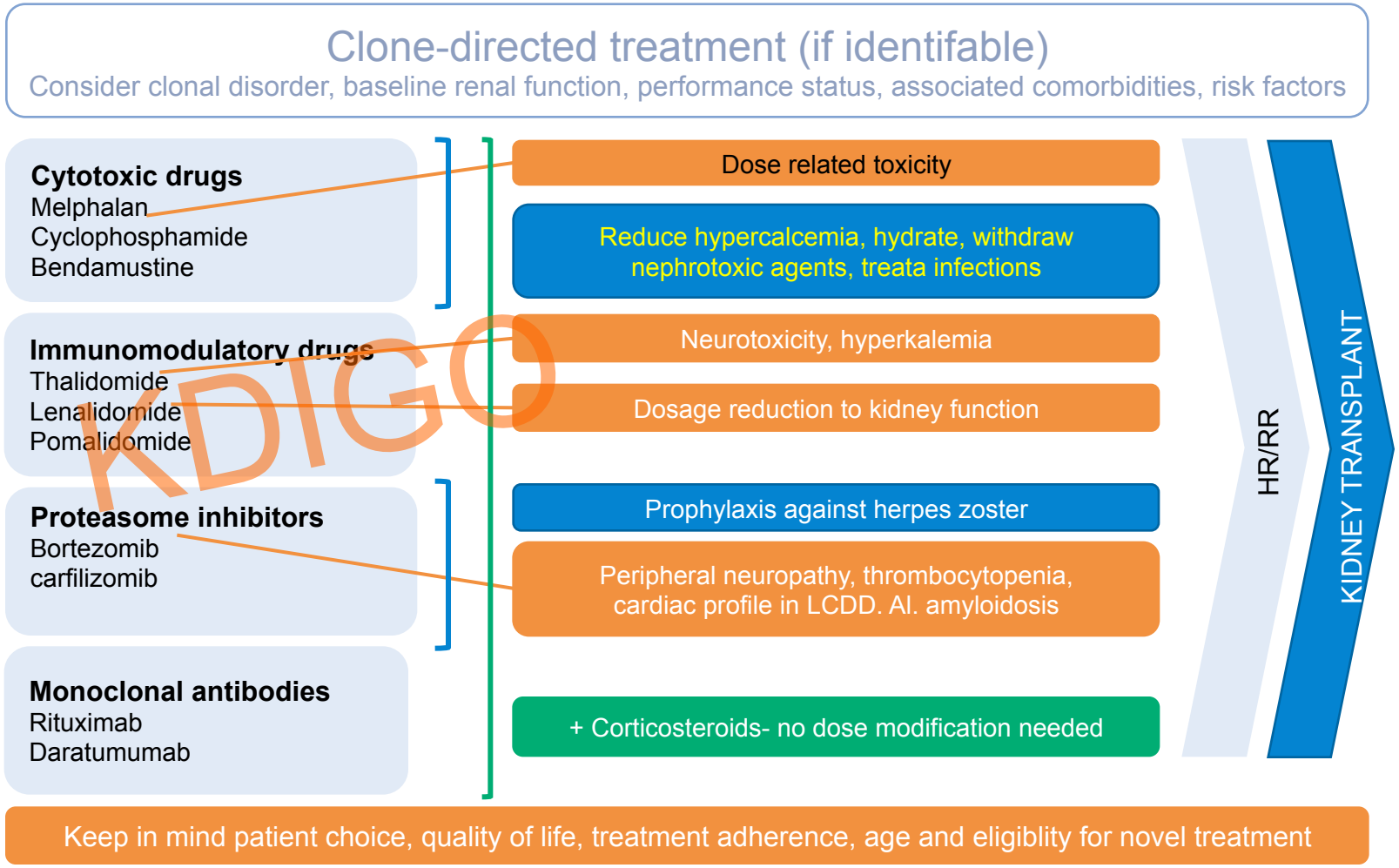
Drug	Character	Disease character	Severity of kidney insufficiency	Reference
Lenalidomide LoDex, MPT	Clinical trial	MM/with RI	149 patients CrCl <30 mL/min, 372 pts CrCl ≥30, <50	Dimopoulos *et al.* [57]
Bendamustine, P, V	Retrospective	MM with RI	18 eGFR <35 mL/min (11 pts eGFR 15 mL/min)	Ponisch *et al.* [58]
RTX, CYC, Dex	Retrospective	Indolent NHL Glomerulonephritis related to MIg	14 pts (71.5% with eGFR <60 mL/min)	Perry *et al.* [59]
POM, LoDex	Clinical trial	Relapsed/refractory MM with RI	Three cohorts—33 eGFR 30–45 mL/min pts, 34 < 30 mL/min eGFR pts, 14 HD pts	Dimopoulos *et al.* [60]
RTX	Clinical trial	Membranous nephropathy	eGFR ≥ 40, Proteinuria ≥ 5 g/24 h	Fervenza *et al.* [61]
VMP versus MP	Clinical trial	MM with RI	34 pts <30 mL/min GFR, 193 pts GFR 31–50 mL/min	Dimopoulos *et al.* [62]
VMPT–VT versus VMP	Clinical trial	MM with RI	33 pts <30 mL/min eGFR, 116 pts eGFR 31–50 mL/min	Morabito *et al.* [63]
Ixazomib Lenalidomide–Dex	Clinical trial	Refractory/relapsed MM	10 pts CrCl <30 mL/min, 169 pts CrCl 30–60 mL/min	Moreau *et al.* [64]
Bentamustine monotherapy/ with RTX	Retrospective	CLL/NHL	104 pts CrCl <40 mL/min	Nordstrom *et al.* [65]
V versus IMiD versus CC	Clinical trial	MM with RI	55 pts CrCl <30 mL/min (9 dialysis), 41 pts CrCl ≥30, <50 mL/min	Roussou *et al.* [66]
T-Dex	Clinical trial data	MM with RI prior to ASCT (induction therapy)	16 pts CrCl < 30 mL/min, 15 pts CrCl 30–50 mL/min (total 7 on HD)	Tosi *et al.* [67]
L-Dex	Two clinical trials	MM RI versus non-RI	16 pts CrCl <30 mL/min, CrCl ≥30 < 60 in 82 pts	Dimopoulous *et al.* [68]
POM–lowDex	Three clinical trials	MM with RI	355 pts with CrCl ≥30 and <60 mL/min (166 pts CrCl ≥30 < 45)	Siegel *et al.* [69]
Carfilzomib Dex versus Bortezomib Dex	Clinical trial	Relapsed/refractory MM	56 pts CrCl <30 mL/min, 128 pts with CrCl 30–50 mL/min	Dimopoulos *et al.* [70]

V, bortezomib; M, melphalan; L, lenalidomide; T, thalidomide-dexamethasone; V, bortezomib; CC, conventional chemotherapy; CLL, chronic lymphocytic leukaemia; NHL, non-Hodgkin lymphoma; pts, patients.

Batko K et al. Nephrol Dial Transplant 2018; 1–13

MGRS. Treatment options

- In the majority of patients, the diagnosis of MGRS is not an indication for the implementation of cytotoxic therapy because the course of the disease for many years can be asymptomatic
- In patients with MGRS an indication for use hematological treatment is the presence of pathogenic protein and the tissue pathology induced by them, not the type and severity of bone marrow pathology, which is non-cancerous.



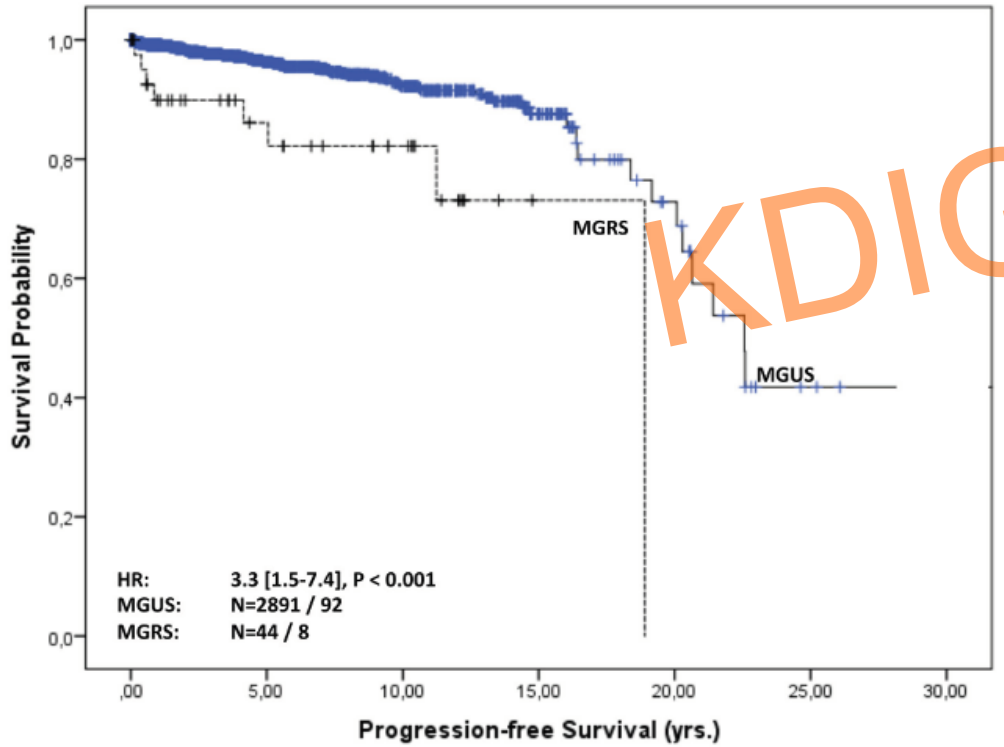
Batko K et al. Nephrol Dial Transplant 2018; 1–13

www.impactjournals.com/oncotarget/ Oncotarget, 2018, Vol. 9, (No. 2), pp: 2344-2356

Research Paper

Monoclonal gammopathy of renal significance (MGRS) increases the risk for progression to multiple myeloma: an observational study of 2935 MGUS patients

Normann Steiner[1,*], Georg Göbel[3,*], Patricia Suchecki[1], Wolfgang Prokop[4], Hannes Neuwirt[2,*] and Eberhard Gunsilius[1,*]



