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Management of Renal Failure in Multiple Myeloma

Daniele Derudas and Claudia Concu

Abstract

Multiple myeloma (MM) is a monoclonal plasma cell neoplasia that commonly involves the kidney. Renal impairment is a serious complication during the course of the disease, and it is associated with increased morbidity and mortality. The most frequent mechanism of injury is represented by the precipitation of monoclonal free light chains (FLCs) in the distal tubule of nephron, defining a dramatic condition known as light chain cast nephropathy (LCCN). A prompt and early identification of the cause of renal disease, particularly in case of acute kidney injury (AKI), is mandatory for its effective management, avoiding the development of chronic kidney disease (CKD). In case of LCCN, in order to achieve renal recovery, it is needed, besides preventive measures, urgent intervention based on vigorous rehydration, correction of precipitating factors and effective anti-plasma cell chemotherapy. Currently, the association of the Proteasome Inhibitor Bortezomib with high-dose of Dexamethasone represents the standard association in newly diagnosed patients. The addition of another drug such as Cyclophosphamide or an Immunomodulatory Drugs may improve FLCs reduction but could be toxic. Interesting is the role of the newest therapeutic agents, particularly anti-CD38 Monoclonal Antibodies, whose efficacy and tolerance have been documented in patients without renal impairment. Despite controversial results from randomized studies, recent data suggest that in patients with LCCN and AKI requiring dialysis the association of systemic therapy with an extra-corporeal approach of FLCs removal, may increase renal response recovery rates. In this chapter, it is summarized physio-pathological basis of MM renal impairment, clinical manifestations, diagnostic procedures, and therapeutic management, included autologous stem cell transplantation.

Keywords: multiple myeloma, renal failure, light chain cast nephropathy, chemotherapy

1. Introduction

Multiple myeloma (MM) is a malignant plasma cell neoplasia with an incidence of about 11 cases per 100,000 patients/year [1]. The clinical manifestations of this tumor are characterized by the presence of one or more signs gathered by the acronym CRAB: Calcium elevated, Renal impairment, Anemia, Bone lesions [2].
The renal failure, as end-stage organ damage related to MM, is defined as a value of serum creatinine of 177 microml/L (>2 mg/dL) or creatinine clearance < 40 mL/min/1.73 m², according with a recent review of diagnostic criteria for the plasma cell dyscrasia [3]. Renal impairment is a frequent complication of MM, that accounts for roughly 40% of newly diagnosis patients (10% requiring dialysis). Notably, this rate increases in the relapsed/refractory population. There is a strong association between the outcome of patients and entity of kidney injury in terms of overall survival and risk of early mortality [4–6]. The MM kidney involvement is mainly due to the toxic activity of monoclonal free light chains (FLCs), which can affect every structure of the nephron, from basement membranes of the glomeruli to renal tubules. The most common cause of acute kidney disease (AKI) is represented by light chain cast nephropathy (LCCN). Less frequent lesions associated with MM are immunoglobulin light chain (AL) amyloidosis, light chain deposition disease (LCDD), and other rarest pathologic entities [7–9]. The diagnosis of the causes of renal impairment is based on blood and urine tests, bone marrow aspirate, and biopsy. The kidney biopsy should be performed only if the cause is not clear and particularly for figuring out lesions different from LCCN as AL amyloidosis, LCDD, or kidney disease not related to MM (i.e. diabetes mellitus or arterial hypertension) [4, 10].

The AKI associated with LCCN is an emergency that can lead rapidly to an end stage renal disease (ESRD) with lifelong dialysis needs. For that reason, it is mandatory on one hand to act on the precipitating factors in order to prevent the onset of AKI, and on the other hand starting an immediate specific therapy with novel agent to achieve a quick reduction of FLCs productions, avoiding the interaction of the toxic proteins with the nephron. Besides the Proteasome Inhibitors, Immunomodulatory Drugs and Steroids, the new Monoclonal Antibodies are becoming an interesting option of therapy for these patients. In the fit population, the autologous hematopoietic stem cells transplantation is feasible, also in presence of dialytic need. The association of mechanical removal of the serum FLCs with the systemic therapy could be useful but is to date under investigation [4, 10, 11]. In this chapter, it is discussed the management of renal impairment associated with symptomatic multiple myeloma a malignant neoplasia. The kidney diseases associated with nonmalignant or premalignant monoclonal gammopathies, defined monoclonal gammopathies of renal significance (MGRS) are not covered here.

2. Renal failure in multiple myeloma

2.1 Epidemiology

Renal impairment is one of the most frequent MM complications and its frequency varies according with the definition used for this condition. Overall, roughly 50% of patients with MM experience acute kidney injury (AKI) or chronic kidney disease (CKD) at some time during the course of their disease. Particularly, between 20 and 50% of newly diagnosed patients experience AKI or CKD during the disease course and a median rate of 1–3% (up to 12%) have a severe acute or chronic renal failure requiring dialysis [12–18]. According to estimated glomerular filtration rate (eGFR), the reported prevalence of AKI was 17% using the current International Myeloma Working Group criterion (<40 mL/min/1.73 m²) [4, 19, 20]. Using the RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease)
criteria, a clinical study showed that the 35% of patients with MM presented AKI [21]. Different kidney pathology lesions were described in patients with MM but only LCCN must be considered a myeloma defining event, because almost always occurs in presence a serum monoclonal (M) spike of >3 g/dL or clonal plasma cells of >10% in bone marrow and others myeloma features [3]. Less frequent myeloma-related renal pathologies are represented by AL amyloidosis. LCDD, proliferative glomerulonephritis with monoclonal immunoglobulin deposits, thrombotic microangiopathy, fibrillar glomerulonephritis, cryoglobulinemia, pyelonephritis, focal segmental glomerulosclerosis, plasma cell infiltration, renal extramedullary hematopoiesis and crystal-line podocytopathy (Table 1) [22].

According with autopsy and kidney biopsy series the LCCN was reported in approximately 30% of patients followed by LCDD and AL amyloidosis between 10 and 20% and 20% respectively [23, 24].

2.2 Pathophysiology

Kidney is a major target for monoclonal immunoglobulins (MIg) produced by MM malignant plasma cells because of its peculiar characteristics:

a. manages the 25% of cardiac output;

b. filters and reabsorbs light chains;

c. presents immunological and immunogenic properties that make it a specific target for immunoglobulins;

d. shows special physiochemical conditions (high concentrations of various solutes, pH, salts concentrations) that allow and facilitate the toxic action of MIg;

e. it is characterized by the presence of specific receptors for immunoglobulins in tubular cells.

<table>
<thead>
<tr>
<th></th>
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<th>LC preference</th>
<th>MGRS</th>
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Abbreviations: AL, immunoglobulin light chain; CLL, chronic lymphocytic leukemia; ITG, immunotactoid glomerulonephritis; LCFN, light-chain Fanconi syndrome; MCN, myeloma cast nephropathy; MG, monoclonal gammopathy; MIDD, monoclonal immunoglobulin deposition disease; MM, multiple myeloma; MPGN, membranoproliferative glomerulonephritis; WM, Waldenström’s macroglobulinemia.

Table 1. From myeloma-related kidney disease [22].
The kidney lesions in MM patients are caused mainly by the production of monoclonal immunoglobulins or their fragments (light or heavy chains) by clonal plasma cells that carry out toxic effects on different nephron's structures.

