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Abstract

Symptomatic multiple myeloma (MM) is commonly complicated by acute kidney injury (AKI), through various mechanisms. The most frequent is the precipitation of monoclonal free light chains (FLC) with uromodulin in the distal tubules, defining light chain cast nephropathy (LCCN). Early diagnosis and identification of the cause of AKI are required for optimizing management and avoiding chronic kidney injury that strongly affects quality of life and patient survival. In LCCN, often manifesting with severe AKI, renal recovery requires urgent intervention based on vigorous rehydration, correction of precipitating factors and efficient anti-plasma cell chemotherapy to rapidly reduce the secretion of nephrotoxic FLC. Currently, the association of the proteasome inhibitor bortezomib with high-dose dexamethasone is the standard regimen in newly diagnosed patients. The addition of another drug such as cyclophosphamide or an immunodulatory agent may improve FLC response, but raises tolerance concerns in frail patients. Further studies are warranted to confirm the role of anti-CD38 monoclonal antibodies, which 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 combination of chemotherapy with FLC removal through high-cutoff hemodialysis, may increase renal response recovery rates. Kidney biopsy may be helpful for guiding management and assessing renal prognosis that appears to depend on the extent of cast formation and interstitial fibrosis/tubular atrophy. Due to continuous improvement in life expectancy of MM patients, renal transplantation is likely to be increasingly considered in selected candidates.

INTRODUCTION

Multiple myeloma (MM) is defined by the malignant proliferation of clonal plasma cells that usually secrete a monoclonal immunoglobulin (MIg) detectable in the serum and/or urine.[1,2] MM is typically preceded by a variable clinically asymptomatic period during which the abnormal plasma cell clone is quiescent and only manifests by the presence of a MIg. This situation is referred to as monoclonal gammopathy of unknown significance (MGUS).[3,4] An active uncontrolled plasma cell proliferation causes symptomatic MM, where organ damage results either from the tumor mass, or from its effect on the immune system leading to secondary immune deficiency and its inherent infectious risk. The MIg may also cause tumor-mass related symptoms, the most common being hyperviscosity and light chain cast nephropathy (LCCN).[5,6]

The intermediate condition between MGUS and symptomatic MM defines indolent or smoldering MM.[1,2] When corresponding to MGUS or smoldering MM, the plasma cell proliferation does not cause tumor-related symptoms by definition. However, it may be associated with organ lesions, either MIg-mediated or due to other mechanisms. These situations, which are featured by a small dangerous B-cell clone causing renal and/or extra renal manifestations, fit with the definition of monoclonal gammopathy of renal significance (MGRS)[7] or monoclonal gammopathy of clinical significance (MGCS).[8]

Consensus expert recommendations regarding the diagnosis and treatment of MG(C)RS have been published.[9-11] The present review will encompass only renal complications of symptomatic MM, focusing on the management of acute kidney injury (AKI) due to LCCN.

EPIDEMIOLOGY

MM is the second most common hematologic malignancy after non-Hodgkin lymphoma, with a global age-standardized incidence of 2.1/100,000 in 2016.[12] The risk increases with age,

with a peak around 65 years. MM is slightly more common in males, about twice more frequent in subjects of African ancestry compared to Caucasians, and has the lowest incidence in Asians.[12-14]

Renal complications are frequent in MM, since acute or chronic renal impairment is thought to occur in half of patients during the course of the disease.[15] AKI is a common initial presentation, but it may also develop at relapse. The prevalence of AKI in patients with newly diagnosed symptomatic MM remains unclear, depending on the definition used.[16] It was reported around 30%, 20% and 15% using a serum creatinine level of 1.5 mg/dl, 2 mg/dl (threshold for renal impairment according to the historical International Myeloma Working Group [IMWG] criteria[1]), or 2.3 mg/dl, respectively.[17,18] In studies using eGFR, prevalence of AKI was 17%[19] using the current IMWG criterion (<40 ml/min/1.73m^2)[16], and varied between 10% and 25% when considering an eGFR of 30ml/min/1.73m^2 or 60 ml/min/1.73m^2, respectively.[20] The use of eGFR has been criticized because it is appropriate for the definition and staging of chronic kidney disease (CKD), but questionable for AKI. However, the usual lack of a baseline serum creatinine level often precludes an accurate assessment of AKI. In the sole study that used the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria, 35% of MM patients had AKI with 5% staged as Risk, 5% as Injury and 25% as Failure.[21]

The establishment of a definitive diagnosis of LCCN relies upon a kidney biopsy. Since no series of patients with renal impairment or AKI and systematic renal examination has been reported, the true incidence of LCCN is unknown. In a cohort of 127 MM patients who presented with AKI, 72 underwent a kidney biopsy, either because of severe renal failure, or significant albuminuria (>30% of total urine proteins). Among these, pure LCCN was diagnosed in 41, while 4 patients had another pathology coexisting with LCCN. Around 25% of patients who presented with AKI had another LC-induced renal disease, including AL

amyloidosis (n=12), light chain deposition disease (LCDD) (n=6), or Fanconi syndrome (n=1). Finally 8 patients had renal lesions unrelated to MM, 6 of whom with vascular atherosclerotic renal disease.[22]

SPECTRUM OF RENAL IMPAIRMENT IN SYMPTOMATIC MM

Renal complications not related to the monoclonal Ig.