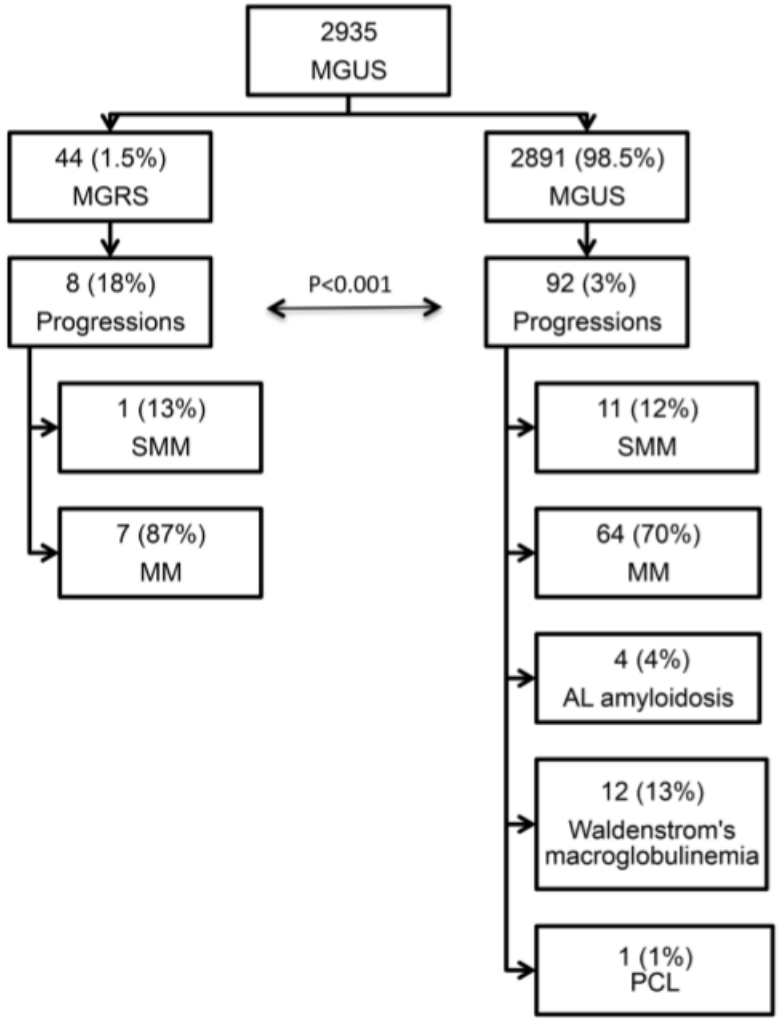


Figure 3: Progression-free survival of MGUS vs. MGRS patients. Progression-free survival in years from MGUS diagnosis stratified by MGUS / MGRS diagnosis. The hazard ratio (HR, 95% CI) was calculated with a Cox regression model adjusted for sex, age and serum creatinine level at baseline.

CONCLUSION:

•MGRS is a nephrotoxic monoclonal gammopathy produced by clones that by itself do not meet criteria for treatment (malignancy)

•MGRS related kidney diseases are the result of the MGRS and can occur independently of clonal proliferative disorder
•Treatment of MGRS should be clone directed

•Goal of therapy should be a hematologic response of VGPR or better

•Awareness of MGRS is critical to improve outcomes in our patients – both in hematology and nephrology

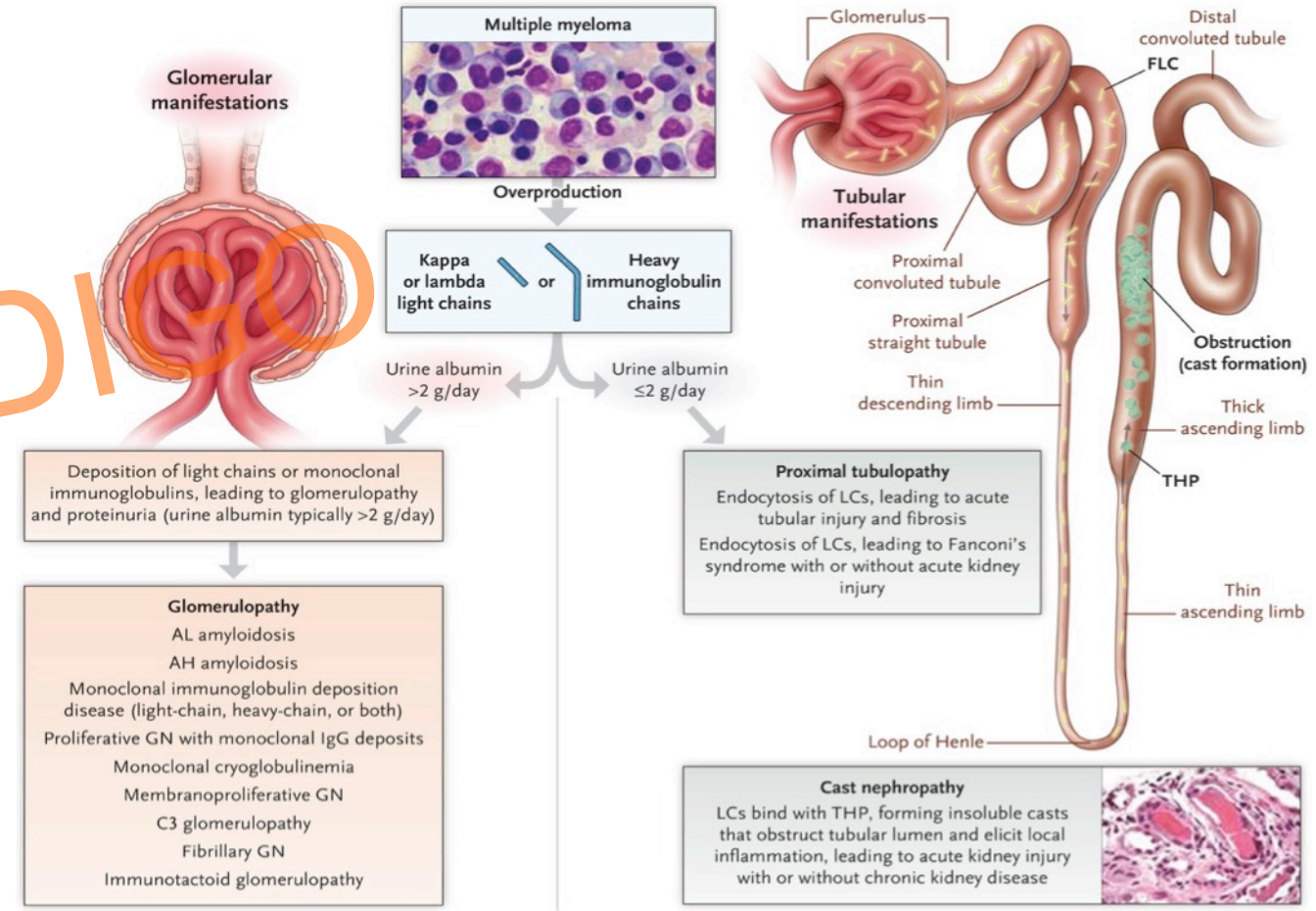
Renal involvment in Multiple Myeloma (MM)

- Renal involvement is a common complication of MM

  Up to 20% of patients will have some degree of kidney disease at diagnosis and a further 40% will develop kidney disease at some point during the course of their myeloma[1]

- Two main pathogenetic mechanism:
  - ✓ intracellular cast formation
  - ✓ direct tubular toxicity by lights chain
- Urinary light chain excretion and/or hypercalcemia are the most important factors and are present in 90% of cases[2]