Rarely the kidney injuries are not related to MIg activity. Following the most frequent:

- Expansion of bladder or ureteral extramedullary plasmocytoma with obstruction of the urinary tract and renal parenchymal plasma cell infiltration, that are uncommon and rarely represent the unique cause of renal failure [25–27];
- Hypercalcemia, that represents a complication of symptomatic MM with a prevalence is 2- to 3-fold higher (25–45%) in patients with high levels of serum creatinine. Hypercalcemia may cause prerenal AKI because of dehydration and vasoconstriction, and it could act as precipitating factor of LCCN [28–30].
- Infections, often associated with AKI [31].
- Dehydration and nephrotoxic agent administration, such nonsteroidal anti-inflammatory drugs, diuretics, and renin-angiotensin-aldosterone system blockers, that may be involved in the development of prerenal AKI and the formation of light chains (LC) casts.
- Specific treatments of MM, frequently associated to development of AKI [32–34]:
  1. Bisphosphonates, especially Zoledronic Acid, are widely used to treat hypercalcemia and MM bone disease and have been involved in the development of acute tubular necrosis [35];
  2. Renal thrombotic microangiopathy is a rare cause of myeloma-associated renal injury and could be a potential complication of proteasome inhibitors, particularly Carfilzomib [36, 37];
  3. Lenalidomide has been described as a cause of acute reversible non-LC–related Fanconi syndrome [38, 39];
  4. Tumor lysis syndrome, very unusual in the past, is increasingly described at the start of chemotherapy because of the high efficacy of the novel agents, particularly in patients with altered kidney function treated with Proteasome Inhibitor–based regimens [40].

The main mechanism of kidney injury related to MIg is deposition or precipitation of the complete MIg or their fragment, usually the serum monoclonal FLCs. Physicochemical characteristics of MIg, particularly of the variable domain, define the localization and pattern of kidney lesions [41]. Two-thirds of AL amyloidosis are due to lambda light chains (LC), while nearly three-quarters of LCDD and light chain proximal tubulopathy is caused by a monoclonal kappa LC [42–45]. Specific lambda or kappa subtypes underlie for a large proportion of these kidney diseases: for example,
lambda VI accounts for more than 40% of AL amyloidosis, while kappa I and IV are specific for LCDD [46, 47].

In presence of high tumor mass, with a production of a huge quantity of FLCs, the characteristic kidney lesions are represented by the LCCN (Figure 1). As mentioned above, the Mlg related renal complications not associated with the tumor mass are more frequently diagnosed in patients with MGRS and rarely cause a severe AKI. The LCCN occurs when a large amount of FLCs are produced by monoclonal plasm cells (rarely by B clonal lymphoid cells as in course of Waldenström Disease or Chronic Lymphoid Leukemia). Physiologically our organism produces roughly 500 mg of polyclonal free light chains, that circulate as monomers of 22 kDa but, particularly the lambda, they may assemble as dimers of 45 kDa, with an intravascular distribution of 15%. After glomerular filtration, the serum FLCs are reabsorbed by proximal tubular cells through a mechanism of endocytosis associated to tandem receptors cubilin and megalin and degraded in the cellular lysosomes. For this reason, a low amount only of FLCs are detected in the final urine (<30 mg/day) [48–52]. In case of a massive production of FLCs, the resorption capacity can be exceeded, with a consequent high concentration of protein into the lumen of the loop of Henle. Moreover, the increased reabsorption can damage proximal tubular cells causing the reduction of their catalytic capacities. FLCs reach the distal part of loop of Henle precipitate in the tubules as a result of binding with a protein named uromodulin (formerly called Tamm–Horsfall

![Image 1](https://example.com/image1.png)

**Figure 1.** Images of LCCN: upper right and left Hematoxilin-Eosin staining; lower right k stain (left picture) and lambda stain (right picture); lower left PAS stain.
mucoprotein, or THMP), normally secreted by cells of the thick ascending limb of the loop of Henle. The uromodulin constitutes the matrix of all urinary casts. This interaction occurs between LC CDR3 hypervariable region that binds to a 9-amino acid sequence of uromodulin [53–56]. Another factor that can favor the uromodulin binding and the predisposition to light chain cast nephropathy may be the isoelectric point (pI) of the involved FLCs. Their pI > 5.1 (that is above the tubular fluid pH in the distal nephron) will have a positive charge, which may promote binding via charge interaction to anionic uromodulin (THMP; pI = 3.2) [57–59]. The binding and precipitation as co-aggregates lead to the formation of obstructing, dense, intratubular casts in the distal and collecting tubules (rarely in proximal tubules and glomerulus). Consequently, it starts a process characterized by a giant cell reaction and interstitial inflammation and fibrosis. The obstructive activity of casts causes decreasing of glomerular filtration rate, tubular rupture, extravasation of monoclonal light chain into the interstitium, further promoting the interstitial inflammatory process. The inflammation could in turn develop an irreversible fibrosis in absence of immediate therapeutic intervention [56, 60, 61]. It is under investigation the role of crystalline organization of LC cast in triggering distal tubulointerstitial inflammation through NOD-like receptor family receptor, pyrin domain containing 3 (NLRP3) inflammasome and interleukin-1beta production [62].

Different factors may facilitate and promote intratubular cast formation:

- volume depletion [63], by slowing flow within the tubules, that can promote the formation of large aggregates;
- metabolic acidosis, because of low urinary pH, loop diuretics, by increasing luminal sodium chloride;
- increased urinary calcium and hypercalcemia, mainly because of consequent volume depletion and renal vasoconstriction;
- radioccontrast media (particularly high-osmolar agents), which may interact with LC;
- nonsteroidal anti-inflammatory drugs (NSAIDs), which may precipitate acute kidney injury in 7–30% of MM patients, particularly in case of LCCN [58, 59, 64–66].

Furthermore, the excessive endocytosis of monoclonal FLCs in the proximal tubules leads to generation of hydrogen peroxide and redox signaling with activation of several pro-inflammatory pathways as mitogen-activated protein kinases ERK1/2, JNK, p38, and nuclear factor-kB. This process is in turn associated to the production of inflammatory cytokines such as interleukin-6 and monocyte chemottractant protein-1 (MCP-1) and the upregulation of apoptotic pathways. Recently it is demonstrated that activation of signal transducer and activator of transcription 1 (STAT1) is the main pro-inflammatory mechanism caused by FLCs reabsorption, leading to the production of interleukin-1b and of the pro-fibrotic agent transforming growth factor b. These molecular processes develop as the consequence of the generation of hydrogen peroxide by the FLCs, which appears to depend on the molecular characteristics of the variable domain [67–70]. This inflammatory process leads to an irreversible fibrotic reaction. Both affinity and concentration of the FLCs determine the pathogenesis of LCCN. In fact, the probability of cast formation presents a linear association
with the serum level of the monoclonal FLCs and the amount of its urinary excretion. LCCN rarely occurs in presence of a serum concentration of <500 mg/l. The risk varies also with the molecular characteristics of each individual FLC. Notably, neither kappa or lambda isotype nor variability subgroups, which are independent of CDR3 molecular sequence, correlate with the risk of LCCN [71, 72].

2.3 Clinical manifestations and diagnosis

A broad spectrum of clinical manifestations can characterize the MM renal complications, from dramatic cases of AKI to slower onset of CKD. These different clinical features can help to define the best diagnosis according with the hypothetical causes, avoiding potentially dangerous intervention as the kidney biopsy.