In symptomatic MM, obstruction of the urinary tract due to expansion of bladder or ureteral extra-medullary plasmocytoma has been rarely described.[23] Similarly, renal parenchymal plasma cell infiltration is uncommon, and is exceptional as the sole cause of renal impairment. In a recent randomized controlled study, where 176 MM patients with AKI due to LCCN underwent a kidney biopsy, malignant plasma cells invading the tubulo-interstitial compartment were found in 4 (2.2%), and always concurrent with LCCN.[24,25]

Hypercalcemia is present in about 15% of MM patients at presentation[26], but the prevalence is 2 to 3 fold higher (25% to 45%) in those with an elevated serum creatinine level.[17,27] Hypercalcemia may induce pre-renal AKI by dehydration and vasoconstriction and it is a common precipitating factor of LCCN.[22,28,29.] Similarly, infections which are major cause of morbidity and death in MM patients are often associated with AKI. A large study reported a 7-fold increase risk of any bacterial infection for MM patients as compared to control, including a 15.6, 7.7 and 2.9-fold increase risk of septicemia, pneumonia and pyelonephritis, respectively.[30] Any cause of dehydration and the use of nephrotoxic drugs, such as non-steroidal anti-inflammatory drugs (NSAIDS), diuretics and renin-angiotensin-aldosterone system (RAS) blockers may be implicated in the development of pre-renal AKI, but usually trigger also the formation of light chain casts.[6,24,25,31] This probably explains why acute tubular necrosis (ATN) is rarely observed without concurrent LCCN in myeloma patients with severe AKI, as described in only 17 (9%) of a series of 190 patients.[32]

AKI can also complicate the treatment of MM. Bisphosphonates, especially zoledronic acid used to treat hypercalcemia and myeloma bone disease, have been rarely involved in the development of ATN.[33,34] Renal thrombotic microangiopathy is a rare cause of myeloma-associated renal damage,[35] and more commonly a potential complication of proteasome inhibitors, particularly carfilzomib.[36-38] Lenalidomide has been associated with acute reversible non light chain-related Fanconi syndrome.[39] Anecdotal observations of acute interstitial nephritis with the use of lenalidomide[40] and bortezomib[41] have been reported. With the recent development of highly effective anti-myeloma chemotherapeutic regimens, tumor lysis syndrome, very unusual in the past, is increasingly described at the initiation of chemotherapy, particularly in patients with altered renal function receiving proteasome inhibitor-based regimens.[42]

Renal complications related to the monoclonal Ig

The main mechanism of kidney injury due to MIg is deposition or precipitation of the entire MIg or a fragment thereof (usually the monoclonal LC).[6,8] Physicochemical peculiarities of the pathogenic MIg, particularly of the variable domain, govern the localization and pattern of renal lesions.[43-49] Some renal complications can only occur in patients with a high tumor mass underlying clone. The paradigm is LCCN which always complicates a symptomatic monoclonal gammopathy, most commonly myeloma (and exceptionally Waldenström macroglobulinemia[50-52] or chronic lymphocytic leukemia[53]). The other MIg-related nephropathies are not dependent on tumor mass and usually do not manifest with severe AKI. They are mainly diagnosed in patients with MGRS, i.e. with an indolent monoclonal gammopathy or MGUS, although they may also develop during the course of a high tumor mass clonal disorder, including symptomatic MM.

When studied at the ultrastructural level, MGRS-related renal diseases are characterized with either organized or non-organized deposits. Organized deposits may display a fibrillar

appearance, such as in AL amyloidosis, or a microtubular structure, as in type I or type II cryoglobulinemic glomerulonephritis and immunotactoid glomerulopathy. Non-organized linear "powdery punctuate" glomerular and tubular basement membrane deposits are characteristic of monoclonal immunoglobulin deposition diseases (MIDD). In contrast, proliferative glomerulonephritis with MIg deposits (PGNMID) is featured by non-organized granular deposits of MIg and complement.[10,11]

Monoclonal LC can also injure proximal tubules causing Fanconi's syndrome.[54-57] Recently, other renal diseases not involving MIg deposition have been described, including glomerulopathies with deposits of C3 only[58-62] and thrombotic microangiopathy.[63] Both disorders derive from deregulation of the complement alternative pathway, likely to be caused by the MIg through autoantibody activity against complement regulatory proteins or direct activation of the complement alternative pathway.[64]

LIGHT CHAIN CAST NEPHROPATHY

Although all MIg-related nephropathies may be observed in patients with symptomatic MM, LCCN is the main cause of AKI in these patients.