Acute kidney injury in multiple myeloma

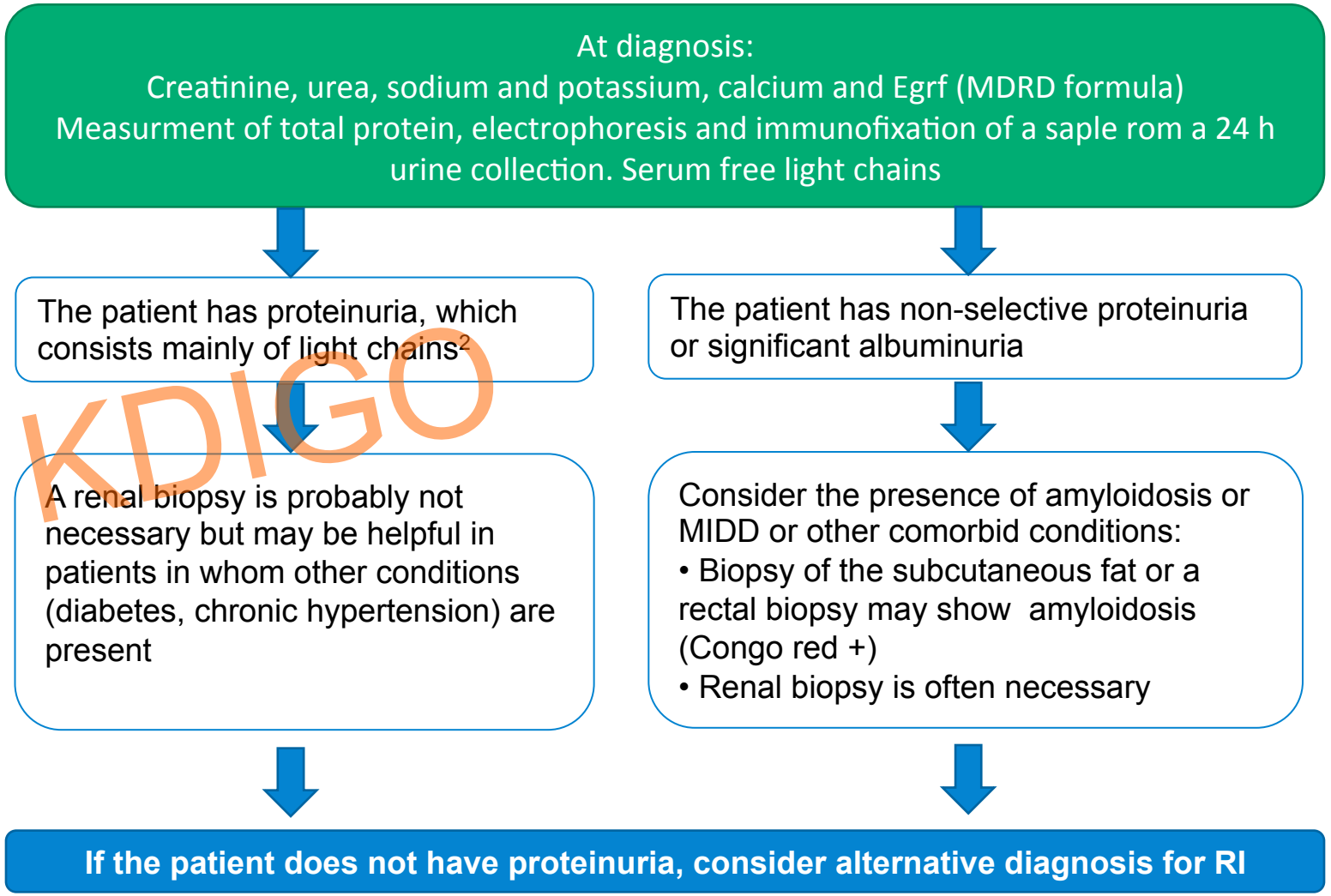


Adapted from: Mitchel H et al., New Eng J 2017; 376:1770-1781

1. Dimopoulos et al. Leukemia 2008;22:1485-93 2. San Miguel et al. Haematologica 1999;84:36-58

Diagnostic Evaluation of Myeloma Patients

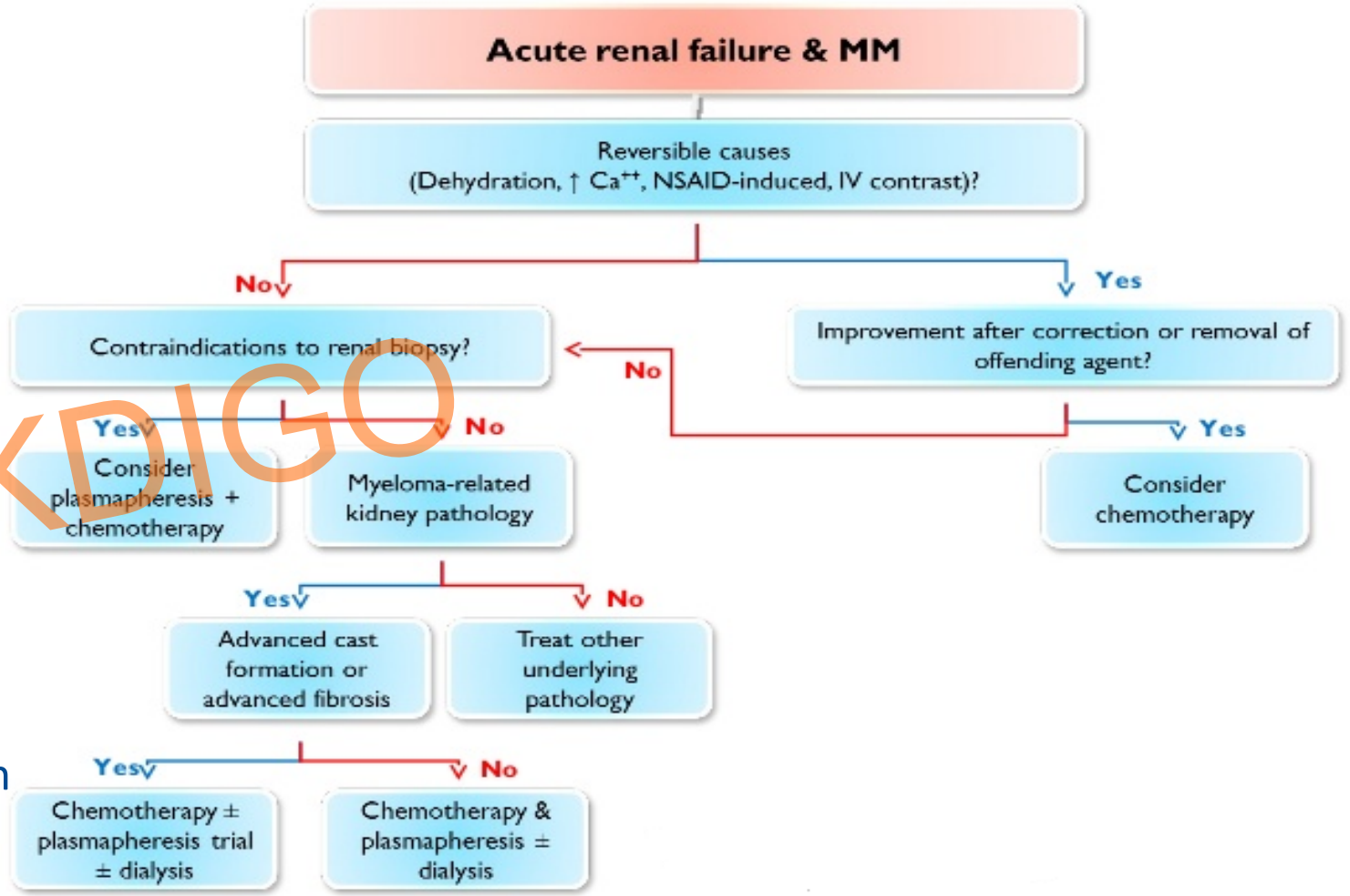
- Early diagnosis at the time when renal impairment is still reversible is extremely important for the diagnosis
- The diagnosis can only be made definitely with a kidney biopsy.
- Differential diagnosis of renal failure should always include monoclonal gammopathy-associated nephropathy [1]



1.Adam Z et al. Vnitr Lek. *2009* Jun;55(6):570-82. 2 Dimopoulos et al. J Clin Oncol 2016;34:1544-57

Management of Renal Impairment

- Managment of renal impairment involves:
  - ✓supportive care (hydration, urine alkalinization, managment of hypercalcemia, avoidance of nephrotoxic agents)
  - ✓mechanical approaches (plasma exchange, conventional hemodialysis, high cut-off hemodialysis
  - ✓antimyeloma treatment [1]
- Reversible causes should alwayes be excluded or corrected acordingly
- High-dose chemotherapy is recommended in patients with presistant renal failure, particulary in the subgroup of patients with chemotherapy- sensitive disease [2]



1. Dimopoulos et al. J Clin Oncol 2016;34:1544-57 2. Adam Z et al. Vnitr Lek. 2009 Jun;55(6):570-82. 3. El-Achkar TM et al. Ther Aper Dial 2005; 9(5): 417-22.

Novel agents in MM kidney treatment

- PI-based regimens (bortezomib, carfilzomibe etc) are the cornerstone of the management of myeloma-related renal impairment:

✓ no dose modification required

✓ renal response in 50 to 60% of patients

✓ triplet combination with high-dose dexamethasone

- Thalidomide is effective in patients with renal impairment and can be given without dose modification
- Lenalidomide is effective in patients with renal impairment but dose modifications are required according to degree of renal impairment
- Pomalidomide is effective in patients with renal impairment and can be given without dose modification

Criteria of renal response in MM

Response	Baseline eGRF (mL/min/1.73 m^2)	Best CrCL response
CRenal	<50 mL/min	≥60 mL/min
PRenal	<15 mL/min	30-59 mL/min
MRenal	<15 mL/min 15-29 mL/min	15-29 mL/min 30-59 mL/min

eGRF-estiamted glomerular filtration rate, based on Modification Diet in Renal eqution; CrCL- clearence of creatinine

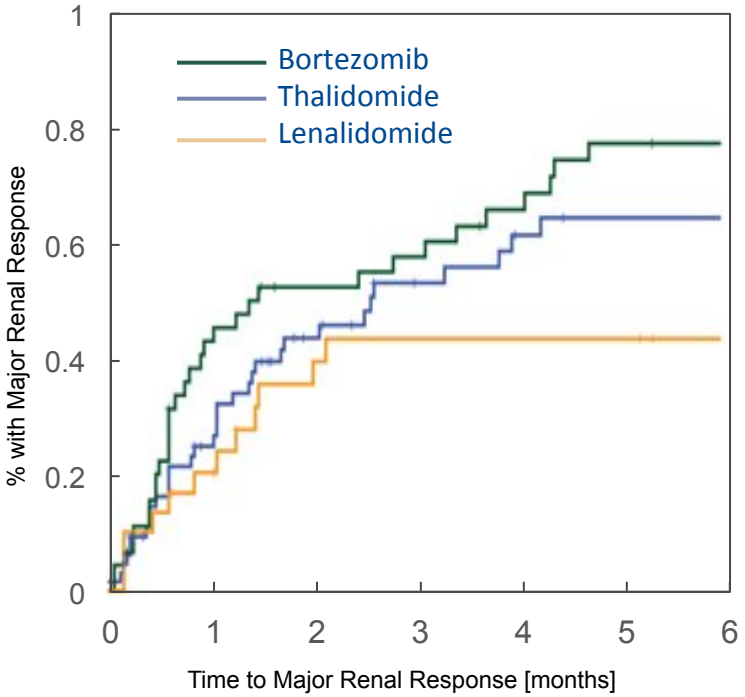
Dimopoulos et al. J Clin Oncol 2010;28:4976

