Paraprotein–Related Kidney Disease: Evaluation and Treatment of Myeloma Cast Nephropathy

Kevin W. Finkel,*† Eric P. Cohen,‡ Anushree Shirali,§ and Ala Abudayyeh† for the American Society of Nephrology Onco-Nephrology Forum

Abstract

Nearly 50% of patients with multiple myeloma develop renal disease, most commonly from AKI caused by cast nephropathy. Development of AKI is associated with poor 1-year survival and reduces the therapeutic options available to patients. There is a great need for more effective therapies. Cast nephropathy is caused by the interaction and aggregation of filtered free light chains and Tamm–Horsfall protein causing intratubular obstruction and damage. The key to treating cast nephropathy is rapid lowering of free light chains, because this correlates with renal recovery. Newer chemotherapy agents rapidly lower free light chains and have been referred to as renoprotective. There is additional great interest in using extracorporeal therapies to remove serum free light chains. Small trials initially showed benefit of therapeutic plasma exchange to improve renal outcomes in cast nephropathy, but a large randomized trial of therapeutic plasma exchange failed to show benefit. A newer technique is extended high–cutoff hemodialysis. This modality uses a high molecular weight cutoff filter to remove free light chains. To date, trials of high–cutoff hemodialysis use in patients with cast nephropathy have been encouraging. However, there are no randomized trials showing the benefit of high-cutoff hemodialysis when used in addition to newer chemotherapeutic regimens. Until these studies are available, high-cutoff hemodialysis cannot be recommended as standard of care.


Introduction

Multiple myeloma (MM) is a hematologic cancer characterized by abundant monoclonal plasma cells in the bone marrow. It represents 1% of all cancers and 13% of hematologic malignancies (1). The incidence of renal impairment in MM ranges from 20% to 50% on the basis of the definition used (2,3). Previously, the International Myeloma Working Group defined it as a serum creatinine above the upper limit of normal or >2 mg/dl or an eGFR <60 ml/min (4). More recently, the Working Group has recommended the use of the Acute Kidney Injury Network or RIFLE criteria for defining AKI in patients with MM (5). However, experience with these graded criteria in this disease is limited. In a small study of 78 patients with MM, worsening stages of AKI by RIFLE criteria were associated increased mortality, although the difference was not statistically significant (P = 0.06) given the small number of patients (6). The most common cause of AKI in patients with MM is cast nephropathy, particularly in those who require RRT. The development of AKI reduces 1-year survival in patients with MM. Also, recovery of renal function is more predictive of survival than the hematologic response to chemotherapy (7). AKI may also affect treatment options available to patients, including certain chemotherapeutic agents and hematopoietic stem cell transplantation (HSCT). Finally, myeloma can cause ESRD, with an incidence of 4.3 patients per 1 million population per year. Although the incidence of ESRD from MM has decreased over the past 2 decades, it is still associated with a higher 3-year mortality rate compared with other causes of ESRD (8).

Pathophysiology of Cast Nephropathy

Free light chains (FLCs) are the cause of cast nephropathy (9). They were first isolated from the urine of a patient with MM and later identified as polypeptide chains associated with IgS (Bence Jones proteins). Light chains are freely filtered by the glomerulus and reabsorbed by proximal tubular cells through the megalin-cubulin receptor system (10). When FLC production exceeds the reabsorptive capacity of the proximal tubule, Bence Jones proteinuria develops. Current methods for measuring the absolute and relative quantities of serum FLCs have improved monitoring of myeloma disease activity and response to treatment, and they may obviate the need for 24-hour urine collections (11).

Amounts of urinary FLCs >1 g/d are particularly apt to cause renal failure, and both κ- and λ-light chains may be involved (12). The pathologic hallmark of myeloma kidney is intratubular cast formation. The casts develop from an interaction between the monoclonal FLCs and Tamm–Horsfall protein (THP) produced by the thick ascending loop of Henle. The resultant obstruction of distal and collecting tubules causes tubular injury and atrophy. Interaction with THP is a necessary component for renal damage to occur. A competitor peptide that blocks this protein–protein interaction inhibits intratubular cast formation and prevents AKI in a mouse model (13).
Tubular obstruction with casts incites an inflammatory response, resulting in interstitial nephritis and fibrosis (14).