In case of AKI or subacute renal injury most of patients are likely to have a LCCN, although other causes can include hypercalcemia, nephrotoxic agents like NSAIDs, Bisphosphonates and antmyeloma agents (Lenalidomide and Carfilzomib) and, rarely, radiocontrast agents. The LCCN typically progresses rapidly, with an increase in creatinine that is observed over 1–3 months. For this reason, it should be suspected in all patients who are >40 years of age with an unexplained documented creatinine increase over a period of less than 6 months and a bland urine sediment. In fact, it is very uncommon that patients with untreated LCCN could show stable kidney function beyond 6 months.

Only in rare cases patients affected by MM develop a subacute or acute kidney disease due to tubulointerstitial nephritis, associated with LC deposition in the tubular basement membrane, plasma cell infiltration, thrombotic microangiopathy (associated to Carfilzomib or Bortezomib treatment), hyper-viscosity syndrome (more frequent in case of Waldenström Disease), through impairment of microcirculation and crystal-storing histiocytosis.

In case of gradual or progressive kidney impairment, with an increase of serum creatinine over 6 months or more, is unlikely that a LCCN could represent the underlying cause of renal impairment, unless the patients experienced different episodes of light chain cast nephropathy without a complete renal recovery leading to CKD. Many forms of kidney complications in MM patients can show, as clinical onset, the presence of some degree of proteinuria, frequently with a nephrotic syndrome, and albuminuria as principal feature. This presentation can help to differentiate the cause of renal complication because the LCCN presents, other that AKI, a proteinuria that is predominantly (90%) composed of monoclonal light chains (Bence Jones protein) and slight amount of albuminuria. The presence of albuminuria and a massive proteinuria is characteristic of an underlying AL amyloidosis and other Mlg related glomerular disorders. The MIDD, particularly in case of LCDD, can show both albuminuria from glomerular damage and light chain excretion with associated cast nephropathy. Other diseases associated with a CKD and predominant albuminuria or nephrotic syndrome are immunotactoid glomerulopathy, monoclonal cryoglobulinemic glomerulonephritis, proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID), or C3 glomerulopathy.

The diagnostic process in patients with a kidney disease and a malignant monoclonal gammopathy depends on clinical presentation through a multistep approach:

- definition of the role of the monoclonal in the pathogenesis of the kidney disease in order to avoid inappropriate toxic treatment;
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- characterization of the pathologic lesions in order to define the more appropriate treatment strategy;
- decision about the opportunity of performing the kidney biopsy.

First of all, it is important to underline that the renal failure as end-organ damage event for symptomatic MM is defined by a value of serum creatinine of 177 microml/L (>2 mg/dL) or creatinine clearance (CrCl) of <40 mL/min/1.73 m², according with a recent review of diagnostic criteria for the plasma cells dyscrasia by the International Myeloma Working Group [3]. For evaluation of CrCl, eGFR, assessed by either the Modification of Diet in Renal Disease (MDRD) formula or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, seems to give accurate results in this MM population. However, CKD-EPI seems to more accurately reflect GFR than does MDRD, mostly in higher levels of GFR [73–76]. Another method that can used to define the renal function is an equation on the basis of both serum creatinine and cystatin-C (CysC). This method is very accurate but it is not easily applicable in all the Centers. β2-microglobulin is another widely used marker that reflects both renal function and tumor burden in patients with MM and for this reason is included in the revised International Staging System [77–79]. Despite the above consideration, eGFR should be used only in patients with stable renal function. In cases of AKI, RIFLE (Risk, Injury, Failure, Loss and End-Stage Kidney Disease) criteria and AKIN (Acute Kidney Injury Network) classification would seem to be more sensitive for the determination and evaluation of this condition [80, 81].

In order to define the best diagnostic strategy, it is mandatory to consider some critical points:

- **LCCN** is still a frequent mode of discovery of a previously unknown MM. In case of AKI of unknown origin, particularly in the elderly in absence of MM features, it is crucial to consider LCCN. Initial diagnostic workup should include serum and urinary protein electrophoresis and measurement of FLC’s, Nephelometric assays such as the Freelite® test (Binding Site, Birmingham, UK) represent a reliable and invaluable tool for the diagnosis and management of LCCN. The presence of a monoclonal spike or hypogammaglobulinemia, a urinary albumin/protein ratio of <10%, and/or a significantly increased level of one FLCs isotype with an abnormal kappa/lambda ratio should prompt to perform a bone marrow examination to define the diagnosis of MM through the evaluation of monoclonal plasma cells;

- in patients with a known diagnosis of Multiple Myeloma, smoldering Multiple Myeloma, or high-risk monoclonal gammopathy of undetermined significance (MGUS) and a unexplained reduced kidney function, there are some mandatory tests as assessment of volume and acid-base status, urinalysis with sediment examination, measurement of serum calcium (corrected for serum albumin concentration), serum uric acid and serum phosphorus, serum protein electrophoresis and immunofixation, serum FLCs assay, 24-h urine electrophoresis with immunofixation, 24-h albuminuria, urinary albumin/total protein ratio < 10% and urinary albumin/creatinine <30 mg/mmol, kidney ultrasound. The urinary FLCs assays, should not be performed because are not helpful in the evaluation of acute or subacute kidney injury in MM patients. It is also important to rule out possible nephrotoxic agent exposure;
• if the diagnostic approach reveals an obstructive uropathy as hydronephrosis, hypercalcemia, hypovolemia, or urate nephropathy, these conditions should be treated or corrected;

• in patients without reversible cause ok AKI or in absence of correction of these disorders a diagnosis of LCCN is highly suspected in case of a serum FLCs concentration >500–1500 mg/l, a predominance of monoclonal light chains in 24-h protein electrophoresis with immunofixation, a bland urine sediment, low amount of urine albuminuria or urinary albumin/total protein ratio < 10% and urinary albumin/creatinine <30 mg/mmol. In this case, the kidney biopsy is not mandatory [4];

• in case of abnormal urine sediment, a serum FLC level < 500 mg/L or a predominance of albumin by 24-h protein electrophoresis with immunofixation or urinary albumin/protein ratio of >10% (or urinary albumin/creatinine >30 mg/mmol) the kidney biopsy is mandatory to exclude a diagnosis of AL amyloidosis, MIDD or Mlgl related nephropathy. If AL amyloidosis is suspected, a subcutaneous fat aspirate in positive for Rosso Congo stain 70% of patients [82]; if the fat biopsy is negative, a renal biopsy is required. Indication for a kidney biopsy should take into account either renal and extrarenal features of monoclonal gammopathy, and also alternative or associated causes of renal disease such as diabetes or atherosclerosis [4]. In fact, in >15% of MM patients with renal impairment a renal biopsy indicated that kidney failure is not associated with the plasma cell dyscrasia: in particularly the main causes were arterio-nephrosclerosis (6%), diabetic glomerulosclerosis (5%), post-infectious glomerulonephritis (2%), or even smoking-related glomerulopathy (0.5%) [33].

Recently it is demonstrated that kidney biopsy may be helpful in the prognostication of LCCN. A retrospective study of patients with MM and LCCN (47% required dialysis at presentation) showed that the number of casts per millimeter square in the cortex and, to a lesser extent, the degree of interstitial fibrosis/tubular atrophy were independent prognostic factors of renal outcome. Another relevant data from the study is that the extent of cast formation could not be predicted by initial clinical data and particularly the level of the involved FLCs [56, 83].