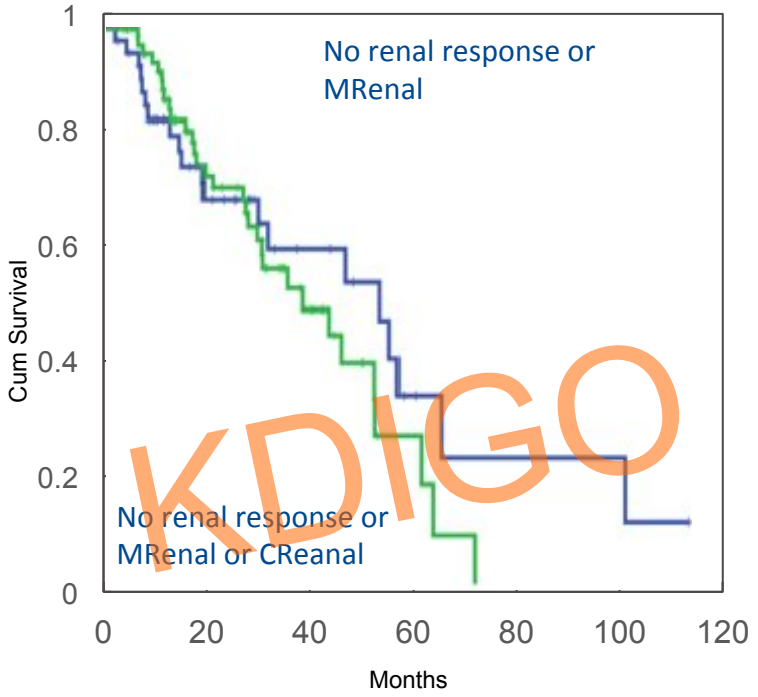
Dose modification of anti-myeloma drugs

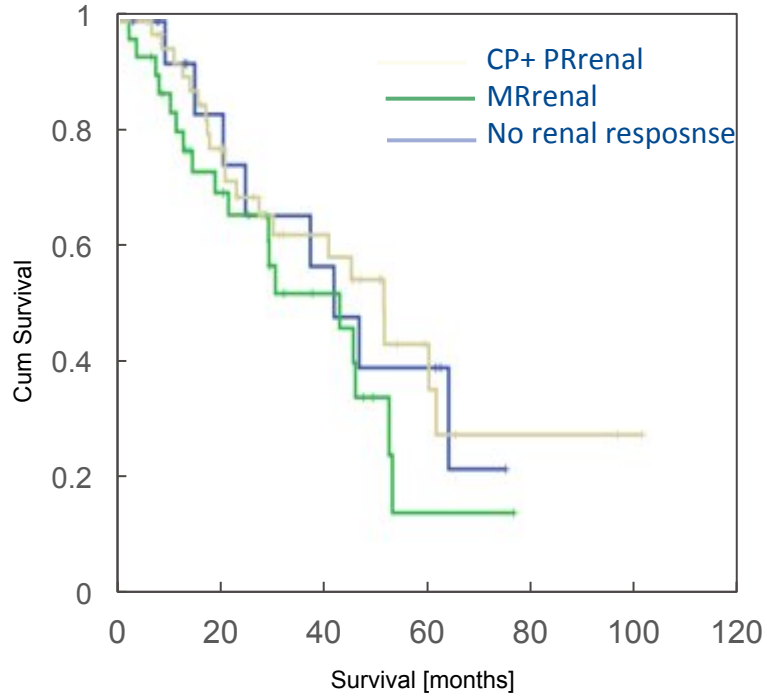
Drug	CrCl > 60 mL/min	CrCl, 30-59 mL/min	CrCl, 15-29 mL/min	CrCl < 15 mL/min	On Dialysis
Dexamethasone	20-40 mg	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Melphalan	Oral melphalan 0.15 to 0.25 mg/kg/d for 4-7 days High-dose melphalan 200 mg/m^2	Oral melphalan reduced 25% (0.11-0.19 mg/kg/d for 4-7 days High-dose melphalan 140 mg/m^2	Oral melphalan reduced 25% (0.11-0.19 mg/kg/d for 4-7 days High-dose melphalan 140 mg/m^2	Oral melphalan reduced 50% (0.0175-0.125 mg/kg/d for 4-7 days). High-dose melphalan 140 mg/m^2	Oral melphalan reduced 50% (0.0175-0.125 mg/kg/d for 4-7 days). High-dose melphalan 140 mg/m^2
Bortezomib	1.3 mg/m^2 on days 1, 4, 8, and 11, or weekly regimens	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Thalidomide	50-200 mg/d	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Lenalidomide	25 mg/d	10 mg per d, can be increased to 15 mg/d if no toxicity occurs	15 mg once every other d, can be adjusted to 10 mg/d	5 mg/d	5 mg/d
Carfilzomib	20 mg/m^2 cycle 1; 27 mg/m^2 cycle 2 and on	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Doxorubicin	According to regimen	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Cyclophosphamide	According to regimen	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Pomalidomide	4 mg/d	No dose modification needed for CrCl ≥ 45 mL/min	Ongoing studies will clarify if modification is needed	Ongoing studies will clarify if modification is needed	Ongoing studies will clarify if modification is needed

Dimopoulos et al. J Clin Oncol 2016;34:1544-57

Impact of novel agents on renal impairment







Predictive factors for response:
- age ≤ 65 years
- creatinin clearance ≥ 30 ml
- bortezomib treatment
- high-dose dexamethasone

133 patients with eGFR< 60 ml/min treated with IMiDs or bortezomib

2-months Landmark analysis

105 patients with eGFR<30 ml/min treated with novel agents or CC

2-months Landmark analysis

Dimopoulos et al. Leukemia 2013;27:423-9
Dimopoulos et al. Ann Oncol 2014;25:195-200

•High-dose chemotherapy with autologous hematopoietic stem cell transplantation (auto-HSCT) improves the outcome of patients with multiple myeloma (MM).

•It seems that auto-HSCT is also a feasible therapeutic option in MM dialysis-dependent (MMDD) patients.

•The data from all Polish Centers belonging to the Polish Myeloma Study Group were collected. Twenty-eight dialysis-dependent MM-patients were enrolled into this retrospective analysis.

•The study population comprised patients diagnosed between 2004 and 2015 in whom an attempt to collect auto-HSC was made (68%: women, median age: 56).

•Patients received granulocyte-colony stimulating factor (G-CSF) alone or in combination with chemotherapy and autologous peripheral blood stem cells (auto-PBSCs) were collected by leukapheresis.

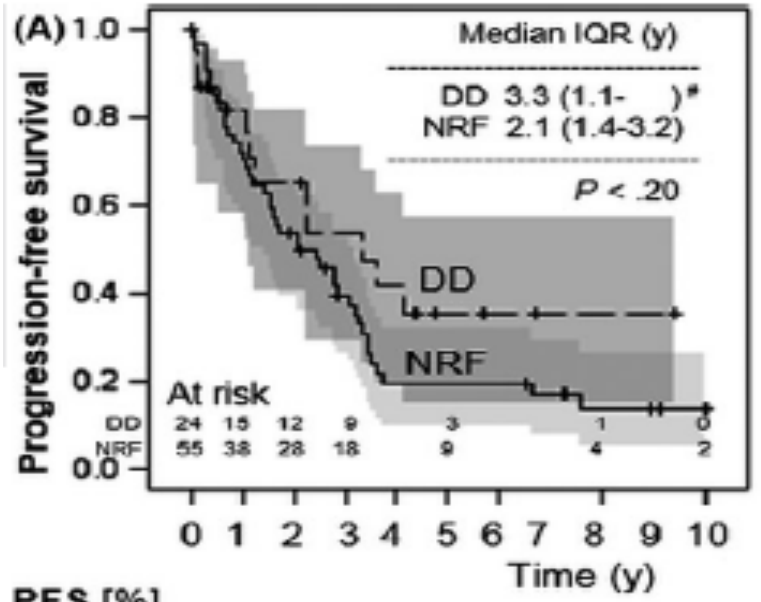
•The success rate in terms of obtaining sufficient number of CD34(+) cells/kg for an auto-HSCT (≥2 × 10x6 cells/kg body weight) during the first mobilization attempt was 92% (26/28 patients), and for 2 auto-HSCTs (≥4 × 10x6 cells/kg) - was 75% (21/28 patients).

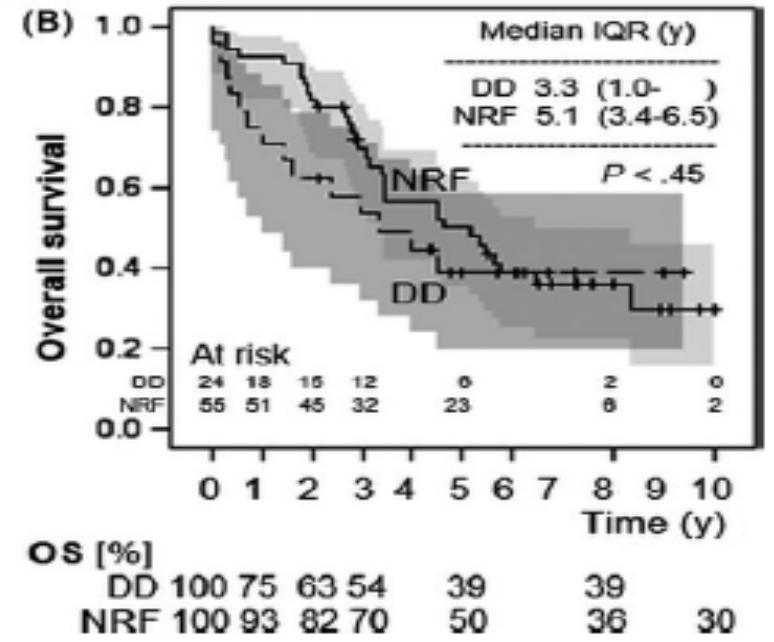
•After the second mobilization attempt (undertaken in 8 patients), a sufficient number of CD34(+)/kg cells for an auto-HSCT was obtained for all patients and the number of CD34(+)/kg collected cells was sufficient for 2 auto-HSCT in 6 additional patients.

•Hematologic toxicity and infections were the most frequent complications. Higher doses of cytarabine (>1.6 g/m2) and cyclophosphamide (> 2 g/m2) should be avoided in MMDD patients due to toxicity.

Stem cell mobilization in patients with dialysis-dependent multiple myeloma: Report of the Polish Myeloma Study Group. - J Clin Apher. 2018 Jun;33(3):249-258. doi: 10.1002/jca.21584. Epub 2017 Sep 18.

- Dialysis-dependent (DD) multiple myeloma patients (MM) have a poor prognosis and high tumour burden, thus may benefit from autologous peripheral blood stem cell transplantation (auto-PBSCT), however, these patients have an increased risk of toxicity.
- Evaluation of the outcomes (toxicity, PFS, OS) of high dose therapy followed by auto-PBSCT during an observational study and after propensity score matching between 2004-2015, 24 DD patients, (aged 38-67 years), ISS 3, treated with auto-PBSCT, requiring dialysis at diagnosis and auto-PBSCT, matched and compared to 55 normal renal function MM patients (NRF) with ISS 3 for outcomes of interest in the Polish Myeloma Study Group
- In DD patients compared to NRF patients risk of mucositis (88% vs 55%), infection (79% vs 51%), parenteral nutrition (50% vs 24%), diarrhoea (71% vs 38%), prolonged duration of hospitalisation (medians: 30 vs 21 days), requirement for RBC transfusion (83% vs 36%) were significantly higher, while no significant differences were found in post-transplant response (ORR; 75% vs 87%), 5-year PFS (36% vs 20%) and OS (39% vs 50%). Subgroup analyses based on toxicity supported these results.
- Despite the increased risk of toxicity in DD patients these events do not significantly affect both the PFS and OS.

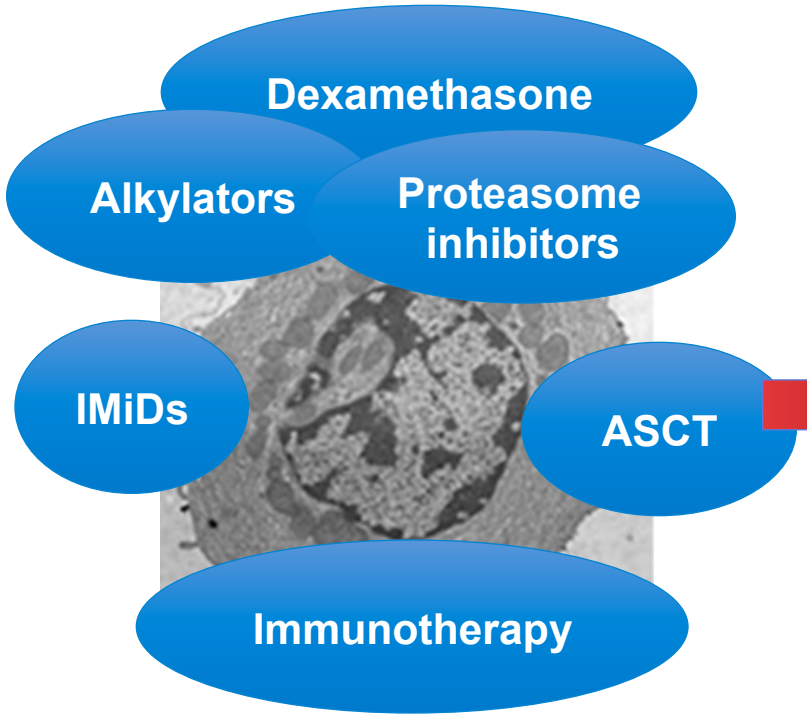




Autologous peripheral blood stem cell transplantation in dialysis-dependent multiple myeloma patients-DAUTOS Study of the Polish Myeloma Study Group. - Eur J Haematol. 2018 Oct;101(4):475-485. doi: 10.1111/ejh.13101. Epub 2018 Jul 4.