On occasion, cast formation is absent on a biopsy in a patient with MM and AKI. In this instance, injury is presumed to result from the direct toxic effects of urinary FLCs on proximal tubule cells (10,15). Cellular degradation of FLCs can trigger an inflammatory response through activation of the NF-κB pathway, resulting in oxidative stress, apoptosis, and fibrosis. In vitro, human proximal tubule cells exposed to human monoclonal FLCs showed kinase–dependent NF-κB activation causing increased production of monocyte chemoattractant protein 1 (16). Kidney biopsy findings include loss of brush border, cell vacuolization, and necrosis.

**Diagnostic Evaluation**

In the past, the diagnosis of cast nephropathy in patients with MM depended on urinalysis, serum and urine protein electrophoresis with immunofixation, and kidney biopsy. However, with the development of an automated immunoassay to quantitatively measure serum FLC concentrations, the diagnostic algorithm has changed and reduced the need for kidney biopsy (Figure 1) (17). In patients with MM and renal insufficiency, the likelihood of cast nephropathy can be determined by measuring serum FLC concentration and urinary albumin excretion. As recommended by the International Myeloma Working Group, patients should have a 24-hour urine protein electrophoresis in addition to a serum FLC assay (5). In patients with high levels of FLCs (>500 mg/L), urinary albumin excretion may discriminate between other forms of monoclonal gammopathies of renal significance and avoid the need for kidney biopsy (Figure 2) (18). On average, one expects that albumin will be the predominant urine protein when there is glomerular disease, such as amyloid or light-chain deposition disease, whereas albumin will typically be ≤10% of the urinary protein in cast nephropathy. The level of urinary light chains may be useful, because amounts <1 g/d point to causes of renal disease other than cast nephropathy. One recent series showed nonmyeloma–related kidney disease in almost one third of patients with myeloma who underwent kidney biopsy (19).

Although there are concerns about the safety of biopsy in patients with MM because of presumed coagulation abnormalities, several case series reported that the procedure is generally safe, with similar rates of adverse events as in the general population (20,21).

Nonparaprotein renal disease may complicate myeloma (e.g., interstitial nephritis caused by incidental [antibiotics] or therapeutic [bisphosphonates] medications, which might only be found by biopsy). Kidney biopsy may also provide prognostic information. Ecotiere et al. (21) showed, in a series of 70 patients with MM and cast nephropathy, that more than two casts per ×200 microscopic field were associated with a lack of renal recovery.

**Treatment of Cast Nephropathy**

**General Measures**

Patients should be adequately hydrated with a goal to maintain a daily urine output of >3 L/d. Medications, such as nonsteroidal anti–inflammatory drugs and renin-angiotensin-aldosterone system inhibitors, should be stopped (Table 1). Use of loop diuretics should be avoided, because they decrease THP solubility by increasing intraluminal sodium. Hypercalcemia should be corrected to prevent renal vasoconstriction and volume depletion from nephrogenic diabetes insipidus. Although urinary alkalinization reduces the net positive charge of FLCs and decreases interaction with THP (22), there are no clinical data to recommend this approach. Colchicine was shown to reduce THP secretion and FLC interaction in rats, but human studies have been disappointing (23,24).

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**Figure 1.** Simplified algorithm for evaluation of suspected paraprotein–related kidney dysfunction. Adapted from reference 13.
Chemotherapy and Stem Cell Transplantation

Recent epidemiologic studies of newly diagnosed MM show that, although the frequency of renal disease did not change over several years, both hematologic response and overall survival for patients with severe AKI significantly improved over the past decade (8,25). This improvement was attributed to the recent introduction of novel highly active chemotherapeutic agents.

Success in treating cast nephropathy is reliant on early initiation of therapy and rapid reduction in FLC concentrations. An early decrease in serum FLC levels is associated with the highest rate of renal recovery. If a significant reduction in FLC levels is achieved by day 21, 80% of patients with severe AKI will have renal recovery (26). Previous studies with conventional chemotherapy protocols showed that high-dose dexamethasone rapidly reduced FLCs. Newer novel agents, such as thalidomide and the proteasome inhibitor bortezomib, also rapidly lower FLC concentrations; this has been referred to as renoprotective chemotherapy.

