RENAL INVOLVEMENT IN HEMATOLOGICAL DISORDERS

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Disclousures

**ADVISORY BOARDS**: KARYOPHARM

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AGENDA

1. Renal involvement in hematological disorders. Introduction
2. Monoclonal gammopathy of renal significance (MGRS)
3. Renal involvement 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.

Clinical presentation of Monoclonal Ig-associated Renal Disease

- Acute renal failure
  - Cast nephropathy (myeloma)
  - Thrombotic microangiopathy
- Nephrotic syndrome
  - CKD
  - Amyloidosis
    - (predominantly glomerular)
  - MIDD
- Nephritic-nephrotic syndrome/RPGN
  - CKD
- Proteinuria/
  - progressive CKD

Hematologic conditions associated with Monoclonal Ig-Renal Disease

- Plasma cell dyscrasia
- B-cell lymphoproliferative disorders

MIDD, light chain proximal tubulopathy
- (often with Fanconi syndrome), amyloidosis
- (predominantly vascular and tubulointerstitial) crystal storing histiocytosis, thrombotic microangiopathy, others

Multiple Myeloma/
- Plasmacytoma
- Waldenström macroglobulinemia
- MGRS

Smoldering multiple myeloma

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

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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?

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>MGUS</th>
<th>MGRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonal BM plasma cell</td>
<td>&lt; 10%</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>Serum M-spike</td>
<td>&lt; 3 g/dl M protein</td>
<td>&lt; 3 g/dl M protein and</td>
</tr>
<tr>
<td>CRAB</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Renal Disease (not cast nephropathy)</td>
<td>Not attributable to the monoclonal gammopathy</td>
<td>Attributable to the monoclonal gammopathy</td>
</tr>
</tbody>
</table>

**MGUS is not equivalent to MGRS**

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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

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

\(^1\) Ciochini M. et all. Int Urol Nephro 2017; 49 (Suppl 1)
MGRS-associated renal lesions

- **Fibrils**
  - Ig-related amyloidosis (AL, AH, AHL)
  - FGN-fibrillary glomerulonephritis

- **Microtubules**
  - Immunotactoid glomerulonephritis
  - Type 1 cryoglobulinaemic glomerulonephritis

- **Crystals or inclusions**
  - LCPT- light chain proximal tubulopathy (with Franconi syndrome)
  - Proximal tubulopathy without crystals
  - Crystal-storing histiocytosis

- **Organised deposits**
  - Ig-related amyloidosis (AL, AH, AHL)
  - FGN-fibrillary glomerulonephritis

- **Non-organised deposits**
  - MIDD-Monoclonal Ig deposition disease (light or heavy chains or a mixture of both)
  - Proliferative glomerulonephritis with monoclonal Ig deposits
  - Monoclonal Ig-associated C3 glomerulonephritis

MGRS. Pathological characteristics

- AL/AH/AH
- MIDD
- FGN
- ITG
- PGNMI
- Type I cryoglobulinemia with GN
- C3 glomerulopathy with MG