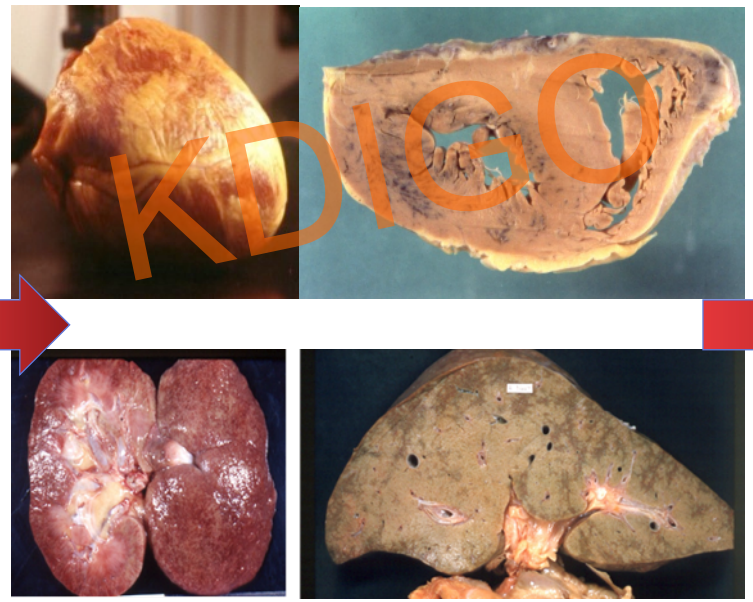
AMYLOIDOSIS AL. – under diagnosis disorder

Anti-plasma cell treatment



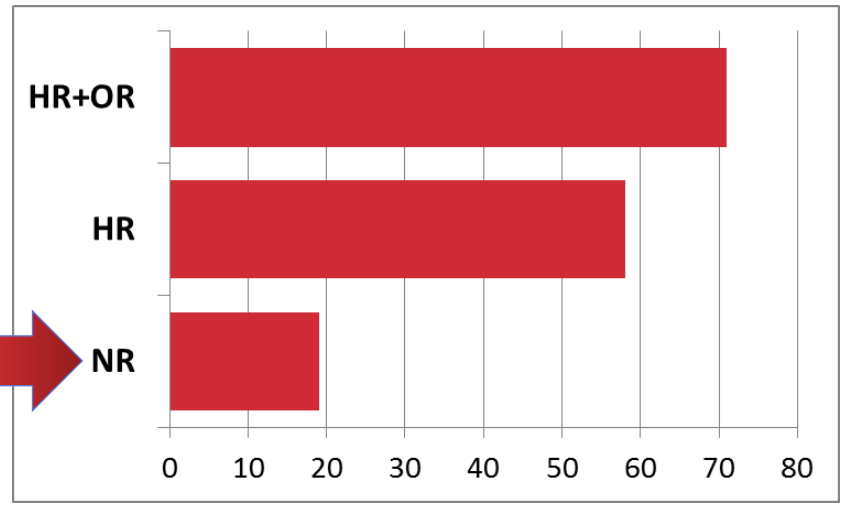
Hematologic response
↓ FLC

Improve organ dysfunction



Organ response
↓ NT-proBNP, proteinuria, ALP

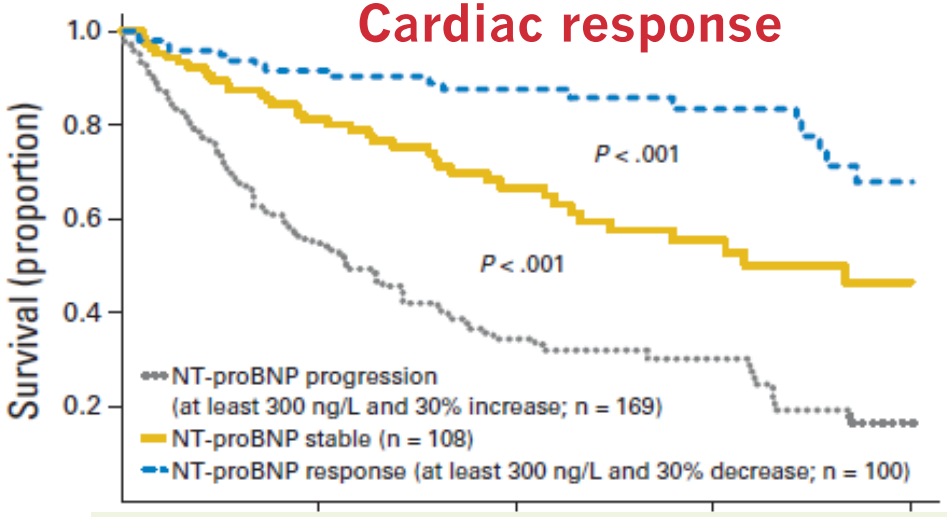
Prolong survival

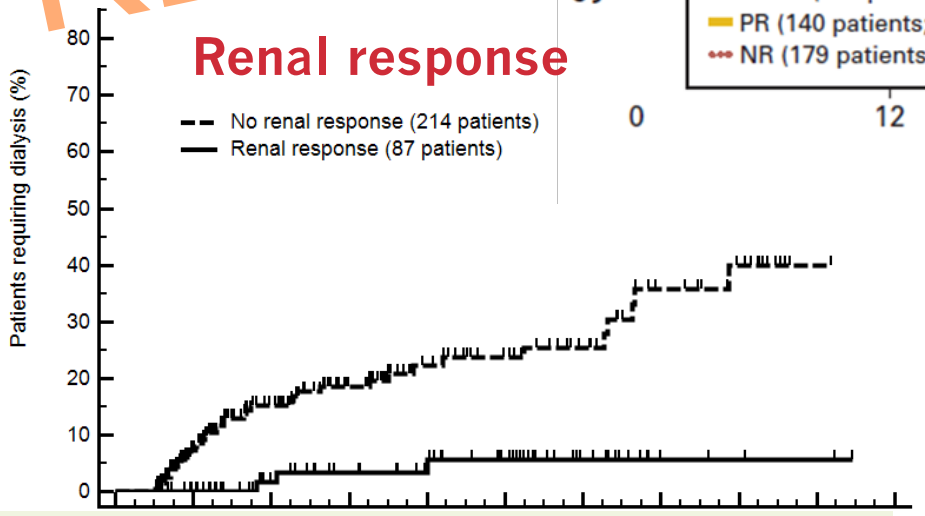


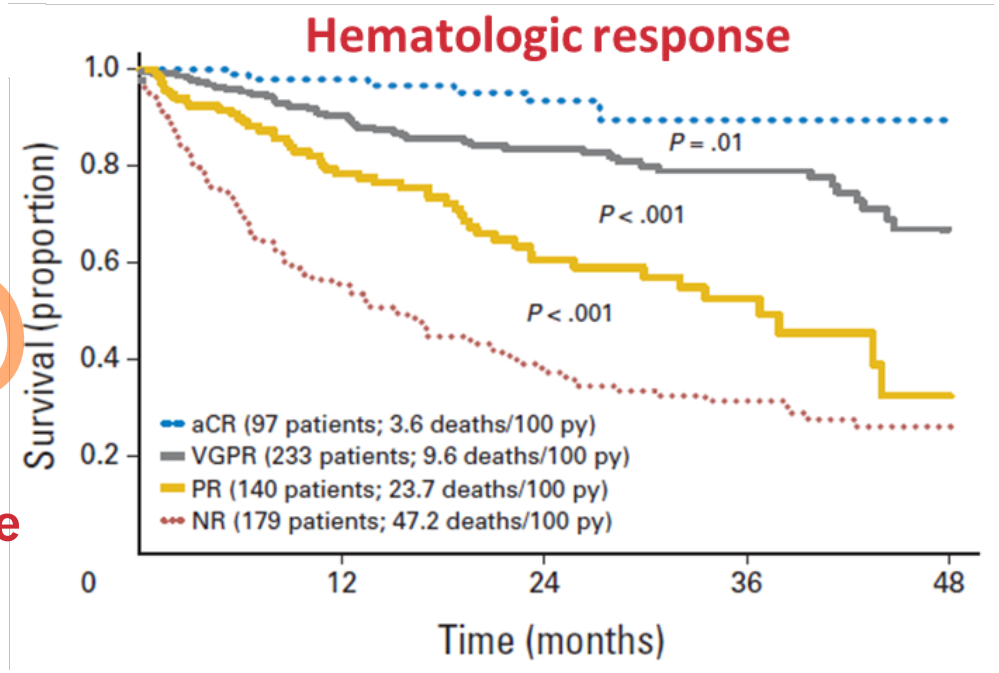
Patients surviving 5 years (%)
data from1065 patients at Pavia ARTC

AMYLOIDOSIS

Response	Definition
Hematologic	**CR:** negative s&u IFE + normal FLCR **VGPR:** dFLC <40 mg/L **PR:** dFLC decrease >50%
For dFLC 20-50 mg/L	**Low-dFLC response:** dFLC <10 mg/L
Cardiac	NT-proBNP decrease >30% & >300 ng/L
Renal	Proteinuria decrease >30%







Organ response criteria can be graded based on depth of decrease of biomarkers

Palladini, et al. JCO 2012
Palladini, et al. Blood 2014
Milani, et al. Blood 2017
Dittrich, et al. Blood 2017
Sidana, et al. Leukemia 2017
Nguyen, et al. Amyloid 2018
Muchtar, et a. Leukemia 2018