Particular clinical cases are represented by the patients with electrolyte abnormalities as the onset of renal impairment, besides the frequent manifestations as hypercalcemia. Normoglycemic glycosuria, aminoaciduria, proximal renal tubular acidosis, hypouricemia, and phosphate wasting are signs of tubular dysfunction [84]. In these cases, light chain proximal tubulopathy could be a rare complication of MM with clinical manifestations of Fanconi syndrome [85].

Furthermore, pseudohyponatremia can occur in MM patients with a severe hyperproteidemia.

3. Management of renal failure

3.1 Prevention and early management

The AKI associated to MM is a medical emergency. The diagnosis must be performed as fast as possible. The supportive care and anti-myeloma treatment should
be started immediately in order to recovery the renal function and, in case of dialysis, make the patients independent from that.

The first step in the management of renal failure is to set preventive measures, particularly in MM patients with high risk of LCCN (i.e., FLCs concentration \( > 1500 \) mg/L) through different actions:

- avoiding of NSAIDS and radiological exams with radiocontrast media
- a careful administration of bisphosphonates
- prompt treatment of infections with non-nephrotoxic antibiotics.

The early therapeutic approach aims to correct the precipitating factors and stabilize hemodynamic conditions, decreasing the tubular precipitation of FLCs with uromodulin. The treatment approach consists in the following procedures [11, 85–87]:

- vigorous rehydration with saline fluids (24-h 4–5 L) in order to achieve a high urine flow. The hydration must be managed carefully in case of oliguric AKI or heart failure. It is necessary to limit the afflux of sodium and chloride in distal tubules using half normal saline fluid. In case of volume depletion, it should be used isotonic fluids for initial volume replacement. In the absence of volume depletion or following, one-half isotonic saline at an initial rate of 150 mL/h, adjusted to maintain the urine output at approximately 100–150 mL/h (approximately 3 L/day), should be administrated. There is no uniform agreement about the administration of isotonic sodium bicarbonate aiming to achieve a urine pH \( > 7 \), particularly in presence of acidic urine pH, that can facilitate cast formation. This approach must be avoided in patients with hypercalcemia because of the risk of calcium phosphate precipitation;

- hypercalcemia must be treated with rehydration and intravenous administration of Bisphosphonate with a dosage and infusion adapted with the eGFR. Among bisphosphonate the Pamidronate is associated lower risk of renal complications than Zoledronic Acid. Considering the pharmacodynamics properties, the anti-receptor activator of nuclear-factor kappa B ligand monoclonal antibody Denosumab represents the best option that may be proposed because this drug does not need dose adjustment according with the eGFR [35, 88];

- the loop diuretics should be used only in presence of severe fluid overload since there is some concern that they may facilitate cast formation;

- treatment with renin-angiotensin-aldosterone system blockers and NSAIDs must be discontinued;

- in case of infections a prompt and vigorous antibiotics therapy with nephrotoxic antibiotics must be started as quickly as possible;

- hyperuricemia, if present, should be treated;

- hyper-viscosity is a rare cause of AKI among MM patients and should be treated with plasmapheresis and appropriate chemotherapy;
conventional dialysis should be initiated for the usual indications (i.e. fluid overload, hyperkalemia, and uremia) and it is not useful for the removal of free light chains. In this MM populations, hemodialysis is the preferred modality and peritoneal dialysis is an option for patients who develop end-stage kidney disease (ESKD) and require chronic dialysis.

3.2 Medical therapy

The goal of any therapy for MM patients with renal impairment will involve either reducing the exposure of the kidney to FLCs either inhibiting the interaction of FLCs with uromodulin. Different studies demonstrated that:

- the recovery of renal function is associated to a reduction in serum FLCs concentration > 50% [89];

- the relationship between the probability of renal recovery and the degree of an early FLCs reduction in myeloma kidney is linear [90];

- besides the degree of reduction, also the speed at which the FLCs reduction occurs is important to reach a recovery of kidney function. It was described that patients who achieved a sustained reduction within 21 days were significantly more likely to recover renal function than those who did not achieve a reduction [90]. It is to date controversial if the FLCs assays can replace 24 h urine collections for monitoring of disease response.

To achieve a rapid reduction of the circulating concentrations of pathological FLCs in patients with LCCN, the production rate of monoclonal proteins by the plasma cell clone must first be quickly decreased for a sustained time. Antimyeloma therapy is the mainstay of treatment for patients with MM associated-AKI. The choice of optimal drug class and therapeutic associations must follow the following principles:

- novel agents in association with Dexamethasone will obtain the fastest and deepest responses;

- the drugs should show safety and efficacy in renal failure, including dialysis;

- the medical therapy should not impair collection of peripheral hemopoietic stem cells if there is any possibility of a future autologous hemopoietic stem cells transplant (ASCT);

- the ASCT should be considered a treatment option also in dialysis-dependent patients in transplant-eligible population.

To date, the MM treatment consists in different classes of drugs administrated in association with Steroids either in transplant-eligible either non-transplant eligible population [4]. The main classes used in clinical practice are represented by Proteasome-Inhibitors (Bortezomib, Carfilzomib, Ixazomib), Immunomodulatory Drugs (Thalidomide, Lenalidomide, Pomalidomide), Monoclonal Antibodies (Elotuzumab, Daratumumab, Isatuximab). The newest class of drugs are the Immunoconjugates anti-BCMA (Belantamab-mafodotin), Selective Inhibitor of
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Nuclear Export (SINE) (Selinexor) and Cellular Therapies as bi-specific antibodies and CAR-T cells (both used in trial), Melfuflen, Iberdomide, Venetoclax. Conventional chemotherapy drugs usually used in association with novel drugs in the treatment of MM or for hemopoietic stem cells mobilization and ASCT conditioning are represented by Cyclophosphamide and Melphalan.

Unfortunately, there are little evidences about the efficacy and safety of these new agents and their association in patients with acute kidney impairment included in the clinical trials because, the threshold of renal function for inclusion is generally an eGFR ≥60 ml/min. Another difficulty in the treatment of patients with Myeloma related-AKI is the need of a dose adjustment according with kidney function because of renal extraction and/or metabolism (Table 2).

- High-dose Dexamethasone is a key component in the treatment of LCCN because of its potent cytotoxic and anti-inflammatory activity properties diagnosis of AKI and can represent a bridge therapy before starting the anti-myeloma treatment [91, 92].