**Light microscopy**

**Immuno fluorescence**

**Electonic microscopy**

https://unckidneycenter.org/kidneyhealthlibrary
MGRS. Treatment options

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Character</th>
<th>Disease character</th>
<th>Severity of kidney insufficiency</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide LoDex, MPT</td>
<td>Clinical trial</td>
<td>MM/with RI</td>
<td>149 patients CrCl &lt; 30 mL/min, 372 pts CrCl ≥ 30, &lt; 50</td>
<td>Dimopoulos et al. [57]</td>
</tr>
<tr>
<td>Bendamustine, P, V</td>
<td>Retrospective</td>
<td>MM with RI</td>
<td>18 eGFR &lt; 35 mL/min (11 pts eGFR 15 mL/min)</td>
<td>Ponisch et al. [58]</td>
</tr>
<tr>
<td>RTX, CYC, Dex</td>
<td>Retrospective</td>
<td>Indolent NHL</td>
<td>14 pts (71.5% with eGFR &lt; 60 mL/min)</td>
<td>Perry et al. [59]</td>
</tr>
<tr>
<td>POM, LoDex</td>
<td>Clinical trial</td>
<td>Relapsed/refractory MM with RI</td>
<td>Three cohorts - 33 eGFR 30–45 mL/min pts, 34 &lt; 30 mL/min eGFR pts, 14 HD pts</td>
<td>Dimopoulos et al. [60]</td>
</tr>
<tr>
<td>RTX</td>
<td>Clinical trial</td>
<td>Membranous nephropathy</td>
<td>eGFR ≥ 40, Proteinuria ≥ 5 g/24 h</td>
<td>Fervenza et al. [61]</td>
</tr>
<tr>
<td>VMP versus MP</td>
<td>Clinical trial</td>
<td>MM with RI</td>
<td>34 pts &lt; 30 mL/min GFR, 193 pts GFR 31–50 mL/min</td>
<td>Dimopoulos et al. [62]</td>
</tr>
<tr>
<td>VMPT–VT versus VMP</td>
<td>Clinical trial</td>
<td>MM with RI</td>
<td>33 pts &lt; 30 mL/min eGFR, 116 pts GFR 31–50 mL/min</td>
<td>Morabito et al. [63]</td>
</tr>
<tr>
<td>Irinotecan Lenalidomide–Dex</td>
<td>Clinical trial</td>
<td>Refractory/refractory MM</td>
<td>10 pts CrCl &lt; 30 mL/min, 169 pts CrCl 30–60 mL/min</td>
<td>Moreau et al. [64]</td>
</tr>
<tr>
<td>Bendamustine monotherapy with RTX</td>
<td>Retrospective</td>
<td>CL1/NHL</td>
<td>104 pts CrCl &lt; 40 mL/min</td>
<td>Nordstrom et al. [65]</td>
</tr>
<tr>
<td>V versus ImiD versus CC</td>
<td>Clinical trial</td>
<td>MM with RI</td>
<td>55 pts CrCl &lt; 30 mL/min (9 dialysis), 41 pts CrCl &gt; 30, &lt; 50 mL/min</td>
<td>Tosi et al. [66]</td>
</tr>
<tr>
<td>T-Dex</td>
<td>Clinical trial</td>
<td>MM with RI prior to ASCT (induction therapy)</td>
<td>16 pts CrCl &lt; 30 mL/min, 15 pts CrCl 30–50 mL/min (total 7 on HD)</td>
<td>Tosi et al. [67]</td>
</tr>
<tr>
<td>L-Dex</td>
<td>Two clinical trials</td>
<td>MM RI versus non-RI</td>
<td>16 pts CrCl &lt; 30 mL/min, CrCl ≥ 30 &lt; 60 in 82 pts</td>
<td>Dimopoulos et al. [68]</td>
</tr>
<tr>
<td>POM−lowDex</td>
<td>Three clinical trials</td>
<td>MM with RI</td>
<td>355 pts with CrCl ≥ 30 and &lt; 60 mL/min (166 pts CrCl ≥ 30 &lt; 45)</td>
<td>Siegel et al. [69]</td>
</tr>
<tr>
<td>Carfilzomib Dex vs Bortezomib Dex</td>
<td>Clinical trial</td>
<td>Relapsed/refractory MM</td>
<td>56 pts CrCl &lt; 30 mL/min, 128 pts CrCl 30–50 mL/min</td>
<td>Dimopoulos et al. [70]</td>
</tr>
</tbody>
</table>

V, bortezomib; M, melphalan; L, lenalidomide; T, thalidomide-dexamethasone; V, bortezomib; CC, conventional chemotherapy; CL1, chronic lymphocytic leukemia; 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.

Clone-directed treatment (if identifiable)
Consider clonal disorder, baseline renal function, performance status, associated comorbidities, risk factors

- **Cytotoxic drugs**
  - Melphalan
  - Cyclophosphamide
  - Bendamustine
  - Dose related toxicity
    - Reduce hypercalcemia, hydrate, withdraw nephrotoxic agents, treat infections

- **Immunomodulatory drugs**
  - Thalidomide
  - Lenalidomide
  - Pomalidomide
  - Neurotoxicity, hyperkalemia
    - Dosage reduction to kidney function

- **Proteasome inhibitors**
  - Bortezomib
  - Carfilzomib
  - Prophylaxis against herpes zoster
    - Peripheral neuropathy, thrombocytopenia, cardiac profile in LCDD. AI. amyloidosis

- **Monoclonal antibodies**
  - Rituximab
  - Daratumumab
  - + Corticosteroids- no dose modification needed
    - Keep in mind patient choice, quality of life, treatment adherence, age and eligibility for novel treatment

Batko K et al. Nephrol Dial Transplant 2018; 1–13
Monoclonal gammopathy of renal significance (MGRS) increases the risk for progression to multiple myeloma: an observational study of 2935 MGUS patients

Normann Steiner, Georg Göbel, Patricia Suchecki, Wolfgang Prokop, Hannes Neuwirt and Eberhard Gunsilius

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 involvement 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.

- Two main pathogenetic mechanism:
  - Intracellular cast formation
  - Direct tubular toxicity by light chain

- Urinary light chain excretion and/or hypercalcemia are the most important factors and are present in 90% of cases.

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

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.

