Myeloma Kidney: Improving Clinical Outcomes?

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Renal impairment is a common complication of multiple myeloma, affecting 20% to 40% of new cases (depending on the definition). Most cases are mild and easily reversible, but it may manifest as severe acute renal injury requiring dialysis. Renal impairment is associated with a large tumor mass and consequently confers a poor prognosis. The prognosis of myeloma has improved with the introduction of novel agents and autologous stem cell transplantation. These improvements appear to apply equally to patients with renal impairment, although the risk of complication is usually higher in this group of patients. In addition to improved overall survival, there is some evidence that novel therapies have improved the renal prognosis. Treatment with high-dose dexamethasone and bortezomib can rapidly reduce light chain production and provide an opportunity for renal recovery. Although trials of plasma exchange (to remove the nephrotoxic light chain) have shown a disappointing lack of benefit, high cutoff dialysis removes larger quantities of light chain; therefore, trials are underway to investigate whether this can improve the renal prognosis independently of chemotherapy. Outcomes in patients with myeloma kidney do appear to be improving, but more trials are needed (some of which are in progress). There is cause for optimism for physicians and for patients suffering from this condition.

Key Words: Multiple myeloma, Renal impairment, Bortezomib, Plasma exchange, High cutoff dialysis

Multiple myeloma is the second most common hematological malignancy and accounts for about 1% of all neoplastic diseases and 13% of hematological malignancies.[1] Median age at diagnosis is about 65 years, and only 2% of patients are aged <40 years.[2] The incidence of multiple myeloma is approximately 58 per million in most high-income countries.[3,4]

Renal impairment is a common complication of myeloma and (depending on the definition) occurs at some point in 20% to 40% of cases.[5,6] Renal impairment (defined as a serum creatinine level >177 μmol/L) is the "R" of the CRAB criteria for myeloma-related organ or tissue injury (the others being hypercalcemia, anemia, and bone disease). The major causes of renal impairment are cast nephropathy and hypercalcemia. Cast nephropathy is caused by filtered light chains exceeding the proximal tubules' reabsorptive capacity and precipitating with Tamm–Horsfall protein in the distal tubule to form characteristic "casts." These casts trigger an inflammatory —and subsequent fibrotic— reaction (Fig 1).[7,8] Excess free light chains do not always cause renal impairment. Nephrotoxicity appears to be light chain-specific, that is, some light chains are extremely nephrotoxic, whereas others, despite being present at high concentration, do not cause kidney injury.[9] The precise characteristics of the light chain that mediates nephrotoxicity remain unknown,[10,11] although nephrotoxic light chains have a greater propensity to self-aggregate under physiological conditions than non-nephrotoxic light chains.[12] Mice injected with light chains obtained from human subjects with kidney injury develop a similar renal lesion, suggesting that the structure of the molecule determines the pattern of any injury.[9]

Light chains are filtered by the glomerulus and may be taken up by mesangial cells (toxicity to which may cause amyloidosis or light chain deposition disease) or tubular epithelial cells where they can activate nuclear factor-kappa B and cause apoptosis or epithelial to mesenchymal transition.[8]

There are numerous other causes of renal impairment (Box 1), which frequently coexist and interact. For example, dehydration increases the urinary light chain concentration, and hence precipitation.

Although in most cases the kidney injury is mild and easily reversed by hydration and control of serum calcium concentration,[6,13] it can be severe in some cases. It is not uncommon for these patients to present with unexplained acute kidney injury.[14] Some series have reported that up to 10% of new cases of myeloma have kidney injury severe enough to require dialysis.[15,16] Multiple myeloma can also cause CKD, which may be progressive.[17] Some authors have suggested this occurs in 25% of patients, although this is not a uniform experience.[18] Severe, irreversible, acute kidney injury and progressive CKD both can result in ESRD.