Pathophysiology

Physiologically, around 500 mg polyclonal free light chains (FLC) are produced daily, of which 15% only are distributed in the intravascular space. These FLC circulate as monomers of 22kDA, but may assemble into dimers of 45kDA, particularly lambda FLC.[6,65] Serum FLC (sFLC) undergo glomerular filtration, followed by reabsorption in the proximal tubules through endocytosis via the tandem receptors megalin and cubulin, and are ultimately degraded in the lysosomes of proximal tubular cells.[66-69] Consequently, only very low amounts are excreted in the final urine. In symptomatic MM featured by massive FLC production, this tubular processing may be overwhelmed, resulting in high luminal FLC

concentration in the loop of Henle. In addition, reabsorption of huge quantities of monoclonal LC alters proximal tubular cells and reduces their catabolic capacities.[70] FLC reaching the distal loop of Henle may interact with locally produced uromodulin (Tamm Horsfall protein), through the LC CDR3 hypervariable region that binds to a 9 aminoacid sequence of uromodulin.[71,72] LC-uromodulin complexes co-aggregate to form casts, which are most commonly found in the distal tubules, and rarely in the proximal tubule or in the glomerulus.[22,28,73,74] These casts, which occasionally display a crystalline organization, obstruct the urine flow, producing a sudden decrease in the glomerular filtration rate, and may cause tubular rupture and extravasation of uromodulin[28,73-76] This cascade of events results in severe local inflammation, often featuring giant cell reaction around casts, that further worsens renal damage.[22,28,73,74] In the absence of appropriate therapeutic intervention, irreversible tubulo-interstitial fibrosis rapidly develops.[22,28,74]

In proximal tubules, the endocytosis of massive amounts of pathogenic monoclonal FLC induces generation of hydrogen peroxide and redox signaling.[67,77-80] This oxidative stress leads to the activation of several pro-inflammatory pathways, including the mitogen-activated protein kinases ERK1/2, JNK, p38,[77] and nuclear factor-kappa B (NF-κB),[80] leading to the production of inflammatory cytokines such as IL-6 and MCP-1 and the upregulation of apoptotic pathways.[81] The mechanisms of injury were recently elucidated by Ying et al., who showed *in vivo* and *in vitro* that STAT1 activation is the main pro-inflammatory mechanism triggered by FLC reabsorption, leading to the production of IL-1β and of the pro-fibrotic agent TGF-β. These effects are specifically induced by the generation of hydrogen peroxide by the pathogenic LC, which appears to depend on the molecular characteristics of the variable domain, i.e. the presence of an invariable tryptophan at amino acid residue 40.[82] Mechanisms of distal tubulo-interstitial inflammation are incompletely understood. A role for the crystalline organization of light chain casts in triggering inflammation and giant cell

reaction through activation of NLRP3 inflammasome and secretion of mature IL-1β remains to be investigated.[83]

The probability of cast formation increases with the serum level of the pathogenic FLC and the amount of its urinary excretion.[6,84,85] LCCN exceptionally occurs below a serum concentration of <500 mg/l.[85] The risk varies with the molecular characteristics of each individual FLC which affinity for uromodulin is governed by the CDR3 amino acid sequence.[45] Thus, both affinity and concentration of the FLC determine the pathogenesis of LCCN. Neither LC isotype (kappa or lambda) nor variability subgroups, which are independent from CDR3 molecular sequence correlate with the risk of LCCN.[45,72]

In addition to LC serum concentration and intrinsic characteristics, several extrinsic factors potentiate cast formation.[6] The main contributor is reduced urine flow, whatever its cause, that rises urinary FLC concentration and thus favors the FLC-uromodulin interaction.[86] Any concurrent condition leading to dehydration including infection/sepsis, gastrointestinal losses, are potential precipitating factors of LCCN. Hypercalcemia is a frequent trigger, through polyuria and increased urine calcium concentration which promotes cast formation *per se*.[87] Aggregation of LC with uromodulin is also enhanced in acidic urine and in the presence of high NaCl concentrations.[87] Besides dehydration, these mechanisms participate to the potential deleterious effect of the loop diuretics.[86] In addition, furosemide has been shown to cause a dose-dependent increase in uromodulin aggregation independent of urine electrolyte modifications.[86] RAS blockers may be potential triggers through modification of renal vascular resistance and redistribution of intra-renal blood flow.[31] Similar hemodynamic mechanisms account for the nephrotoxicity of NSAIDs, which are currently the most frequent precipitating factor of LCCN,[24,25] because of their common use as pain killers. Finally, iodinated contrast media have been classically associated with the development of AKI in

MM. However, with modern low-osmolality agents the risk is low, estimated at 1.6% in a retrospective review[88] and established at 1.8% in a recent large prospective study.[24,25]