Kidney Complications of HSCT

CASE REPORT

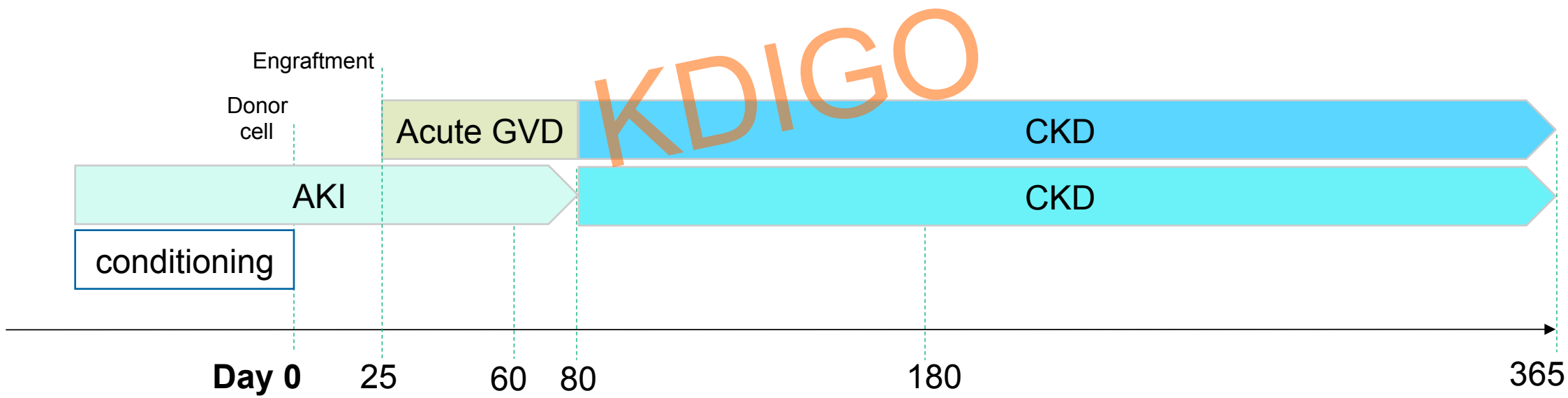
Patient J.P. 47 years old with multiple myeloma - light chain disease (kappa), D-S III B, R-ISS 3. dgn march 2017. High risk – t(4;14). Renal failure – hemodialysis 3x week
Induction 6xVTD. Status post auto-PBSCT (November 2017). Bone osteolysis (cervical and thoracic segment of the spine, left humerus, ribs). Chronic renal failure - dialysis 3x per week from diagnosis. CR (negative IF) – march 2018. Compression fracture Th11.
Status post radiotherapy 20 cGy local recurrence in the left femur (AUGUST 2018).
Maintenance Vel-Dex cycle from sepetembr 2018.
September 2018 – stop dialysis after 2 doses of bortezomib

Is it good time for next auto-PBSCT now?
How long Velcade maintenace?
Should we do kidney biopsy now?

He has now MRD negative…

Kind of kidney complications

The HSCT process is a risk for the kidneys. Potential, acute kidney injury (AKI) and chronic kidney disease (CKD) may be complications of radiation, anemia, chemotherapeutic agents, graft-versus-host disease (GVHD), infections, altered immunologic responses, fluid imbalance, and medications.



The time course of kidney compilcations after hematopoietic stem cell transplantation

Hingorani S. N Engl Med. 2016:809-821

Causes of Acute Kidney in HSCT

Prerenal

- Extracellular fluid depletion (poor oral intake, vomiting, diarrhea)
- Sepsis/shock
- Drugs
  (eg, calcineurin inhibitors, NSAIDs)
- Hepatorenal syndrome
  (eg, veno-occlusive disease/ sinusoidal obstruction syndrome)
- Capillary-leak syndrome
- Decreased cardiac output
  (eg, pericardial effusion or tamponade)

Intrinsic renal

- Acute tubular necrosis
  - ✓ Ischemic (eg, sepsis, shock)
  - ✓ Nephrotoxic agents (iv iodinated contrast media, aminoglycosides, amphotericin, cyclophosphamide/ifosfamide, cisplatin, methotrexate)
- Acute interstitial nephritis
  - ✓ Medication-associated (eg, antibiotics, PPIs, NSAIDs, thiazides, furosemide)
- Infection-associated (eg, pyelonephritis, systemic infection)
- Vascular
  - ✓ Acute TTP/HUS
  - ✓ Renal vein thrombosis

Postrenal

- Intratubular obstruction
  - ✓ Tumor lysis syndrome/acute urate nephropathy
  - ✓ Tubular drug precipitation (eg, acyclovir, methotrexate)
- Extrarenal obstruction
  - ✓ Bladder outlet &/or ureteral obstruction
    (eg, hemorrhagic cystitis as a complication of cyclophosphamide, fungal ball, clots)

Singh N et al. Am J Kidney Dis. 2013;374:2256-67

Management of AKI

- AKI after HSCT is associated with high mortality, and in those requiring dialysis, mortality may be greater than 70%-80% [1]
- The incidence of AKI is lower with:

✓ autologous compared with allogeneic HSCT [2,3]

✓a nonmyeloablative versus a myeloablative conditioning

✓hepatic veno-occlusive disease

Avoidance of risk factors associated with the development of AKI remains the main stay of management [4]
Use of the reduced intensity-conditioning regimen wherever possible
Closer monitoring of nephrotoxic medications such as amphotericin or use of liposomal preparations
Use of alternative antifungals such as fluconazole and voriconazole for prophylaxis against infection
Early identification and management of sepsis
Use of diuresis and alkalization of urine in conditions such as tumor lysis syndrome or marrow infusion toxicity
Early identification and management of hepatic SOS with defibrotide
More importantly, early involvement of the nephrologist in the disease course is helpful in prevention of AKI and related complications.

1. Hahn T et al. Bone M. Trans. 2003;32(4):405-410 2. Fadia A et all. Kidney Int. 2003;63(5):1868-1873.3. Merouani A et al. Kidney Int. 1996;50(3):1026-1031 4. Krishnappa V et al. Inter J Neph.2016

Chronic kidney disease (CKD) after HSCT

- CKD develops in 15%-20% of recipients [1]
- The most common causes of CKD after HSCT:

✓ chronic CNI nephrotoxicity

✓ chronic GVHD-associated glomerulonephritis

✓ HSCT associated thrombotic microangiopathy (TA-TMA)

- TA-TMA has an associated mortality risk estimated to be as high as 50%-90% at 1 year after the onset of TA-TMA.

Etiologies Of CKD After HSCT [2]
Idiopathic Chronic calcineurin inhibitor exposure Graft vs host disease •Nephrotic syndrome •Thrombotic microangiopathy
Radiation nephritis/bone marrow transplant nephropathy Thrombotic microangiopathy
Glomerular disease •Focal segmental glomerulosclerosis •Membranous nephropathy •Minimal change disease •Immunoglobulin A nephropathy

1.Cohen EP et al. Nephron. 1995;70(2):217-222. 2.Sawinsky D. Adv Chronic Kidney Dis. 2014; 21: 95-105

Diagnosis of chronic kidney disease

	TA-TMA	chronic CNI nephrotoxicity	chronic GVHD-associated glomerulonephritis
Cause	Endothelial injury; multifactorial but primarily due to chemotherapy radiation	Vasoconstriction, arteriolar lesions, and tubular injury	T-Cell activation leads to immune complex–mediated damage to glomeruli
Clinical presentation	CKD ≥ 6 mo after bone marrow transplantation	CKD	CKD with nephrotic syndrome skin, mucosal, and liver involvement from GVHD
Proteinuria	+	±	+
Hypertension	+	+	-
Anemia	+	+	+
Elevated serum LDH	+	-	-
Schistocytes	+	-	-
Renal histology	TMA mesangiolysis, subendothelial expansion, glomerular basement membrane duplication (double contour), IF-TA	Nonspecific; typical features include obliterative arteriolopathy with medial hyalinosis and expansion of afferent arteriolar wall; patchy interstitial fibrosis and compensatory glomerular hypertrophy	Membranous nephropathy, minimal change disease, MPGN or FSGS
Progression to CKD/ ESRD	16 increased risk of ESRD in patients who progressed to CKD	ESRD in 10%-30%	ESRD rarely reported

Singh N et al. Am J Kidney Dis. 2013;374:2256-67

Managment and prevention of TA-TMA

- Treatment of TA-TMA involves medical management (**control of hypertension, use of recombinant erythropoietin, packed red blood cell transfusions, use of ACE inhibitors or angiotensin receptor blocking agents (ARBs), plasma exchange**) and discontinuation of any inciting agents
- Several small uncontrolled studies have reported success with new therapies such as daclizumab, rituximab, defibrotide, and eicosapentaenoic acid
- Prevention or minimization the risk of TA-TMA should involve:

✓using of kidney shielding during total-body irradiation

✓using of minimum effective doses of fractionated radiation

✓using of ACE inhibitors/ARBs,

✓minimization of CNI dosage or substitution with mycophenolate/sirolimus

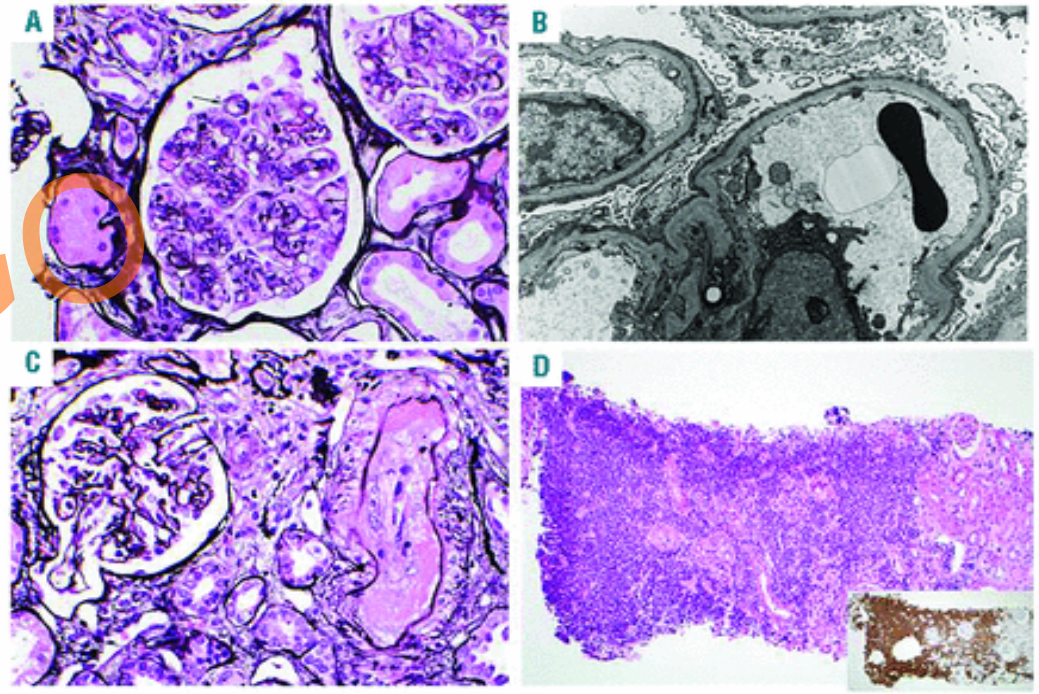
Singh N et al. Am J Kidney Dis. 2013;374:2256-67