- Conventional anti-myeloma agents most used in treatment of MM are Cyclophosphamide and Melphalan. Cyclophosphamide is preferred to

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<td>20-27 mg/m²</td>
<td>No modification</td>
<td>No modification</td>
<td>No modification</td>
<td>No modification</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>No</td>
<td>4 mg/die</td>
<td>No modification</td>
<td>3 mg/die</td>
<td>3 mg/die</td>
<td></td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>No</td>
<td>10 mg/kg</td>
<td>No modification</td>
<td>No modification</td>
<td>No modification</td>
<td>No modification</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>No</td>
<td>16 mg/kg</td>
<td>No modification</td>
<td>No modification</td>
<td>No modification</td>
<td>No modification</td>
</tr>
<tr>
<td>Isatuximab</td>
<td>No</td>
<td>10 mg/kg</td>
<td>No modification</td>
<td>No modification</td>
<td>No modification</td>
<td>No modification</td>
</tr>
<tr>
<td>Belantamab mafodotin</td>
<td>No</td>
<td>2.5 mg/kg</td>
<td>No modification</td>
<td>No data</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Selinexor</td>
<td>No</td>
<td>160 mg</td>
<td>No modification</td>
<td>No modification</td>
<td>No modification</td>
<td>No data</td>
</tr>
</tbody>
</table>

Table 2. Dose-adjustment of anti-myeloma drugs according with creatinine clearance.
Melphalan, which is eliminated by the kidneys, because it does not need a dose adjustment according to eGFR and is frequently associated to novel agents and Steroids. Melphalan, in combination or as conditioning regimen, needs adequate dose reductions according with renal failure to avoid severe cytopenias and non-hematologic toxicities. The cardiac toxicity of Doxorubicin limits its indications in this setting of patients.

- The Proteasome Inhibitors (PIs) are a class of drugs which primary mechanism of action is the inhibition of catalytically active subunits of proteasome, a large multi-catalytic protein complex that degrades many cellular proteins. Besides anti-apoptotic activity, PIs also act as immunosuppressants and inhibit bone resorption. Currently, three PIs, Bortezomib, Carfilzomib, and Ixazomib, are used for the MM treatment, mainly in association with other agents, either in MM newly diagnosed (NDMM) patients either in MM relapsed/refractory (RRMM) population.

Bortezomib is a reversible PI, administered in intravenous or subcutaneous way, licensed for NDMM and RRMM patients in association with novel agents and conventional chemotherapy. It represents the mainstay in the treatment of patients with MM-related nephropathy, particularly LCCN. The rationale for use of Bortezomib in this setting lies in:

1. the short time of a sustained response;
2. high overall and complete response in combination regimens;
3. good tolerability with a similar toxicity in patients with a renal impairment;
4. half-time life independent of renal clearance,
5. direct anti-inflammation activity in myeloma kidney disease.

Particularly the inhibition of nuclear factor κB (NFkB), which activation is involved in the development of irreversible tubulointerstitial fibrosis, is likely to contribute to improved renal outcomes through prevention of progressive inflammation and fibrosis. Reversal of renal impairment has been observed in several studies of patients with MM-related renal impairment, including some patients who became independent of dialysis after treatment with Bortezomib. Remarkably, renal responses in patients treated with Bortezomib-based schedules tend to occur rapidly, usually within the initial two to three cycles of treatment and this response is consistent and sustained. Bortezomib should be administered after the dialysis procedures, because they may reduce the drug concentrations [93–96].

Carfilzomib is a tetrapeptide epoxyketone PI that irreversibly binds to the β5-proteasome subunit and the LMP7 (iβ5) subunit of the immunoproteasome with greater affinity than Bortezomib, characterized by an intravenous administration. It is indicated for the treatment of RRMM patients mainly in association with Lenalidomide and Dexamethasone or only Dexamethasone with different dosages. Based on the pharmacokinetic data, no adjustment of the initial dose is recommended for patients with mild, moderate, or severe baseline
renal impairment, or in case of chronic dialysis therapy. Particularly, the data from real-word evaluations and clinical trials suggest that Kd56 (Carfilzomib 56 mg/2 plus Dexamethasone) has a favorable benefit-risk profile and should be considered an in patients with RRMM, regardless of kidney function. A warning is represented by its potential cardiac and some rare complications as thrombotic microangiopathy, that could preclude its use as a standard for LCCN [97–100].

Ixazomib is an oral, highly selective, and reversible PI that binds and inhibits the chymotrypsin-like activity of the β5-subunit of 20S proteasome, which leads to the disruption of cellular regulatory mechanisms, which in turn inhibits cell growth and survival pathways leading to the induction of apoptosis. According to the pharmacokinetics and safety results, a reduced Ixazomib dose of 3 mg (on days 1, 8, and 15 of the 28-day cycles) is recommended in MM patients with severe renal insufficiency or ESRD requiring hemodialysis, compared to the recommended standard 4 mg dose for patients with normal renal function or mild or moderate RI. The drug can be administered regardless of the time of dialysis in patients requiring hemodialysis with ESRD [101, 102].

The Immunomodulatory Drugs (IMiDs) are oral agents approved for the treatment of NDMM and RRMM populations in association with other novel drugs or only with Dexamethasone. IMiDs have been reported to have a multitude of activities, including anti-angiogenic, cytotoxic, and immunomodulatory: Recently the recent discoveries that the IMiDs bind to cereblon and thus regulate the ubiquitination of key transcription factors including IKZF1 and IKZF3, have provided greater insight about their mechanism of action. To date, the three IMiDs used for the treatment of MM patients include Thalidomide, Lenalidomide and Pomalidomide. Iberdomide is a novel, orally administered and highly effective cereblon-modulator, currently under investigation as promising novel agent for the treatment of heavily pretreated RRMM patients.

Thalidomide is not excreted by the kidneys and can be used even in patients requiring chronic dialysis without dose adjustment. However, some toxic effects, such as unexplained hyperkalemia, can lead to a careful use in patients receiving dialysis. Other warning is represented by the thrombogenic properties, with the need of prophylactic anti-coagulation, and poor tolerability, because of neurotoxicity, particularly in elderly patients. Besides these side effects, Thalidomide has shown a significant improvement of renal function in a high proportion of patients with MM presenting renal insufficiency and can represent an option in association with Bortezomib, Dexamethasone, and Daratumumab for the NDMM patients transplant-eligible as induction and consolidation therapy [103–105].

Lenalidomide is a second-generation IMiD that represents the backbone in different associations for the treatment of NDMM, either eligible and non-eligible transplant patients, and RRMM populations. Because of primary excretion by the kidney, a dose-adjusted treatment according to renal function is mandatory for patients with MM and renal impairment. The main toxicities observed in patients with renal impairment is represented by thrombocytopenia. The data from clinical trials and real-word experiences demonstrated the efficacy of this drugs in achieving a renal recovery but only if dose modification is provided [106–108].
Pomalidomide is the third generation IMiD, indicated for the treatment in different combinations for RRMM population. Before its excretion, Pomalidomide is largely metabolized by CYP450 in the liver, and only 2% of the drug that has not been metabolized is excreted in urine. This agent does not need a dose modification according to renal function and this property makes Pomalidomide is highly attractive for the therapy of population with MM-related nephropathy. Data from clinical trials, in association with Dexamethasone or with other agents (i.e. Isatuximab, Bortezomib), showed benefit from a therapy with Pomalidomide with an acceptable safety profile also in population with severe kidney impairment [109, 110].

- Monoclonal antibodies (MoAbs) currently used for the treatment of MM patients are represented by anti-CD38 MoAbs Daratumumab and Isatuximab and anti-CS1 MoAb Elotuzumab.

- Daratumumab is a human IgG1κ MoAb that binds to a unique CD38 epitope leading to a killing of Myeloma cells shortly through a variety of mechanisms, including complement-mediated cytotoxicity, antibody-dependent cytotoxicity, and antibody-dependent phagocytosis. An immunomodulatory action has been demonstrated as well. It represents an important agent in combination for the treatment of NDMM and RRMM. Recently, besides the intravenous administration, a subcutaneous formulation has been approved for the MM therapy. The data from different studies demonstrated a rapid hematological response as well as a strong renal response also in patients with a severe renal impairment and dialysis need. The safety profile was acceptable in this population. No dose modification is needed according to renal function [111–114].