Clinical presentation and diagnosis

LCCN is still a frequent mode of discovery of a previously unknown MM, being one of the myeloma-defining events, regrouped under the acronym CRAB (hypercalcemia, renal failure, anemia and bone lesions).[1,2] Clinical presentation associates AKI of variable severity, usually associated with symptoms of high tumor mass MM.[6,24,25,74,89] Concomitant infection is a frequent circumstance of diagnosis.[24,25] With recent improvement in management and increased life expectancy of MM patients, LCCN often occurs in the context of relapsing or refractory disease, either as AKI or as progressive CKD with parallel increase in LC proteinuria and serum creatinine level.[22]

When facing AKI of unknown origin, particularly in the elderly and when other MM manifestations are missing or misleading, it is crucial to consider LCCN. Initial diagnostic workup should include serum and urine protein electrophoresis. In addition, measurement of sFLC should be performed systematically. Importantly, although nephelometric assays such as the Freelite® test are only semi-quantitative and do not measure the actual concentration of the monoclonal LC, they represent a reliable and invaluable tool for the diagnosis and management of LCCN. A monoclonal spike or hypogammaglobulinemia, a urine albumin/protein ratio <10%, and/or significantly increased level of one LC isotype with abnormal kappa/lambda ratio, should prompt to perform a bone marrow examination.[6] This will establish MM diagnosis by showing clear infiltration by atypical plasma cells, which clonality is indicated by phenotypic and molecular characteristics. Myeloma work-up should be completed by bone imaging techniques.[90]

In any MM patient who presents with or develops renal insufficiency, the combination of low urinary albumin excretion (urine albumin/total protein ratio <10% and urinary

albumin/creatinine <30 mg/mmol), and high sFLC level (>500 mg/l) strongly argues for the diagnosis of LC-CN.[6,7,10,11] and systematic histological confirmation is not required.[85] In contrast, a kidney biopsy should be considered if significant albuminuria is present, particularly if sFLC is below 500 mg/L. More generally, monitoring and characterization of proteinuria is mandatory during follow-up of any monoclonal gammopathy including MM, and urine albumin/protein ratio >10% (or urine albumin/creatinine >30mg/mmol) should raise suspicion of MIg-related glomerulopathy such as AL amyloidosis or monoclonal immunoglobulin deposition disease (MIDD), rather than LCCN.[10,11] Indication for a kidney biopsy should take into account renal and extra-renal presentation, characteristics of the monoclonal gammopathy and also alternative or superimposed causes of renal disease such as diabetes, or atherosclerosis. A clinical suspicion of AL amyloidosis should lead to perform a non-invasive biopsy at first, due to the risk of bleeding complications.[10,11]

Pathology and role of the kidney biopsy

As already mentioned, kidney biopsy is required whenever the diagnosis of LCCN is clinically questionable. Studies have shown that it can be safely performed in MM patients, with risk similar as in other populations.[22,24,25,74,89,91]

Histologically, LCCN is defined by the presence of atypical casts in distal tubules and collecting ducts that exhibit LC restriction on immunofluorescence or immunohistochemistry. The casts typically show irregular shapes and lamellated appearance and are often cracked or fractured. They appear hypereosinophilic on hematoxylin and eosin, periodic acid-Schiff negative, and silver-negative (Figure 1).[22,28,73,74] Ultrastructurally, they display highly electron dense homogeneous granular texture or exhibit lattice-like substructure.[74] They are almost always associated with acute tubular injury (luminal ectasia, epithelial simplification and vacuolization, enlarged nuclei with hyperchromasia) and intratubular inflammatory reaction.[22,28,73,74] A hallmark of LCCN is giant cell reaction around the casts, but this feature

is lacking in about a third of cases.[74] Interstitial inflammation may vary from minimal to intense, depending on the severity and duration of cast formation, and progressive interstitial fibrosis and tubular atrophy ensue if the kidney biopsy is performed late. Other features include variable degree of tubulitis, tubular rupture, and uromodulin extravasation into the interstitium and/or accumulation in Bowman's space due to tubular obstruction.[22,28,73,74] Glomeruli and vessels appear unremarkable or show changes related to co-existing conditions, including diabetes, hypertension and atherosclerosis.[22,74] LC casts should be distinguished from myoglobin and hemoglobin casts which typically do not induce an adjacent inflammatory reaction.[92] Cast formation can be observed in patients with pancreatic acinar or mixed acinar neuroendocrine carcinoma.[93] In these situations, immunofluorescence studies are determinant by showing the absence of LC restriction.