Chronic Lymphocytic Leukemia

CLL and renal involvment

- Chronic lymphocytic leukemia (CLL) is a B-cell origin
- Kidney diseases in CLL are manifestation of the disease process such as:
  - ✓acute kidney injury with infiltration
  - ✓or with a paraneoplastic glomerular disease
  - ✓or as a manifestation of extra renal obstruction
  - ✓and tumor lysis syndrome
- Kidney disease at diagnosis of CLL or during follow-up had a significantly decreased overall survival compared with those without kidney disease

Most common findings on kidney biopsy



(A-MPGN,B-MCD, C-thrombotic microangiopathy, D-CLL infiltrate)

Haematologica September 2015 100: 1180-1188; doi:10.3324/haematol.2015.128793

Acute kidney injury in CLL

- AKI developed in 16% of patients during follow-up
- AKI is associated with older age, male gender and certain CLL characteristics (IGHV UM, CD49dþ, CD38þ, ZAP-70þ, del17p, or del11q)
- The mechanism of AKI with CLL infiltration is not clearly established but has been hypothesized to involve tubular/microvascular compression causing intrarenal obstruction in addition to an infiltration-associated inflammatory/ cytokine response
- Common causes: hypoperfusion, TLS, hemophagocytic syndrome, direct infiltration of malignant cells and infection

Summary of various causes of kidney injury in CLL

Type of etiology	Potential causes
Prerenal	Poor oral intake; sepsis and hypoperfusion; heart failure; cirrhosis; medications such as diuretics, non-steroidal anti-inflammatory agents, angiotensin receptor blockers and angiotensin-converting enzyme inhibitors
Intrinsic renal	Glomerular diseases
	TMA
	Acute tubular necrosis—sepsis, nephrotoxic agents and in some cases hyperviscosity and therapy agents
	Acute interstitial nephritis—infections such as BK or adenovirus, urinary tract infections, medication or chemotherapy induced or malignant cell infiltration
Postrenal	Obstruction from extrinsic compression of pelvacalcyceal system by tumor or lymph nodes
	TLS—uric acid nephropathy and intratubular obstruction from cancer itself or related to the use of CLL-directed therapy

Wanchoo R et al. 2018; Clin K J, 5, 670-680

CLL. Treatment

- The current standard of care for a fit patient with CLL without comorbidities is a chemo-immunotherapeutic regimen that includes the purine analog **fludarabine** in combination with **cyclophosphamide and rituximab**
- Treatment evolves from regimens with significant impact on long-term outcomes and associated concomitant toxicities to the use of novel agents that specifically target dysregulated pathways.
- Targeted agents include the monoclonal antibody **obinutuzumab**, the Bruton's tyrosine kinase inhibitors **ibrutinib** and **acalabrutinib**, the phosphatidylinositol 3-kinase inhibitor idelalisib and the BCL-2 inhibitor venetoclax
- The newer agents used to treat CLL had fewer renal toxicities than the older agents

Waldenström macroglobulinemia

Kidney Involvement in Waldenström macroglobulinemia

- Characteristics

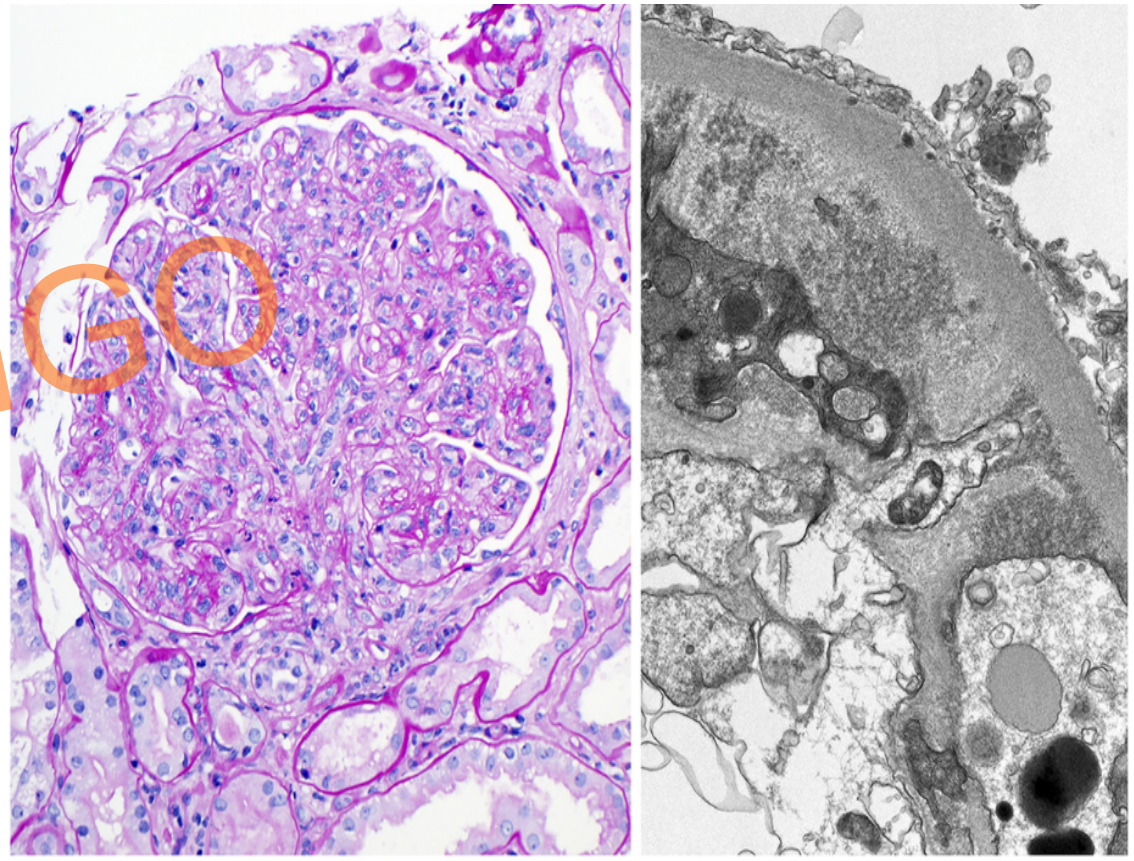
lymphoproliferative disorder characterized by the presence of an IgM monoclonal protein 1 g/dl and 10% lymphoplasmacytic in filtrate in the bone marrow

- Kidney diseases in Waldenström macroglobulinemia can caused by:

✓ malignancy (high tumor burden)

✓ monoclonal gammopathy of renal significance where the clonal mass is low

- Membranoproliferative GN and lymphomatous infiltration are the most often lesions, amyloid deposits and acute tubular injury are much less common



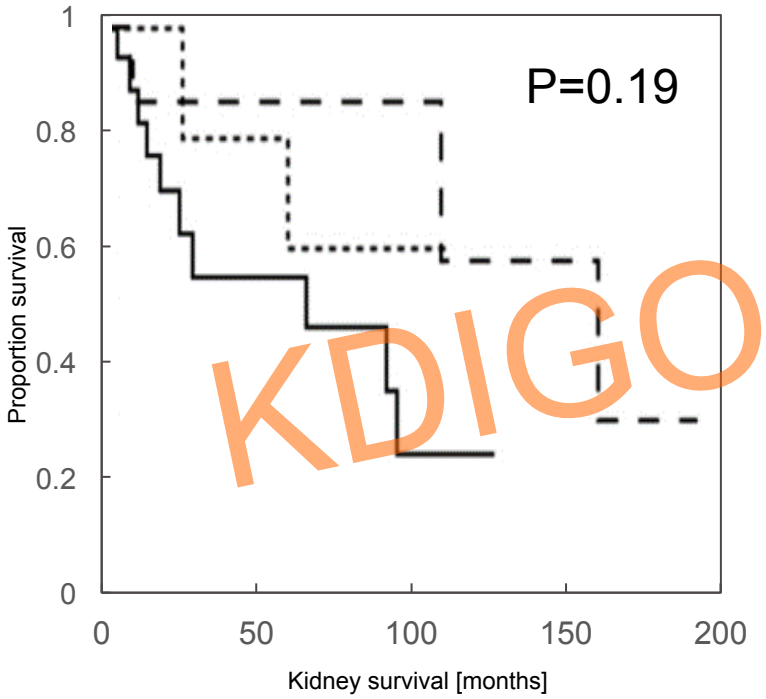
Cryoglobulinemic GN

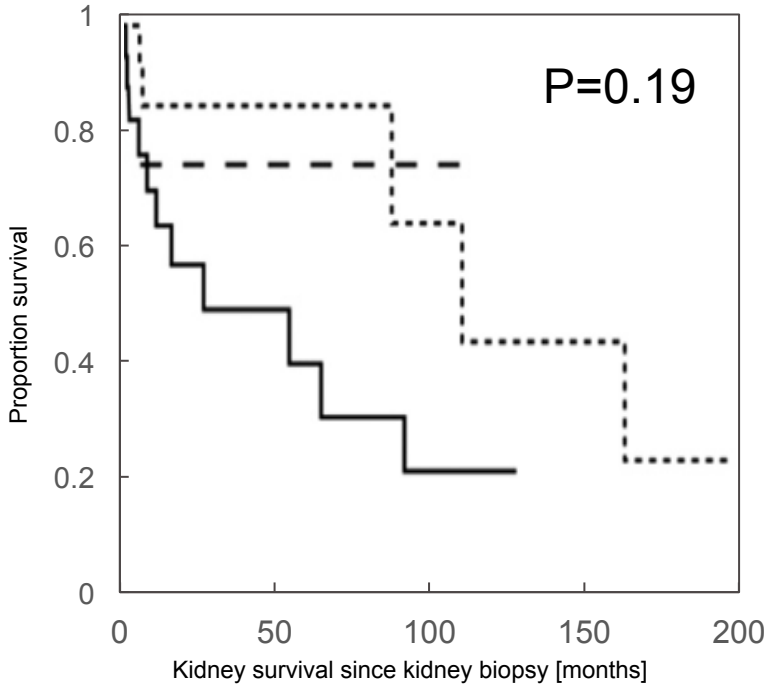
Higgins L et al.2018 Clin J Am Soc Nephrol 13: 1037–1046,