- Isatuximab is a IgG1 MoAb that targets a specific epitope on CD38 using different mechanisms of action against Multiple Myeloma. Sub-analysis of phase III studies, in association with Pomalidomide and Dexamethasone and Carfilzomib and Dexamethasone in a RRMM population, shown clinical effectiveness with a manageable safety profile in patients with renal insufficiency. Like Daratumumab, it is not necessary a dose modification on kidney impairment [115].

- Elotuzumab is a humanized immune-stimulatory IgG1 MoAb that targets the signaling lymphocyte activation molecule F7 (SLAMF7, also referred to as CS1), a glycoprotein that is expressed in monoclonal plasma cells and natural killer cells but not in normal tissue. The associations with Lenalidomide-Dexamethasone or Pomalidomide-Dexamethasone are licensed for the therapy of RRMM patients. No dose adjustment is mandatory for this MoAb in case of renal impairment of any degree. The combinations of Elotuzumab in phase III studies were well-tolerated by MM patients with renal impairment, including patients with terminal renal failure, and effective [116, 117].

- The first immunoconjugate used outside clinical trials is the Belantamab mafodotin, first-in-class anti-BCMA immunoconjugate with a humanized IgG1 anti-BCMA monoclonal antibody conjugated by a protease-resistant maleimidocaproyl linker to a microtubule-disrupting agent, monomethyl auristatin F (MMAF). In patients with mild or moderate renal impairment
(eGFR >30 mL/min) no dose adjustment is necessary. Currently, insufficient data are available for patients with severe renal impairment to support any dose recommendation. Clinical trials including patients with various degrees of renal impairment are ongoing to address this issue [118, 119].

- **Selinexor** is an oral, reversible, covalent Inhibitor of XPO1-mediated Nuclear Export. The administration of Selinexor leads to the nuclear retention of TSPs (p53, Rb, FOXO1, survivin and IκB) and blocks the export of eIF4E-bound oncoprotein mRNAs (c-Myc, cyclin D1, Bcl-6, Mdm2 and Pim), resulting in growth inhibition and apoptosis. No adjustment of the Selinexor dose is necessary in patients with mild, moderate, or severe renal impairment. No data are available for patients ESRD or hemodialysis [120, 121].

- No data are available about dose modifications of promising and effective treatment as CAR-T cells [122–124] therapy, bi-specific antibodies [125–127], and other agents as Venetoclax [128–130], Melfuflen [131–133], and Iberdomide [134, 135] in case of renal impairment, and particularly dialysis-dependence.

According to the clinical data and the international guidelines for the management in patients with MM-related kidney impairment, and particularly in presence of LCCN, Bortezomib-based treatment is the gold standard in term of efficacy in hematologic and renal response and safety profile. The best agents to be associated to Bortezomib and high-dose of Dexamethasone is still under debate, because of lack of clinical trial. Cyclophosphamide and Thalidomide can be optimal options for efficacy, safety, pharmacokinetic characteristics without impact on peripheral stem cells collection for the transplant-eligible patients. In this setting, the introduction of Daratumumab could increase the efficacy in terms of hematological and renal responses without increased toxicity. The NDMM non-transplant eligible population can benefit from the association of Daratumumab with Bortezomib-Melphalan and Prednisone. Lenalidomide could be used in transplant-eligible and non-transplant eligible populations but is more difficult to manage because the need of dose adjustment on renal function and its myelotoxicity.

Different regimens can be exploited in the treatment of RRMM patients. It is mandatory to consider not only the efficacy but also the need of adjustment of dosage according to renal failure in order to achieve the best results with an acceptable safety profile. This is more and more important in the heavily pretreated patients, where the comorbidities and side effects remarkably impact on the outcomes and quality of life. Furthermore, the RRMM patients present a higher risk of renal impairment with a lower probability of recovery. Monoclonal Antibodies, Pomalidomide, and Carfilzomib (with a careful assessment for cardiologic side effects) represent the best options in different associations.

Despite the availability and the efficacy of novel agents, high-dose therapy with hemopoietic peripheral stem cells transplantation (ASCT) represents currently the standard of care for NDMM defined transplant-eligible for age (<70 years) and fitness, according to comorbidity and performance status [136–138]. In recent years, several reports have shown that the use of ASCT is safe and effective in MM patients with renal impairment. However, there still have some considerable variabilities in reported survival outcomes and renal recovery from the limited literature because the available studies (cohort studies, retrospective studies, and case report) are
characterized by different priorities in clinical and renal response. The cohort analysis seemed to take more attention to the clinical response. On the other side, the retrospective studies were more interested to renal function change [139]. One of major issue has been represented by the dosage of Melphalan as conditioning: it is demonstrated a large interpatient variability in melphalan exposure for the patients undergoing ASCT [136]. However, the use of higher dosage of Melphalan has been shown to improve survival with an increased but acceptable transplant-related toxicities [136, 140]. According to the reports of meta-analysis and the data from the literature it is possible to conclude that:

- renal impairment and dialysis should not be considered an exclusion criterion for the eligibility to ASCT;
- ASCT could be a feasible therapy and can lead to similar remission outcomes to those without advanced renal failure;
- patients with MM-related kidney disease after ASCT have a good overall results and improvement of renal function but present a low survival rate (rate of mortality from 4% to 29%) [4];
- renal impairment does not affect the quality of stem cell collection or engraftment [4];
- the clinical responses of the conditioning Melphalan therapy in patients with renal failure remains controversial as well as the best dosage in this population (140–200 mg/m²) [139];
- In this population, it is advisable to reduce the dose of Melphalan by 25% in case of creatinine clearance between 10 and 45 ml/min and by 15% in patients with a creatinine clearance between 46 and 60 ml/min: particularly full Melphalan dose of 200 mg/m² is safe and effective in case of creatinine clearance between 30 and 60 ml/min [141, 142];
- ASCT can lead to dialysis-independence (up to 29% of patients) [143]. This population needs careful evaluation prior to ASCT by a multidisciplinary team and dose adjustment for all drugs in order to avoid serious toxicities should be taken into consideration [144].

Following are reported some practice recommendations for management of transplant-eligible patients with MM-related kidney disease:

- an induction Bortezomib-based (in association with Cyclophosphamide or Thalidomide and, if possible, Daratumumab) is preferable for short time of response and absence of myelotoxicity and no need of dose adjustment on renal function. In case of a combination with Lenalidomide is mandatory to reduce the dosage according with renal function;
- PBSC collection should be accomplished using either Cyclophosphamide combined with G-CSF, or, if in stringent complete remission/complete remission G-CSF, 15–30 mg/kg daily for 5 days associated with Plerixafor;
The doses of Cyclophosphamide in stem cell mobilization prior to ASCT are Low dose (LD-Cy) from 1 to 1.5 g/m$^2$ intravenously, Intermediate dose (MD-Cy) from 3 to 4 g/m$^2$ intravenously, High dose (HD-Cy) from 5 to 7 g/m$^2$ intravenously: the first option is the most preferred in the practical use and clinical trial to avoid long-term cytopenias and extra-hematological toxicities [145–147];

The doses of G-CSF in stem cell mobilization prior to ASCT are 5 mcg/kg twice daily (i.e. 10 mcg/kg/day) subcutaneously twice daily for 4–5 days [148];

The dose of Plerixafor is 0.24 mg/kg subcutaneously, one dose to be given the night before stem cell collection: this agent is used in case of MM poor mobilizer patients [149, 150];

avoid dialysis on the day of Melphalan, administered over 30 min in 1 or 2 days;

stem cell reinfusion should be performed after 24 h over 1 or 2 days, post dialysis;

double ASCT could be considered in fit patients according to the results and safety of first ASCT;

consider consolidation and maintenance therapy in order to improve the overall response and outcome of patients.