In 12-16% of cases, LCCN may coexist with other monoclonal Ig-related kidney lesions, particularly AL amyloidosis, classic LCDD and light chain proximal tubulopathy.[22,24,25,32,74] Identification of any of these superimposed lesions requires clinical assessment for extrarenal involvement and yields prognostic value regarding kidney outcome.[74,94] Associated direct interstitial infiltration by malignant plasma cells is rare.[25] Some cases of LCCN exhibit concomitant diffuse linear staining of glomerular, tubular and vascular basement membranes for one Ig light chain by immunofluorescence without features of LCDD by light or electron microscopy, a pattern referred to as "LCDD by immunofluorescence only".[95] A distinctive histologic variant of LCCN is congophilic "amyloidogenic" LCCN, where atypical casts are composed of Congo red-positive amyloid fibrils. A minority of patients with this variant have evidence for concurrent renal and/or extrarenal amyloidosis.[96]

Kidney biopsy may be helpful in the prognostication of LCCN.[22,28,29] In a recent retrospective study of 178 MM patients with LCCN, of whom 47% required dialysis at presentation, the number of casts/mm^2 in the cortex and, to a lesser extent, the degree of IFTA

were independent prognostic factors of renal outcome. Importantly, the extent of cast formation could not be predicted by initial clinical data, including the level of the involved FLC.[74]

Therapeutic management of LCCN

Treatment of AKI due to LCCN is an emergency. It is based on the combination of symptomatic measures, high dose steroids, and chemotherapy. In addition, extracorporeal removal of circulating FLC may be considered.

Symptomatic measures and chemotherapy

Symptomatic measures are crucial, aiming at correcting precipitating factors and optimizing hemodynamic conditions to decrease intra-luminal precipitation of monoclonal LC with uromodulin. Unless contraindicated (oliguric AKI or heart failure), a high urine flow should be established through vigorous rehydration using saline fluids. Half normal saline fluid may be used to limit the afflux of sodium and chloride in distal tubules. Although controversial, the administration of isotonic sodium bicarbonate may be considered to obtain a urine pH $\geq$7.[97-100] However, sodium bicarbonate should be avoided in hypercalcemic patients, due to the risk of calcium-phosphate precipitation. Treatment of hypercalcemia is based or rehydration combined with IV bisphosphonates (which are not contraindicated, provided that dose and infusion modalities are adapted to eGFR value). Pamidronate should be preferred to zoledronic acid, because of a lower risk of renal complications.[33,101] Alternatively the anti-RANL ligand monoclonal antibody denosumab that inhibits osteoclasts may be proposed.[34] The use of loop diuretics should be considered only in the situation of severe fluid overload. RAS blockers and NSAIDS should be stopped. Any concurrent infection should be treated with non-nephrotoxic antibiotics.[97-100]

High-dose steroids and chemotherapy

High-dose dexamethasone is a key component in the treatment of LCCN, because of its potent cytotoxic, anti-inflammatory and catabolic properties. It should be introduced rapidly, immediately after the diagnosis of AKI.[102,103]

Anti-plasma cell chemotherapeutic agents are required to decrease the tumor burden, in order to reduce the pathogenic monoclonal LC secretion. Only few prospective studies have addressed the issue of the best combinations of anti-myeloma drugs in patients with LCCN. Current recommendations rely upon expert opinion derived from small retrospective series and advocate for rapid introduction of chemotherapeutic agents, the choice of which should consider their renal metabolism and toxicity profile.[16] Among conventional anti-myeloma agents, cyclophosphamide is more commonly used than melphalan which is eliminated by the kidneys,[24,25,90] whereas the cardiac toxicity of doxorubicin limits its indications. The so-called novel anti-myeloma agents comprise two main categories, immunomodulatory drugs (IMiDs) and proteasome inhibitors. Among IMiDs, thalidomide is associated with a dose-dependent risk of irreversible peripheral neuropathy when used for more than 3 months.[104] The renal benefit of pomalidomide, which contrary to lenalidomide does not undergo renal elimination,[105] has not been assessed yet. Regarding proteasome inhibitors, carfilzomib induces higher hematologic response rates compared to bortezomib.[106,107] However, its potential cardiac and renal toxicity,[108] including thrombotic microangiopathy,[36,37,108] precludes its use as a standard for LCCN. Finally, monoclonal anti-CD38 monoclonal antibodies, which significantly improve the rapidity and depth of hematologic responses in both newly diagnosed and refractory myeloma,[109-112] represent a promising tool for the treatment of LCCN.

Currently, the standard of treatment combines high-dose dexamethasone with the proteasome inhibitor bortezomib, which efficacy and tolerance are established without dose adaptation, whatever the degree of renal impairment, including in patients requiring dialysis.[113-118] The

bortezomib-dexamethasone doublet can be reinforced to further improve hematologic responses,[119,120] as documented in patients with newly-diagnosed or relapsed MM with preserved renal function.[121,122] Using a triplet regimen increases the risk of deleterious events such as infection, hemodynamic instability and drug toxicity, and finally may compromise renal recovery in patients with LCCN.[89] In these patients, often old and frail with pre-existing co-morbidities, a careful assessment of the efficacy/toxicity balance of anti-myeloma combinations is crucial. The sole randomized study that compared a doublet to a triplet regimen[25] did not document a beneficial effect for renal outcomes of reinforcing BD with cyclophosphamide for renal outcomes. The slightly higher efficacy of C-BD in reducing pathogenic LC was not sufficient to counterbalance the incidence of adverse events, particularly severe infections. The later study strengthened the bortezomib-dexamethasone doublet as the reference treatment of inaugural LCCN, especially in frail patients.[25] In fit patients, a triplet regimen may be considered, although the best drug combination remains to be defined. In the near future, the association of bortezomib with monoclonal anti-CD38 antibodies is likely to become the backbone of chemotherapy for optimizing renal recovery in LCCN.[123]