National and international registries report that about 1% of all patients starting renal replacement therapy (RRT) have multiple myeloma as the primary cause of renal disease. The classification of primary renal diseases (and those relating to paraproteinemias in particular) used by these registries has been criticized, and it may lead to either over- or underestimation of the true incidence of such conditions.[19] RRT was started in 3298 patients with multiple myeloma in the United States between January 1992 and June 1997,[20] 2453 patients with

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Box 1. Causes of Renal Impairment in Multiple Myeloma

Cast nephropathy (light chain precipitation in distal and collecting tubules)
Hypercalcemia
Dehydration
Hyperuricemia
Nonsteroidal anti-inflammatory drugs
Nephrotoxic antibiotics (eg, gentamicin)
Intravenous radiographic contrast agents
AL/AH amyloidosis
Monoclonal immunoglobulin deposition diseases
Direct infiltration of kidney by plasma cell
Fanconi syndrome

multiple myeloma in the countries observed by the European Dialysis and Transplant Association registry between 1985 and 2005.[21]

When considering clinical outcomes in patients with myeloma kidney (ie, renal impairment due to underlying multiple myeloma), 2 main outcomes of interest are observed: overall survival and survival independent of RRT. Both of these are strongly linked to the characteristics of the underlying plasma cell clone (including stage of disease) and its response to treatment. Before considering whether clinical outcomes have improved, it is worth reviewing the effect of renal impairment on clinical outcomes in patients with multiple myeloma.

CLINICAL SUMMARY

- Renal impairment is a common complication of myeloma and is associated with a large tumor mass, and therefore indicates a poor prognostic group.
- The prognosis of patients with myeloma has improved recently after the introduction of novel agents and ASCT. These improvements appear to apply to patients with renal impairment, although the risk of complications is higher.
- The renal prognosis also appears to be improved with these novel treatments, although few trials have investigated this.
- Renal prognosis may also be improved by mechanical removal of the light chain with high cutoff dialysis (but not plasma exchange), and trials testing this hypothesis are ongoing.

Prognostic Impact of Renal Impairment in Multiple Myeloma

Early studies suggested that renal impairment was associated with a worse prognosis in patients with multiple myeloma. An analysis of the Medical Research Council's fourth myelomatosis trial (published in 1984) showed that patients presenting with a new diagnosis of multiple myeloma and a urea concentration >15 mmol/L had a dramatically worse outcome than those with urea concentration ≤15 mmol/L ($P < .0001$).[22] In a review of 5 similar, later MRC trials conducted between 1980 and 2002, renal impairment was more common in patients who died early (ie, <60 days from presentation).[23] However, a logistic regression model did not identify renal impairment as being associated with increased odds of an early death. Severe acute kidney injury is associated with a poor prognosis: 1 series showed that the median survival was 10.2 months (compared with 3-4 years for patients with myeloma as a whole).[1,24] However, other series have not identified renal impairment as an independent marker of poor prognosis once myeloma cell mass is adjusted for.[25]

Before the introduction of the International Staging System (ISS),[26] the most commonly used staging system was that of Durie and Salmon (Table 1).[27] This was developed from data on 71 patients as a method of estimating myeloma cell mass from clinical and laboratory characteristics, as this was well known to be a strong determinant of prognosis. Although serum creatinine level was removed from their model used to estimate the tumor cell mass, it was included in the staging system because it strongly predicted both response to treatment and survival within each group of tumor cell mass. However, the ISS does not incorporate serum creatinine level or eGFR (Table 1).

In the 1980s, serum β_2-microglobulin was first identified as a strong prognostic indicator in multiple myeloma.[28] One of the strengths of serum β_2-microglobulin is that it integrates both myeloma cell mass and renal function. In the 10,750 patients whose data were used to develop the ISS, it had the strongest association with prognosis (hazard ratio 1.81 for β_2-microglobulin ≥3.5 mg/L compared with <3.5 mg/L, which was not attenuated by multivariable adjustment).[26] Although serum creatinine level was also associated with prognosis after multivariate adjustment (hazard ratio 1.28 for serum creatinine level ≥177 μmol/L compared with <177 μmol/L), it was not included in the final staging system because it only identified a relatively small proportion (17%) of patients. More recently, a risk score developed using data from 198 patients identified eGFR and β_2-microglobulin as the major variables predicting prognosis, but serum albumin level was not included in the model because results were not available for all patients.[29]

The sum of the evidence suggests that renal function is closely correlated with myeloma cell mass, that is, patients with a large tumor burden are more likely to have renal impairment. In the ISS cohort, 1138 of 1382 (82%) patients with serum creatinine level ≥177 μmol/L were in stage III.[26] Similarly, 1138 of 2662 (43%) patients in stage III