At diagnosis:
- Creatinine, urea, sodium and potassium, calcium and Egrf (MDRD formula)
- Measurement of total protein, electrophoresis and immunofixation of a sample from a 24-hour urine collection. Serum free light chains

If the patient does not have proteinuria, consider alternative diagnosis for RI

Management of Renal Impairment

- Management of renal impairment involves:
  - Supportive care (hydration, urine alkalization, management of hypercalcemia, avoidance of nephrotoxic agents)
  - Mechanical approaches (plasma exchange, conventional hemodialysis, high cut-off hemodialysis)
  - Antimyeloma treatment

- Reversible causes should always be excluded or corrected accordingly

- High-dose chemotherapy is recommended in patients with persistant renal failure, particularly in the subgroup of patients with chemotherapy-sensitive disease

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

<table>
<thead>
<tr>
<th>Response</th>
<th>Baseline eGRF (mL/min/1.73 m²)</th>
<th>Best CrCL response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRenal</td>
<td>&lt;50 mL/min</td>
<td>≥60 mL/min</td>
</tr>
<tr>
<td>PRenal</td>
<td>&lt;15 mL/min</td>
<td>30-59 mL/min</td>
</tr>
<tr>
<td>MRenal</td>
<td>&lt;15 mL/min 15-29 mL/min</td>
<td>15-29 mL/min 30-59 mL/min</td>
</tr>
</tbody>
</table>

eGRF-estimated glomerular filtration rate, based on Modification Diet in Renal equation; CrCL- clearance of creatinine
# Dose modification of anti-myeloma drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>CrCl &gt; 60 mL/min</th>
<th>CrCl, 30-59 mL/min</th>
<th>CrCl, 15-29 mL/min</th>
<th>CrCl &lt; 15 mL/min</th>
<th>On Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>20-40 mg</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Oral melphalan 0.15 to 0.25 mg/kg/d for 4-7 days</td>
<td>Oral melphalan reduced 25% (0.11-0.19 mg/kg/d for 4-7 days)</td>
<td>Oral melphalan reduced 25% (0.0175-0.125 mg/kg/d for 4-7 days).</td>
<td>Oral melphalan reduced 50% (0.0175-0.125 mg/kg/d for 4-7 days).</td>
<td>Oral melphalan reduced 50% (0.0175-0.125 mg/kg/d for 4-7 days).</td>
</tr>
<tr>
<td></td>
<td>High-dose melphalan 200 mg/m²</td>
<td>High-dose melphalan 140 mg/m²</td>
<td>High-dose melphalan 140 mg/m²</td>
<td>High-dose melphalan 140 mg/m²</td>
<td>High-dose melphalan 140 mg/m²</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² on days 1, 4, 8, and 11, or weekly regimens</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>50-200 mg/d</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>25 mg/d</td>
<td>10 mg per d, can be increased to 15 mg/d if no toxicity occurs</td>
<td>15 mg once every other d, can be adjusted to 10 mg/d</td>
<td>5 mg/d</td>
<td>5 mg/d</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>20 mg/m² cycle 1; 27 mg/m² cycle 2 and on</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>According to regimen</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>According to regimen</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
<td>No dose modification needed</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>4 mg/d</td>
<td>No dose modification needed for CrCl ≥ 45 mL/min</td>
<td>Ongoing studies will clarify if modification is needed</td>
<td>Ongoing studies will clarify if modification is needed</td>
<td>Ongoing studies will clarify if modification is needed</td>
</tr>
</tbody>
</table>
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

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Dimopoulos et al. Leukemia 2013;27:423-9
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 ($\geq 2 \times 10^6$ cells/kg body weight) during the first mobilization attempt was 92% (26/28 patients), and for 2 auto-HSCTs ($\geq 4 \times 10^6$ cells/kg) - was 75% (21/28 patients).

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

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.
AMYLOIDOSIS AL. – under diagnosis disorder

Anti-plasma cell treatment
- Dexamethasone
- Alkylators
- Proteasome inhibitors
- IMiDs
- ASCT
- Immunotherapy

Improve organ dysfunction
- Hematologic response ↓ FLC
- Organ response ↓ NT-proBNP, proteinuria, ALP

Prolong survival
- Patients surviving 5 years (%)
  - data from 1065 patients at Pavia ARTC
<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>CR: negative s&amp;u IFE + normal FLCR</td>
</tr>
<tr>
<td></td>
<td>VGPR: dFLC &lt;40 mg/L</td>
</tr>
<tr>
<td></td>
<td>PR: dFLC decrease &gt;50%</td>
</tr>
<tr>
<td></td>
<td>Low-dFLC response: dFLC &lt;10 mg/L</td>
</tr>
<tr>
<td>For dFLC 20-50 mg/L</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>NT-proBNP decrease &gt;30% &amp; &gt;300 ng/L</td>
</tr>
<tr>
<td>Renal</td>
<td>Proteinuria decrease &gt;30%</td>
</tr>
</tbody>
</table>