Extracorporeal FLC removal

Even if chemotherapy could completely suppress the malignant plasma cell production, considering an additional strategy dedicated to remove the pathogenic LC from the circulation is logical. Indeed, in LCCN and AKI the reduced renal catabolism of the monoclonal LC results in a marked increase in its half-life (from few hours to 2-3 days) and huge accumulation in both vascular and extra-vascular compartments.[6,65] Rapid FLC depuration may be achieved either through plasmapheresis or intensive hemodialysis using new generation “high cutoff” protein leaking dialyzers with very high permeability to proteins.[124]

It should be stressed that these therapies are pointless if used without efficient chemotherapy. The renal effect of their combination with anti-plasma cell regimens is debated. A randomized trial, performed before the era of novel anti-myeloma agents and limited by the absence of pathological demonstration of LCCN, failed to show a benefit of plasmapheresis.[125] This was later challenged by retrospective data in patients with biopsy-proven LCCN, in whom the combination of plasmapheresis with high-dose dexamethasone and bortezomib or thalidomide, was reported to produce renal response rates of up to 75%.[126,127]

In myeloma patients requiring dialysis, hemodialysis using conventional high-flux dialyzers with a protein cutoff of 15 to 20 kDa, provides only limited clearance of FLC. High cutoff (HCO) dialyzers, which allow the removal of proteins up to 65kDa, produce highly efficient clearing of both kappa and lambda LC, at the price of significant but acceptable albumin loss. Because of the predominant (around 80 to 85%) extravascular distribution of FLC, prolonged HCO hemodialysis sessions are needed to remove high quantities of FLC, given the post-dialysis intravascular rebound.[128] In pioneering retrospective studies, the combination of intensive HCO hemodialysis and novel anti-myeloma regimens was associated with hemodialysis independence rates of about 60%,[124,129-134] which compared favorably with the usual 30% rate reported in patients receiving conventional hemodialysis.[114,117-119]

Other techniques of FLC depuration have been investigated in a limited number of MM patients with AKI. The main consisted of hemodialysis using adsorptive polymethylmetacrylate dialyzers[135], hemodiafiltration using high-flux or very high-flux membranes,[136,137] supra-hemodiafiltration with endogenous reinfusion after FLC adsorption (« SupraHFR »),[138] or continuous venovenous hemofiltration with high cutoff filters.[139] Their efficacy on FLC removal as compared to HCO hemodialysis remains to be assessed.

Two randomized trials, MYRE[24] and EuLite[89], evaluated HCO hemodialysis in comparison with standard high-flux hemodialysis. Their design presented noticeable differences (Table 1).

Briefly, i) in EuLite randomization was upfront. In MYRE it was preceded by a pre-inclusion phase dedicated to symptomatic measures and high-dose dexamethasone, and accordingly, only patients with persisting AKI still requiring hemodialysis were randomized. ii) In EuLite, the HCO hemodialysis schedule was very intensive whereas the control group used a standard regimen. In MYRE, both HCO and control groups received the same intensive dialysis dose. iii) EuLite involved few specialized centers. MYRE was conducted in standard hemodialysis facilities from many centers iii) In EuLite, the chemotherapeutic regimen used three drugs. In MYRE, patients received the BD doublet.

In the HCO groups of both studies, dialysis independence rates at 6 months were around 60%. In contrast, results differed in control groups, being significantly lower in MYRE (35%), and not different in EuLite. Of note, the primary endpoint in MYRE was set at 3 months, where hemodialysis withdrawal rates were not significantly different (Table 1). Tolerance of HCO hemodialysis was good in MYRE.[24] The HCO group of EuLite experienced a high rate of serious adverse events, particularly of severe infections, which resulted in frequent treatment interruptions.[89] Finally, overall survival was similar in the two groups of the MYRE study, whereas mortality rate was higher in the HCO group of EuLite, as compared to the control group. Both studies confirmed the efficacy of HCO dialyzers for removing circulating FLC, whatever the isotype, kappa or lambda. Despite the discordant results of these trials, many investigators currently consider that combining an effective chemotherapy with HCO hemodialysis is still a relevant therapeutic option in patients with LCCN. Whether or not novel anti-plasma cell regimens introducing monoclonal anti-CD38 antibodies will push to the side extracorporeal treatment requires evaluation through specific phase 2 studies, which are much realistic than large randomized phase 3 trials.