Significant improvement in renal function has been reported for patients with MM treated with bortezomib–based regimens, and they are, therefore, considered the treatment of choice for patients with MM presenting with AKI (27–29). Bortezomib rapidly reduces FLC concentrations. In addition, it inhibits NF-κB pathways, reducing the release of local inflammatory cytokines and inducing antiapoptotic pathways specific for tubular cells (30). The addition of a proteasome inhibitor to human proximal tubule cells reduces monocyte chemoattractant protein 1 production induced by human monoclonal FLCs (16). Bortezomib metabolism is unaffected by renal function, and therefore, it can be safely administered at full doses to patients with renal function impairment (31,32). In a substudy of the Velcade as Initial Standard Therapy in M ultiple Myeloma: Assessment of Melphalan and Prednisone Trial comparing velcade (bortezomib)-melphalan-prednisone (VMP) with melphalan-prednisone, the complete response rates were significantly better with VMP versus melphalan-prednisone. In the VMP arm, there were no observed differences in response rates across groups on the basis of the degree of renal dysfunction (33). In a subgroup of patients with a baseline serum creatinine ≥2 mg/dl enrolled in the Dutch-Belgian Hemato-Oncology Cooperative Group and German Multicenter Myeloma Group High Dose 4 Trial, those randomized to receive bortezomib, adriamycin, and dexamethasone versus vincristine, adriamycin, and dexamethasone had a significantly longer 3-year overall survival (74% versus 34%, respectively) (34).

Thalidomide and lenalidomide are two related chemo- therapeutic agents that are also effective in the treatment of MM. Studies have shown that regimens with thalidomide or lenalidomide are more effective in reversing AKI than traditional therapy with alkylating agents. Dimopoulos et al. (29) evaluated the effectiveness of thalidomide, bortezomib, and lenalidomide in the management of patients with MM presenting with renal dysfunction. Their analysis showed that all three agents resulted in a significant improvement in renal function, with bortezomib being superior to both thalidomide and lenalidomide (renal recovery in 77%, 55%, and 43% of patients, respectively) (29). In their multivariate analysis, bortezomib-based therapies were independently associated with higher probability as well as rate of renal recovery, with the median time to improvement being 1.3 months versus 2.7 and 6 months for thalidomide- and lenalidomide-treated patients, respectively (29).

Two additional novel agents, pomalidomide and carfilzomib, have been recently approved for use in patients with refractory disease (5,35). Carfilzomib is another proteasome inhibitor, whereas pomalidomide acts by

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**Table 1. Management of paraprotein–related kidney dysfunction**

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<thead>
<tr>
<th>General measures</th>
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<tr>
<td>Discontinue nephrotoxic medications</td>
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<tr>
<td>Volume expansion with crystalloid solutions</td>
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<tr>
<td>Avoid diuretic medications</td>
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<tr>
<td>Avoid iv radiocontrast</td>
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<tr>
<td>Measure serum calcium and uric acid levels</td>
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<tr>
<td>RRT if indicated</td>
</tr>
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**Hypercalcemia**

- Volume expansion with crystalloid solutions
- Avoid loop diuretics
- Calcitonin for initial correction of severe hypercalcemia
- Bisphosphonate therapy

**Hyperuricemia**

- Volume expansion with iv saline
- Allopurinol
  - Reduces urate formation by inhibiting xanthine oxidase activity
- Rasburicase
  - Converts urate to water-soluble allantoin

**Elevated serum free light chains**

- Volume expansion with iv saline
- Chemotherapy
  - Consider proteasome inhibitor (bortezomib) and/or thalidomide- or lenalidomide-containing regimen
  - Consider extracorporeal therapy to lower free light–chain levels (preferably as part of a clinical trial)
direct antamyeloma, stroma support inhibitory, and immuno-
modulatory effects. Both agents have been proven more effec-
tive than high-dose dexamethasone in inducing remission in
patients with refractory MM. There are few data on the re-
versal of renal impairment with these agents. However, a re-
trospective subgroup analysis of a phase 3 trial assessed renal
recovery comparing pomalidomide with low-dose dexameth-
asone to high-dose dexamethasone in patients with MM re-
fractory or relapsed after bortezomib and lenalidomide (36).
Despite improved disease–free survival with the use of poma-
lidomide, in 149 patients with an eGFR of <60 ml/min before
treatment, there was no difference in the rate of renal recovery
between the two groups (42% and 47%, respectively.).