Cardiac response

- NT-proBNP decrease >30% & >300 ng/L

Renal response

- Proteinuria decrease >30%

Organ response criteria can be graded based on depth of decrease of biomarkers.
Kidney Complications of HSCT
CASE REPORT


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 complications after hematopoietic stem cell transplantation
## Causes of Acute Kidney in HSCT

<table>
<thead>
<tr>
<th>Prerenal</th>
<th>Intrinsic renal</th>
<th>Postrenal</th>
</tr>
</thead>
</table>
| - 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)  | - 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 | - 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) |

Management of AKI

- AKI after HSCT is associated with high mortality, and in those requiring dialysis, mortality may be greater than 70%-80%.
- The incidence of AKI is lower with:
  - autologous compared with allogeneic HSCT
  - nonmyeloablative versus a myeloablative conditioning
  - hepatic veno-occlusive disease

Avoidance of risk factors associated with the development of AKI remains the mainstay of management.

- 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 alkalinization 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.

References:
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

---

## Diagnosis of chronic kidney disease

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

Management 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

Chronic Lymphocytic Leukemia

KDIGO
CLL and renal involvement

- 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)
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, CD49d⁺, CD38⁺, ZAP-70⁺, 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

<table>
<thead>
<tr>
<th>Type of etiology</th>
<th>Potential causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal</td>
<td>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</td>
</tr>
<tr>
<td>Intrinsic renal</td>
<td>Acute tubular necrosis—sepsis, nephrotoxic agents and in some cases hyperviscosity and therapy agents</td>
</tr>
<tr>
<td></td>
<td>Acute interstitial nephritis—infections such as BK or adenovirus, urinary tract infections, medication or chemotherapy induced or malignant cell infiltration</td>
</tr>
<tr>
<td></td>
<td>Glomerular diseases</td>
</tr>
<tr>
<td></td>
<td>TMA</td>
</tr>
<tr>
<td></td>
<td>Obstruction from extrinsic compression of pelvocalcyeal system by tumor or lymph nodes</td>
</tr>
<tr>
<td></td>
<td>TLS—urate acid nephropathy and intratubular obstruction from cancer itself or related to the use of CLL-directed therapy</td>
</tr>
</tbody>
</table>

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

KDIGO
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

KDIGO
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 tubulointerstitial nephropathies.

Median kidney survival was reached only by patients with amyloid-related glomerulopathy (94.2 months).
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\(^2\)
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 dL\(^{-1}\) with 19% of patients presenting with levels >6,000 mg dL\(^{-1}\). 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 (P<0.02).

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

- **coagulation factor Xa (recomb.), inactivated-zhzo** (reversal of anticoag due to life-threatening or uncontrolled bleeding with apixaban or rivaroxaban)
- **avatrombopag** (thrombocytopenia with chronic liver disease, peri-procedural)
- **methoxy PEG-epoetin beta** (anemia due to pediatric CKD)
- **lusutrombopag** (thrombocytopenia with chronic liver disease, peri-procedural)
- **emicizumab-krwh** (prophylaxis in hemophilia A without inhibitors)
- **eltrombopag** (severe aplastic anemia, prev. untreated, in comb. with IST)
- **denosumab** (prevention of skeletal events in MM)
- **fostamatinib** (chronic ITP, prev. treated)
- **filgrastim-jmjb** (biosimilar to Neupogen/Procrit)
- **filgrastim-aafi** (biosimilar to Neulasta)
- **antihemophilic factor** (recomb), PEGylated-aucI (hemophilia A, previously treated)
- **emapalumab-izsg** (primary HLH, refractory or recurrent)

- **arsenic trioxide** (newly diagnosed low-risk APL, in comb. with ATRA)
- **nilotinib** (pediatric CML)
- **brentuximab vedotin** (newly diagnosed St. 3 or 4 cHL, in comb. with chemotherapy)
- **lisocabtumab** (pre-B ALL in CR1 or CR2 with MRD≥0.1%)
- **daratumumab** (newly diagnosed MM, transplant-ineligible, in comb. with VMP)
- **venetoclax** (CLL/SLL, after at least 1 prior therapy)
- **mogamulizumab-kpvc** (R/R mycosis fungoides or Sezary Syndrome)
- **ivosidenib** (R/R AML with IDH1 mutation)
- **moxetumomab pasudotox-tdfk** (R/R hairy cell leukemia, after ≥2 prior therapies)
- **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.)
- **gilbertinib** (FLT-3 mut AML, prev. treated)
- **rituximab-abb** (biosimilar to Rituxan, FL and low-grade lymphoma)

*New Molecular Entity
*Biosimilar

*Refer to US Prescribing Information for details.

*Age ≥ 75y, or with comorbidities that preclude intensive chemo.
VIII Myeloma and Lymphoma International Conference in Kraków

SEPTEMBER 6-7 2019