Determinants of outcomes

Since precipitating factors, particularly dehydration and the use of NSAIDs are often implicated in the development of LCCN, preventing measures based on patient and medical staff information are of paramount importance. Early diagnosis with adapted energetic intervention is also crucial. The combination of supportive measures with high-dose dexamethasone may be sufficient enough to induce rapid recovery of renal function by preventing the emergence and/or the worsening of LCCN.[102]

For those patients with persisting AKI, hematologic response is the main predicting factor of renal survival. This particularly holds true for patients requiring dialysis, in whom achievement of serum level of the involved sFLC level below 500 mg/L after the first cycle of chemotherapy is an independent factor of renal recovery.[24] Among patients without indication for dialysis, a ≥90% reduction in pathogenic sFLC level is also associated with an increased probability of renal response.[25] In any case, early assessment of hematologic response based on serial sFLC measurements is crucial. If a rapid and deep hematologic response is not achieved, reinforcing the previous regimen should be considered, either by introducing an IMiD and/or an anti-CD38 monoclonal antibody.

The severity of renal impairment also conditions renal prognosis. In the absence of dialysis requirement, AKIN stage 3 was recently shown as an independent predictor of poor renal outcome, in addition to preexisting CKD.[25] In these patients, performing a kidney biopsy may help predicting renal prognosis and potentially guide therapeutic decisions, such as the reinforcement of chemotherapy with extracorporeal FLC removal.[74] We suggest that the kidney biopsy report of LCCN cases may include two key predictive histologic features, i.e. highest number of casts/mm^2 in the cortex and degree of IFTA (Table 2). We propose that such a standardized approach of kidney biopsy reporting should be used in future studies of AKI in myeloma, to evaluate whether it translates into improved management and renal outcomes.

Life expectancy of patients with end-stage renal failure due to LCCN has increased over the last decade, but remains inferior to 2 years in those established on chronic dialysis.[140,141] Because of improved overall prognosis, a growing number of patients are potential candidates for kidney transplantation, but eligibility criteria remain to be defined. Transplantation may be considered in young patients with newly diagnosed MM lacking high-risk cytogenetic abnormalities (particularly del17p) and who have achieved sustained complete hematologic response as defined by negative minimal residual disease (MRD) using flow cytometry or molecular analysis.[141,142]

Although it has been shown that renal recovery can lead to improved survival in patients with MM,[143-145] a cohort of 1135 consecutive patients showed that the life expectancy of patients with reversal of renal impairment remains inferior to patients with normal renal function at diagnosis.[19] Criteria for renal response were proposed by the IMWG, defining complete, partial and minor responses, but their clinical relevance at the individual level remains to be evaluated.[16] Practically, improvement in renal function, defined by a stable eGFR value ≥40 ml/min/1.73m^2, is likely to be a desirable goal,[19,25] particularly in young patients otherwise eligible for high dose chemotherapy and autologous stem cell transplantation (ASCT). ASCT is still a reference treatment for newly-diagnosed myeloma. However, many investigators consider that it should be considered with caution in patients with severe renal impairment (i.e. eGFR <40 ml/min/1.73m2), because of a questionable benefit to risk ratio.

Conclusions and future directions

Recent advances in the management of monoclonal gammopathies, particularly MM, have resulted in a frank improvement in patient survival. In parallel, the introduction of the concept of MGRS/MGCS has clarified the diagnostic process of the various associated renal disorders.

For LCCN, which is still a frequent and critical complication of symptomatic MM, further progress is eagerly required. Prevention and early diagnosis should be improved. The

introduction of monoclonal anti-CD38 antibodies is likely to optimize the efficacy/toxicity balance of the indispensable chemotherapy, and ultimately to enhance renal recovery which strongly affects morbidity and mortality. In patients requiring dialysis, further studies addressing the modalities of the combination of HCO-HD with chemotherapy are warranted. Therapeutic decisions may be guided by improved prediction of renal outcomes, through wider use of the kidney biopsy in patients with severe AKI. Collaboration between nephrologists and hematologists is mandatory throughout the disease evolution.

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Legend to figure 1

Figure 1. Biopsy findings in light chain cast nephropathy. (A) Numerous periodic acid–Schiff [PAS]-negative cortical casts associated interstitial fibrosis and tubular atrophy (PAS, original magnification ×100). (B) Intraluminal hypereosinophilic casts distending the tubules, resulting in tubular ruptures (hematoxylin and eosin, original magnification ×200). (C) Sharp-edged and fractured PAS-negative cast surrounded by a cellular reaction (PAS, original magnification ×400). Immunofluorescence staining for anti-κ (D) and anti-λ (E) showing kappa light chain restriction (original magnification ×100). (F) Congo Red staining showing anomalous colors under polarized light in congophilic "amyloidogenic" variant of light chain cast nephropathy (Congo Red, original magnification ×400).