HSCT is an important and potentially curative therapy
in MM. Because significant renal dysfunction often excludes
patients from consideration for an HSCT, it is imperative that
cast nephropathy be treated early with agents that rapidly
reduce FLC concentrations. Nevertheless, recent studies have
shown that HSCT may be safe and effective in patients with
renal failure (37). A 10-year retrospective review of patients
receiving autologous HSCTs for MM with serum creatinine
>3 mg/dl (50% required dialysis) was reported from the
Mayo Clinic (38). Hematologic response was achieved in
all patients on dialysis, although only one of 15 was able
to discontinue dialysis. These findings suggest that renal
failure does not necessarily exclude patients from HSCT.

Extracorporeal Removal of FLCs

FLCs are relatively small molecular mass proteins (22.5–45 kD)
(11). Because of their size, there has been a keen interest in the
use of extracorporeal therapy as a means of FLC removal.

Therapeutic Plasma Exchange. It was initially thought
that therapeutic plasma exchange (TPE) would efficiently
lower FLC concentrations and improve kidney function.
However, data supporting this conclusion were flawed by
study design. In the largest randomized, controlled trial of
104 patients with presumed cast nephropathy (30% requiring
dialysis), TPE did not show any benefit on the composite
outcome of death, dialysis, or reduced renal function at
6 months. However, most of TPE trials were done before the
availability of bortezomib-containing regimens. In a recent
report of 14 patients with presumed myeloma kidney treated
with bortezomib and TPE, 12 had complete or partial renal
response by 6 months. The study had no control patients and
therefore, could not assess the additional benefit of TPE when
added to effective chemotherapy (39). Therefore, the use
of TPE in cast nephropathy cannot be recommended on the
basis of the current evidence.

High-Cutoff Hemodialysis. On the basis of the molec-
ular weight of FLCs, high-cutoff hemodialysis (HCO-HD)
has been recommended as another means of extracorporeal
removal. In this technique, a hemofilter with a large pore
size (10 nm) is used for repeated dialysis treatments over
several weeks to remove FLCs. High-cutoff dialyzers have a sieving curve that is shifted to the right compared
with that of high-flux dialyzers (Figure 3) (40). Because the
pore size of a high-cutoff dialyzer is twice that of a high-
flux dialyzer, its cutoff for molecular mass of filtered
substances is approximately 60,000 D (that is, >10% of
filtered substances at or below that molecular mass will
be filtered). Light chains will, thus, be removed by HCO-HD.
This cutoff value is slightly higher than that of the filters
used for continuous RRT. An in vitro study using mathe-
matic modeling of light-chain production, distribution, and
metabolism showed that an HCO-HD membrane is capable
of removing 90% of FLCs over a 3-week period (41).

In a pilot trial, three of five patients with biopsy–proven
myeloma kidney requiring dialysis treated with dexam-
ethasone, thalidomide, cyclophosphamide, and extended
HCO-HD (4–10 h/d) became dialysis independent after a
mean of 16 dialysis sessions (41). Daily treatments were more
effective in reducing FLC concentration than alternate day
treatments. Of note, the two nonresponder patients had their
chemotherapy suspended because of complications, and they
had rapid rebounds in the FLC concentrations after dialysis.
This suggests that chemotherapy is actually responsible for
the therapeutic effect rather than the addition of HCO-HD.

HCO-HD was also used in an open label study of 19
patients with biopsy–proven cast nephropathy and dialysis-
dependent AKI treated with cyclophosphamide, thalidomide,
doxorubicin, and dexamethasone (42). Patients with relapsing
disease received bortezomib. In total, 13 patients were able
to discontinue dialysis at a median of 4 weeks. Chemotherapy
was interrupted in six patients, and only one recovered renal
function. This finding again suggests that extracorporeal FLC
removal does not independently improve renal outcome
compared with highly active chemotherapy.