### 3.3 Mechanical therapy

The medical therapy is finalized to a rapid and sustained suppression of malignant plasma cells clone but it could be not enough fast and effective to translate into an immediate reduction of monoclonal FLCs, leading to prolonged renal exposure to these pathologic proteins. For this reason, it has been considered the possibility of using of complementary mechanical strategies, dedicated to remove the monoclonal light chains from the circulation.

The mechanical approach should avoid the prolonged exposition of nephron to elevated serum concentration of monoclonal LC.

The $\kappa$ and $\lambda$ FLCs are middle molecules that are physiologically present in the serum as monomers and dimers, with molecular weights of 22.5 kDa and 45 kDa, respectively. However, in MM patient monoclonal LC are frequently present as polymers of various sizes. In healthy individuals, the monomers and dimers are filtered freely at the glomerulus with serum half-lives of between 3 h and 6 h, and FLCs represent an early marker of myeloma response to chemotherapy when renal function is normal [151, 152]. In presence of severe renal failure, the serum half-lives of FLCs are prolonged with a consequent increasing of absolute serum concentrations. Therefore, in this context, serum half-lives are about 2–3 days and the reticuloendothelial system becomes the most important mechanism of clearance. The serum concentrations can remain elevated for long periods because of reduced renal clearance, even if an effective chemotherapy is promptly started with a reduction of FLCs production [153–155]. This prolonged kidney exposure to high FLCs levels could explain why it is reported a significantly lower rate of renal recovery in dialysis-dependent at disease presentation than in those with moderate renal impairment treated with Bortezomib-based therapy (approximately from 30% to 60%) [156]. These observations led to
consider that the strategies to remove FLCs directly from the serum could have a particularly high effective role in the population with a significantly reduced FLCs clearance.

Rapid FLCs depuration may be achieved either through plasmapheresis or intensive hemodialysis using new-generation “high-cutoff” (HCO) protein-leaking dialyzers with very high permeability to proteins.

Before choosing the best approach for these patients with a severe renal impairment due to a LCCN is mandatory to subline preliminary considerations:

- these therapies are pointless if used without efficient associated chemotherapy;
- the renal effect of their combination with anti-plasma cell regimens is still debated;
- FLCs, because of their molecular weight, re-equilibrate freely between intravascular and extravascular compartments and approximately 80% of FLCs are extravascular at any one time. Direct removal of FLCs from the serum could have an affective benefit therefore only if the whole body is cleared of monoclonal light chains to achieve a sustained reduction in serum FLC concentrations.

Plasma exchange would seem to be a logical treatment for LCCN because of technical characteristics. However, despite the effective FLCs plasma removal provided, the short duration of each session (typically 2 h or less) results in a limited clearance of the extra-vascular compartment. Furthermore, in case of increasing the dose of plasma exchange, there is the disadvantage of the non-targeted removal of FLCs. Plasma exchange also removes many essential proteins including intact immunoglobulins and clotting factors. About clinical efficacy, randomized trials, performed before the era of novel anti-myeloma agents and with a limitation of the absence of pathological demonstration of LCCN, failed to show a benefit of plasmapheresis. A more recent retrospective data evaluation in patients with biopsy-proven LCCN treated with the combination of plasmapheresis with high-dose Dexamethasone and Bortezomib or Thalidomide reported renal response rates of up to 75% [89, 157, 158].

For the MM LCCN patients requiring dialysis, another promising tool is represented by hemodialysis using conventional high-flux dialyzers, with a protein cutoff of 15–20 kDa. It provides only limited clearance of FLCs.

HCO dialyzers in reverse allow the removal of proteins up to 65 kDa and produce highly efficient clearing of both kappa and lambda LC with acceptable albumin loss. Because of the uppermost extravascular distribution of FLCs, prolonged HCO hemodialysis sessions are needed to achieve a removal of high quantities of LCs, with the risk of post-dialysis intravascular rebound. The first experiences with the association of intensive HCO hemodialysis and chemotherapy with novel agents showed hemodialysis independence rates of nearly 60% [90, 159–162], in comparison with 30% rate reported in patients receiving conventional hemodialysis1 [36, 163].

Other techniques of FLCs removal consist in hemodialysis using adsorptive polymethylmetacrylate dialyzers, supra-hemodiafiltration with endogenous reinfusion after FLC adsorption hemodiafiltration using high-flux or very high flux membranes, or continuous veno-venous hemofiltration with HCO filters. Their efficacy on FLCs removal as compared to HCO hemodialysis remains to be assessed and little data are available in patients with MM and AKI.
Two randomized trials, MYRE [26] and EuLite [164], evaluated HCO hemodialysis in comparison with standard high-flux hemodialysis. Their clinical designs (Table 3) presented noticeable differences in terms of randomization, hemodialysis and chemotherapy schedule and expertise of centers. Notably, also the results were discordant: both studies demonstrated dialysis independence rates at 6 months of 60% but, in contrast, data differed in control groups, being significantly lower rate in MYRE trial (35%). At primary end point (3 months), in MYRE study the hemodialysis withdrawal rates were not significantly different. In a hand, the HCO group of EuLite experienced a high rate of serious adverse events (frequent severe infections), which resulted in frequent treatment interruptions, in the other hand tolerance of HCO hemodialysis was good in MYRE. Overall survival was similar in the 2 groups of the MYRE study, whereas mortality rate was higher in the HCO group of EuLite. Regarding the light chain isotype, no difference was observed in both studies in terms of HCO dialyzers. Despite the non-concordant data from these trials, the combination of HCO hemodialysis with an effective chemotherapy can be considered a therapeutic option for LCCN patients. Additional data are required for define the role of anti-CD38 MoAbs in this mechanical/chemotherapy approach.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MYRE</th>
<th>EuLite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of randomized patients</td>
<td>98</td>
<td>90</td>
</tr>
<tr>
<td>Randomization</td>
<td>After a preinclusion period of 4–15 d, including symptomatic measures and high-dose steroids (dexamethasone 40 mg/d orally, 4 d)</td>
<td>Upfront</td>
</tr>
<tr>
<td>Chemotherapy regimens</td>
<td>Bortezomib dexamethasone (and/or cyclophosphamide in patients without hematological response after 3 cycles)</td>
<td>Bortezomib-dexamethasone-doxorubicin</td>
</tr>
<tr>
<td>Hemodialysis schedule</td>
<td>Identical in the HCO and control groups 8 sessions of 5 h over the first 10 d and then thrice weekly</td>
<td>Intensive HD in the HCO group Daily sessions of 8 h over the first 10 d, then 8-h sessions thrice weekly from day 12 to day 21, and finally 6-h sessions thrice weekly Standard HD in the control group 4-h sessions thrice weekly</td>
</tr>
<tr>
<td>HCO dialyzers</td>
<td>Single HCO Theralite dialyzer (Gambro Dialysatoren GmbH, Hechingen, Germany) of 2.1 m² in surface</td>
<td>2.1 m² HCO dialyzers in series</td>
</tr>
<tr>
<td>Premature treatment discontinuation</td>
<td>4 (8.7%) in the HCO group² 2 (4.2%) in the control group</td>
<td>9 (20.9%) in the HCO group 2 (4.2%) in the control group</td>
</tr>
<tr>
<td>Dialysis independence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 3 mo</td>
<td>41% (HCO) vs. 33% (control) P = 40.42 56% (HCO) vs. 51% (control) P = 40.81</td>
<td></td>
</tr>
<tr>
<td>At 6 mo</td>
<td>56.5% (HCO) vs. 35% (control) P = 40.04 58% (HCO) vs. 66% (control) P = 40.76</td>
<td></td>
</tr>
<tr>
<td>At 12 mo</td>
<td>61% (HCO) vs. 37.5% (control) P1/40.02 58% (HCO) vs. 66% (control) P = 40.76</td>
<td></td>
</tr>
</tbody>
</table>