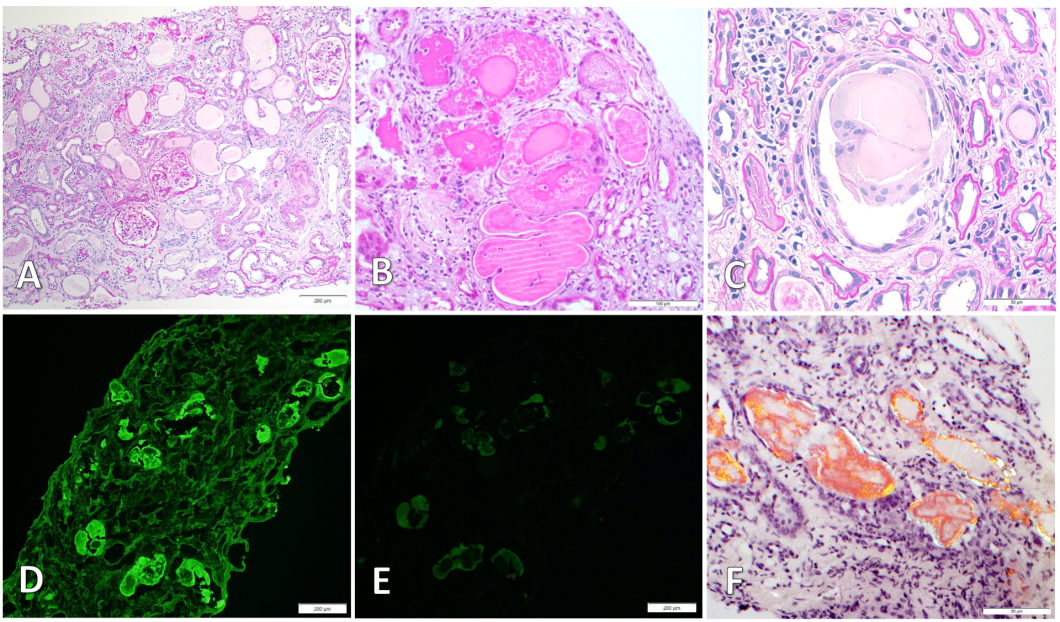
A
B
C
D
E
F

Table 1. Main differences between MYRE and EuLite randomized controlled trials (HCO hemodialysis *vs*. conventional high-flux hemodialysis)

	MYRE	**EuLite**
Number of randomized patients	98	90
Randomization	After a pre-inclusion period of (4 to 15 days) including symptomatic measures and high – dose steroids (Dexamethasone 40 mg/d orally, 4 days)	Upfront
Chemotherapy regimens	**Bortezomib Dexamethasone** (± Cyclophosphamide in patients without hematological response after 3 cycles)	**Bortezomib-Dexamethasone-Doxorubicin**
Hemodialysis schedule	**Identical in HCO and control groups** 8 sessions of 5hours over the first 10 days, then thrice weekly	**Intensive HD in HCO group** Daily sessions of 8hours over the first 10 days, then 8hour-sessions thrice weekly from day 12 to D21, then 6 hour-sessions thrice weekly. **Standard HD in the control group** 4hour-sessions thrice weekly
HCO dialyzers	Single HCO Theralite® dialyzer of 2.1 m^2 in surface	2 1.1m^2 HCO dialyzers in series
Premature treatment discontinuation	4 (8.7%) in HCO group* 2 (4.2%) in control group	9 (20.9%) in HCO group 2 (4.2%) in control group
Dialysis independence		
At 3 months[#]	41% (HCO) *vs*. 33% (Control) p= 0.42	56% (HCO) *vs*. 51% (Control) p= 0.81
At 6 months	56.5% (HCO) *vs.* 35% (Control) p= 0.04	58% (HCO) *vs*. 66% (Control) p= 0.76
At 12 months	61% (HCO) *vs.* 37.5% (Control) p= 0.02	58% (HCO) *vs.* 66% (Control) p= 0.76

* including 1 patient for intolerance of the hemodialysis protocol
[#] Primary endpoint

Abbreviations: HCO, high cutoff; HD, hemodialysis

Table 2. Definitions and scores of the predictive histologic features in kidney biopsy report for light chain cast nephropathy

Variable	*Definition*	*Score*
Highest number of light chain casts per millimeter square in the cortex (Ca)	Highest number of light chain casts in one 20x field divided by the area of one 20x field in mm^2	Ca1: <5 casts/mm^2 Ca2: 5 to 10 casts/mm^2 Ca3: >10 casts/mm^2
Interstitial fibrosis/tubular atrophy (T)	Thickened tubular basement membranes with flattened epithelial cells, expanded interstitium with fibrosis, whichever is the highest	T0: <10% T1: 10%-24% T2: 25%-50% T3: >50%

Adapted from reference 74 Royal V, Leung N, Troyanov S, et al. *Blood*. 2020;135:1833-1846