Survival in Waldenström macroglobulinemia

Median survival was 64.4 months in patients with amyloid-related glomerulopathy and 160.5 months in the nonamyloid-related glomerulopathy group but had not been reached in patients with ubulointerstitial nephropathies

Median kidney survival was reached only by patients with amyloid-related glomerulopathy (94.2 months).





patients with amyloid-related glomerulopathy

patients with tubulointerstitial nephropathies

patients with nonamyloid-related glomerulopathy

Higgins L et al.2018 Clin J Am Soc Nephrol 13: 1037–1046,

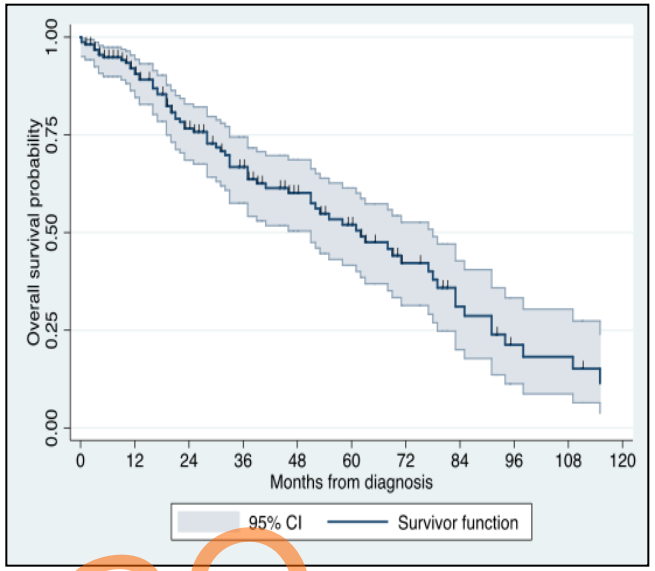
Waldenström macroglobulinemia treatment

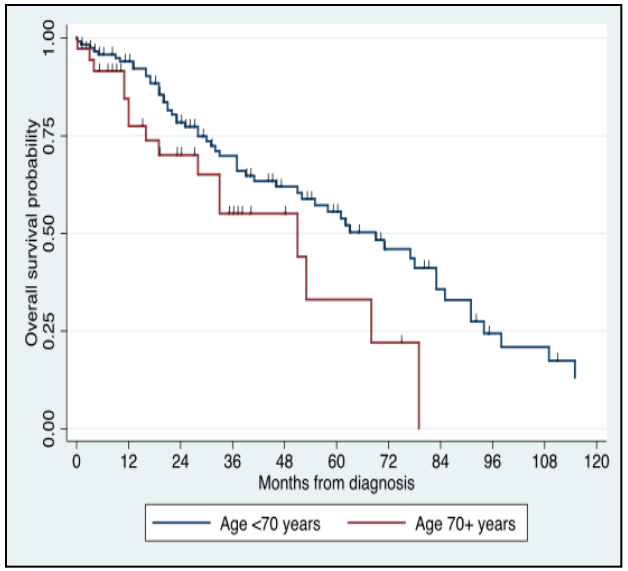
- Attributing the renal failure to WM is clinically relevant because this represents a potential indication to initiate therapy[1]
- The diagnosis of specific renal pathologies by kidney biopsy (such as AL-amyloidosis or LCDD), will impact clinical management and treatment choices [2]
- There are no significant differences in terms of timing of treatment, pre- or post-kidney biopsy
- Lack of correlation between the hematologic response and kidney outcomes [2]

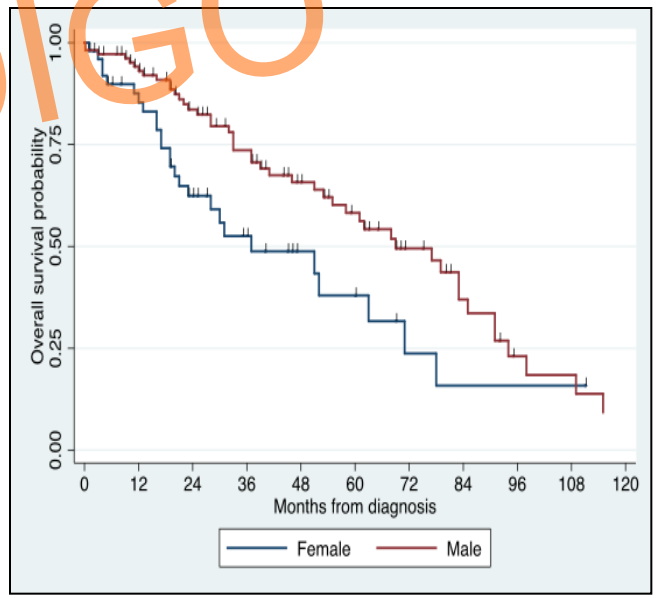
1.Dimopoulos et al, 2014 2. Sayed et al, 2015 3. Higgins L et al.2018

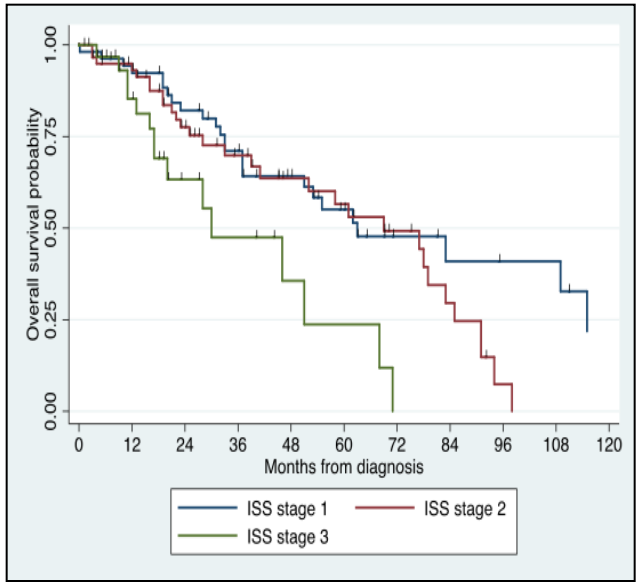
IgM myeloma is a rare hematologic malignancy for which the clinicopathological features and patient outcomes have not been extensively studied. We carried out a multicenter retrospective study in patients with diagnosis of IgM myeloma defined by >10% marrow involvement by monoclonal plasma cells, presence of an IgM monoclonal paraproteinemia of any size, and anemia, renal dysfunction, hypercalcemia, lytic lesions and/or t(11;14) identified by FISH. A total of 134 patients from 20 centers were included in this analysis. The median age at diagnosis was 65.5 years with a male predominance (68%). Anemia, renal dysfunction, elevated calcium and skeletal lytic lesions were found in 37, 43, 19, and 70%, respectively. The median serum IgM level was 2,895 mg dL21 with 19% of patients presenting with levels >6,000 mg dL21. International Staging System (ISS) stages 1, 2, and 3 were seen in 40 (33%), 54 (44%), and 29 (24%) of patients, respectively. The malignant cells expressed CD20 (58%) and cyclin D1 (67%), and t(11;14) was the most common cytogenetic finding (39%). The median overall survival (OS) was 61 months. Higher ISS score was associated with worse survival (P50.02).

Patients with IgM myeloma present with similar characteristics and outcomes as patients with more common myeloma subtypes.









IgM myeloma: A multicenter retrospective study of 134 patients . Am J Hematol. 2017 Aug;92(8):746-751. doi: 10.1002/ajh.24753. Epub 2017 May 26.

Summary

- Monoclonal immunoglobulin can cause a variety of renal diseases resulting from the direct or from an indirect mechanism
- In this group of renal disorders the differential diagnosis can be a clinical challenge and a multi-disciplinary collaboration between nephrologist, pathologist and hematologist is a priority
- Diagnosis requires a detailed hematologic evaluation and kidney biopsy. Morphologic alterations on light microscopy and immunofluorescence often need to be integrated with the changes on electron microscopy.
- Successful treatment is based on chemotherapy that should be adapter to the underlying clone and renal function.

2018 FDA Approvals for Hematology Indications*

New Molecular Entity
Biosimilar

Non-Malignant / Hematology Support

Malignant

coagulation factor Xa (recomb), inactivated-zhzo (reversal of anticoag due to life-threatening or uncontrolled bleeding with apixaban or rivaroxaban)

denosumab (prevention of skeletal events in MM)

fostamatinib (chronic ITP, prev. treated)

avatrombopag (thrombocytopenia with chronic liver disease, peri-procedural)

epoetin alfa-epbx (biosimilar to Epogen/ Procrit)

pegfilgrastim-jmdb (biosimilar to Neulasta)

methoxy PEG-epoetin beta (anemia due to pediatric CKD)

filgrastim-aafi (biosimilar to Neupogen)

lusutrombopag (thrombocytopenia with chronic liver disease, peri-procedural)

antihemophilic factor (recomb), PEGylated-aucl (hemophilia A, previously treated)

emicizumab-kxwh (prophylaxis in hemophilia A without inhibitors)

pegfilgrastim-cbqv (biosimilar to Neulasta)

eltrombopag (severe aplastic anemia, prev. untreated, in comb. with IST)

emapalumab-lzsg (primary HLH, refractory or recurrent)

Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec

arsenic trioxide (newly diagnosed low-risk APL, in comb. with ATRA)

brentuximab vedotin (newly diagnosed St. 3 or 4 cHL, in comb. with chemotherapy)

nilotinib (pediatric CML)

blinatumomab (pre-B ALL in CR1 or CR2 with MRD≥0.1%)

tisagenlecleucel (R/R large B-cell lymphoma)

daratumumab (newly diagnosed MM, transplant-ineligible, in comb. with VMP)

venetoclax (CLL/SLL, after at least 1 prior therapy)

pembrolizumab (R/R primary mediastinal large B-cell lymphoma)

ivosidenib (R/R AML with IDH1 mutation)

mogamulizumab-kpkc (R/R mycosis fungoides or Sezary Syndrome)

moxetumumab pasudotox-tdfk (R/R hairy cell leukemia, after ≥ 2 prior therapies)

duvelisib (R/R CLL/SLL, after ≥ 2 prior ther.) (R/R FL after ≥ 2 prior ther.)

elotuzumab (R/R MM, in comb. with PomDex)

brentuximab vedotin (newly diagnosed PTCL, in comb. with chemo)

venetoclax (newly diag. AML†, in comb.)

glasdegib (newly diag. AML†, in comb.)

gilterinib (FLT-3 mut AML, prev. treated)

rituximab-abbs (biosimilar to Rituxan, FL and low-grade lymphoma)

**Refer to US Prescribing Information for details.*

†age ≥ 75y, or with comorbidities that preclude intensive chemo

KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES · KDIGO

VIII Myeloma and Lymphoma International Conference in Kraków SEPTEMBER 6-7 2019