HCO, high cutoff; HD, hemodialysis.

Table 3. MYRE and EuLite trials.
3.4 New treatment approach

The main problem in the treatment of LCCN is the dependence on fast and sustained FLCs reduction. Because no therapy is 100% effective against LCCN and it remains to be determined if mechanical devices can reduce FLCs in association with chemotherapy, new therapeutic approaches are needed to face this issue.

Recently a competitive inhibitor peptide (AHXCLSADSSGSYLYVCKK) capable of interrupting the binding between FLC and uromodulin, preventing obstruction, was described as effective in animal models. Earlier another agent, a polypeptide pituitary adenylate cyclase–activating poly-peptide with 38 residues (PACAP38), has demonstrated high activity at blocking cellular damage from FLCs in an in vitro setting [165]. Despite additional data regarding the clinical efficacy and the potential role in this setting are warranted, therapeutic approaches that can target the monoclonal protein rather than the plasma cell are extremely attractive, avoiding the use of toxic chemotherapy, in patients with AL amyloidosis who may be too frail to be treated with medical therapy.

3.5 Prognosis and response criteria

Early assessment of hematologic response through serial FLCs assessment is crucial for the management of MM-related kidney diseases, particularly in case of LCCN. The absence of rapid and deep hematologic response can lead to the need to reinforce the previous regimen either by introducing an Immunomodulatory Drug or an anti-CD38 Monoclonal Antibody because:

- in case of persisting AKI, hematologic response is the main predicting factor of renal survival, particularly for patients requiring dialysis, in whom the achievement of involved FLCs level below 500 mg/l after the first cycle of chemotherapy is an independent factor of renal recovery [26].

- without indication for dialysis, a reduction of >90% monoclonal FLCs concentration is also associated with a high probability of renal response [27].

Besides the early and sustained FLCs reduction, another prognostic factor for renal recovery is represented by the severity of renal impairment. It was demonstrated the AKIN 3 stage is an independent predictor of poor renal outcome [27]. In this population the kidney biopsy may help predict renal prognosis and potentially guide therapeutic decisions (i.e. the reinforcement of chemotherapy with extracorporeal FLC removal) though two key predictive histologic features (Table 4) [56]:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest number of light chain</td>
<td>Highest number of light chain casts in one 20 field divided by the area of</td>
<td>Ca1: &lt;5 casts/mm²</td>
</tr>
<tr>
<td>casts per millimeter square in</td>
<td>one 20 field in millimeter square</td>
<td>Ca2: 5–10 casts/mm²</td>
</tr>
<tr>
<td>the cortex (Ca)</td>
<td></td>
<td>Ca3: &gt;10 casts/mm²</td>
</tr>
</tbody>
</table>

| Interstitial fibrosis/tubular     | Thickened tubular basement membranes with flattened epithelial cells,       | T0: <10%            |
| atrophy (T)                       | expanded interstitium with fibrosis, whichever is the highest               | T1: 10–24%          |
|                                  |                                                                           | T2: 25–50%          |
|                                  |                                                                           | T3: >50%            |

Table 4.
From [56].
Degree of interstitial fibrosis and/or tubular atrophy

Highest number of cortex cast for millimeter square

Although life expectancy of patients with ESRD caused by LCCN has increased over the last decade, it remains inferior to 2 years in those requiring chronic hemodialysis [166]. Moreover, it has been shown that renal recovery can lead to improved survival in patients with MM but the life expectancy of patients with reversal of renal impairment remains inferior to patients with normal renal function at diagnosis. The International Myeloma Working Group defined criteria for renal response, defining complete, partial, and minor responses, but their clinical relevance remains to be evaluated (Table 5) [4]. In the clinical practice improvement in renal function, defined by a stable eGFR value \( \geq 40 \text{ ml/min/1.73 m}^2 \), is represents desirable goal, particularly in fit eligible for ASCT.

<table>
<thead>
<tr>
<th>Renal response</th>
<th>Baseline eGFR, mL/min/1.73 m(^2)</th>
<th>Best CrCl response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>&lt;50</td>
<td>( \geq 60 \text{ mL/min} )</td>
</tr>
<tr>
<td>Partial response</td>
<td>&lt;15</td>
<td>20–59 mL/min</td>
</tr>
<tr>
<td>Minor response</td>
<td>&lt;15</td>
<td>15–29 mL/min</td>
</tr>
<tr>
<td></td>
<td>15–29</td>
<td>30–59 mL/min</td>
</tr>
</tbody>
</table>

Abbreviations: CrCl, creatinine clearance; eGFR, estimate glomerular filtration rate. eGFR is based on the Modification of Diet in Renal Disease formula, or the Chronic Kidney Disease Epidemiology Collaboration equation.

Table 5. Criteria for the definition of renal response to antimyeloma therapy.

- Degree of interstitial fibrosis and/or tubular atrophy
- Highest number of cortex cast for millimeter square

4. Conclusion

Renal diseases associated to MM represent frequent complications of this malignant disease. The diagnosis could be challenging and it is mandatory to define the effective role of underlying MM in the renal pathology development and rule other cause as, for example, MGRS. Particularly, the LCCN is a dramatic renal complication of MM that need a prompt and fast diagnosis and therapy to avoid dialysis-dependence and improve the outcome of this population of patients. Despite the recent advances in the management of MM-related AKI further progress is required:

- prevention and early diagnosis should be eagerly improved;
- definition of the best therapeutic regimen, and likely the introduction of newest agent as anti-CD38 MoAbs, is mandatory to optimize the efficacy and reduction of toxicity of treatment and to enhance renal recovery that affects morbidity and mortality;
- in patients requiring dialysis, further studies are needed to set the optimal modalities of the combination of HCO hemodialysis with chemotherapy;
- therapeutic decisions, like change or enhancing therapy, should be guided by improved prediction of renal outcomes through pathology data from a wider use
of the kidney biopsy in patients with severe LCCN AKI. For example, the chemotherapy in association with HCO hemodialysis could effective in patients with high risk of ESRD according with assessment of renal prognosis with kidney biopsy (high number of pathologic cast);

• a more extensive multidisciplinary approach is mandatory to improve the management of these complications, particularly LCCN.

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