The largest study of HCO-HD and chemotherapy in-
cluded 67 patients with MM and dialysis–requiring kidney
failure. Over one half of the patients (57%) underwent kid-
ney biopsy, which showed cast nephropathy in the major-
ity (87%) (43). Most patients (85%) received combination
chemotherapy with dexamethasone and either bortezomib
or thalidomide. All HCO-HD treatments were extended
(>4 hours), and the medium number of sessions was 11. Treatment was not randomized, and there was no control arm. Overall, 42 patients (63%) became dialysis independent. The factors that predicted renal recovery were the degree of FLC reduction at days 12 and 21 and the time initiating HCO-HD. The lack of a control group makes it difficult to assess the benefit of HCO-HD compared with renoprotective chemotherapy alone.

An observational prospective study was reported by Zannetti et al. (44), in which all consecutive patients (n=21) with MM and AKI, confirmed because of cast nephropathy by biopsy in 71% of patients, were treated with bortezombased regimens together with intermittent HCO-HD (minimum of six treatments in 2 weeks). Dialysis independence was reached in 76% of patients at a median time of 32 days; moreover, the 3-year progression-free survival was 76%, and the 3-year overall survival rate was 67%. Again, the lack of a control group limits interpretation of the role of HCO-HD in this patient population.

The benefit of HCO-HD over current chemotherapeutic regimens is uncertain. What is clear is that bortezombiebased chemotherapy is highly effective in reversing kidney failure in a significant percentage of patients. As reported by Dimopoulos et al. (45) in a series of 83 patients with severe renal failure (eGFR<30 ml/min), of which 31 (37%) required dialysis, 72% of patients experienced improved renal function. Nearly one half (48%) became dialysis independent. Such findings will make it difficult for future studies using HCO-HD to significantly improve on these results. Two randomized trials of HCO-HD have been undertaken in Europe. In both the European Trial of Free Light Chain Removal by Extended Dialysis (EuLITE) and the Multiple Myeloma and Renal failure Due to Cast Nephropathy (MYRE) French MYRE Trial, patients with dialysis-requiring AKI from biopsy–proven cast nephropathy received bortezomib-based chemotherapy and either standard dialysis or HCO-HD (46,47). The MYRE Trial is ongoing; preliminary results of the EuLITE were presented at the 2016 Meeting of the British Renal Society. Among 90 patients randomized to HCO-HD or high-flux dialysis, HCO-HD was not associated with greater recovery of kidney function but was associated with an increased rate of infectious complications (Cockwell, et al., unpublished data).

Adsorption. In addition to HCO-HD and TPE, other extracorporeal techniques have been used to reduce serum FLC concentrations through a combination of convection and membrane adsorption. Granger Vallée et al. (49) reported that online high-efficiency hemodiafiltration was more effective than high-flux dialysis in removing both κ- and λ-light chains in six patients with myeloma. However, this study did not record renal function outcomes. Other modalities include hemodiafiltration with endogenous reinfusion, enhanced adsorption dialysis, and coupled plasma filtration adsorption. Clinical experience with these techniques is quite limited and confined to case series with very few patients. These methods should be considered experimental.

Prognosis

Recent cohort studies of patients with confirmed myeloma cast nephropathy who need dialysis and do not recover renal function have shown a 50% survival at <1 year. This improves to 50% survival at 3 years for those who are able to discontinue dialysis. There may be room for optimism. Data from the US Renal Data System were evaluated for temporal trends from 2001 to 2010, and it seems that the incidence of ESRD from myeloma may be decreasing and that survival may be increasing (8). These favorable trends can be attributed to increasingly effective chemotherapies, including thalidomide, lenalidomide, and bortezomib.

Conclusion

Cast nephropathy is the most common cause of AKI in patients with MM. Irreversible AKI is associated with reduced survival in patients with myeloma. Although recent evidence has shown the importance of the interaction between FLCs and THP in the development of cast nephropathy, there are no effective means of interfering with this process. The introduction of accurate serum FLCs assays has improved the ability to diagnose plasma cell dyscrasias and determine the risk for cast nephropathy. Chemotherapeutic regimens using renoprotective agents are able to reverse cast nephropathy in a significant number of patients, including those requiring dialysis. Although extracorporeal removal of serum FLCs may be an effective adjunct to chemotherapy, clear evidence from randomized, controlled trials is still lacking.

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Disclosures

None.

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