

Management of multiple myeloma patients with renal disease

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ABSTRACT

Multiple myeloma (MM) is a plasma cell dyscrasia, accounting for 10% of all hematological malignancies, which translates into a global age-standardized incidence and mortality rate of 2:1 per 100.000 and 1.39 per 100.000 respectively (1). Kidney disease is a very common complication of MM, increasing the mortality and being a poor prognostic factor. Renal impairment is often the first reason for patient admission, leading to the plasma cell dyscrasia as being the cause. 40% of patients with cast nephropathy had previously undiagnosed myeloma (2). The aim of this paper is to show that Prompt diagnosis and initiation of therapy warrants better patient survival and delays, or even prevents organ damage in multiple myeloma.

Keywords: multiple myeloma, kidney disease, chemotherapy, immunomodulatory drugs, kidney transplant

INTRODUCTION

Multiple myeloma (MM) is a plasma cell dyscrasia, accounting for 10% of all hematological malignancies, which translates into a global age-standardized incidence and mortality rate of 2:1 per 100.000 and 1.39 per 100.000 respectively (1). Kidney disease is a very common complication of MM, increasing the mortality and being a poor prognostic factor. Renal impairment is often the first reason for patient admission, leading to the plasma cell dyscrasia as being the cause. 40% of patients with cast nephropathy had previously undiagnosed myeloma (2). In terms of survival, some studies indicate that it is reduced at only 1 year in patients with severe AKI that do not recover renal function. It was shown that renal function recovery after reversibility of the myeloma-associated kidney injury predicts patient survival more accurately than the response to chemotherapy (3,4).

Kidney disease in MM often presents as renal insufficiency and proteinuria, sometimes with signs of tubular dysfunction (improper acidification and concentration of the urine), cast nephropathy leading to AKI, or, less often, the Fanconi syndrome. The nephrotoxic process varies from malignancy hypercalcemia (HCM), dehydration, immunoglobulin deposition, amyloidosis to nephrotoxic agents and infections.

Prompt diagnosis and initiation of therapy warrants better patient survival and delays, or even prevents organ damage. Clear improvement of outcome in patients with MM has been shown in the last decade, as novel therapies have emerged, regimens which also have seemed to improve MM associated renal damage (5). An important predictor for patient survival and renal function recovery is the early, prompt reduction of serum FLCs (6).

Management of renal impairment/failure in MM patients begins with immediate initiation of specific

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therapeutic measures – antimyeloma therapy (if not yet administered), followed by supportive care, additional mechanical means, including plasma exchange, hemodialysis using specific filters and kidney transplant.

DRUG REGIMENS USED IN MANAGEMENT OF MM PATIENTS

The first therapy regimen used in MM since 1960 is melphalan-prednisone (MP), and is still widely accepted in elderly patients who are not eligible for high-dose therapy (7). High-dose dexamethazone regimens, as VAD (vincristine, adriamycin, dexamethasone) or pulse-dexamethasone (DEX), have been used since 1990 with response rates of 40%, with fewer complications for DEX (4% DEX vs. 27% VAD) (8). MP regimen is preferred to M-Dex as comparison reference for new treatments with innovative drugs (9).

Novel agents like Thalidomide, Lenalidomide, Bortezomib, in combination with dexamethasone +/- other drugs, proved to have high response rates and lead to renal function recovery and independence from dialysis.

Bortezomib is a proteasome inhibitor. In association with dexamethasone, is the first choice of antimyeloma therapy in MM patients with renal impairment and it was proven to be the most effective therapy in severe AKI associated MM. Dose adjustment is not required in renal failure. It has a rapid onset of action, being very effective in the prevention of permanent kidney injury (10,11). Approximately 50% of MM patients with AKI will have a significant and rapid improvement in renal function, if there is response to therapy with Bortezomib (12,13).

Thalidomide and Lenalidomide, a potent derivate, are immunomodulatory drugs used as novel therapies in MM patients. In patients with advanced disease, triple therapy which includes thalidomide or cyclophosphamide, bortezomib and dexamethasone is recommended. Lenalidomide needs to be carefully used in CKD, with mandatory dose reduction, due to its renal clearance. However, Lenalidomide is not nephrotoxic and a dose of 5-10 mg/day can be used (2). Similarly with Bortezomib, Thalidomide's efficacy does not seem to be affected by renal function, but there are evidence of unexpected hiperkalemia in these patients (14). It's also been shown that safety and efficacy of Thalidomide regimens in renal impairment is similar to Bortezomib, but has the advantage to preserve stem cell transplant options (15).

Carfilzomib is a second-generation proteasome inhibitor, approved for treatment of relapse/refractory MM (RRMM) in regimens with lenalidomide and dexamethasone or with dexamethasone alone. In the ENDEVOUR trial, Carfil-

zomib+dexamethasone showed longer progression free survival over Bor-Dex regimen, in patient with RRMM and complete renal response (CrCl raise over 60 ml/min in any 2 consecutive visits with baseline CrCl < 50 ml/min), rates were 15.3% and 14.1% for those who received Car-dex vs. Bor-Dex regimens (16). Carfilzomib is also safe for patients with any grade of renal disease, as it is enzymatically metabolized (17).

Monoclonal antibodies are a very important therapeutic breakthrough for MM patients in the last decade. Several trials have been conducted for monoclonal anti-cd38 antibodies – Daratumumab and Isatuximab as first line treatment strategies as well as for refractory disease management.

Anti-SLAMF7 antibody Elotuzumab, in combination with Lenalidomide or Thalidomide, may improve clinical outcomes for patients with refractory or relapsed disease. Belatumumab mafotidin is an antibody drug conjugate against B cell maturation antigen. It has been approved for use in monotherapy in advanced disease (18). Isatuximab (Isa), a monoclonal CD38 antibody, is approved for the treatment of patients with relapsed/refractory MM, in combination with pomalidomide (Pd) and dexamethasone, who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor.

It is necessary to investigate more about these agents renal safety and efficacy on renal disease improvement. In a 2021 ICARIA MM subgroup analysis, complete renal response rates were significantly higher in the Isa-Pd regimen group vs. Pd alone (71.9% vs. 38.1%). Moreover, the data suggests there is no need for dose adjustment in patients with renal impairment (19).

A subgroup analysis of IKEMA study examined renal response and safety as well as efficacy of Isa-Car and Dexamethasone vs. Car-Dex in RMM patients with renal impairment. Results showed the Isa regimen improved progression free survival and disease response, but also reversal of renal impairment and long term renal response compared to Car-dex (20).

SUPPORTIVE CARE

Alongside specific therapies, a major role in recovery of renal function in patients with MM is attributed to supportive care. Adequate hydration by high fluid intake, urine alkalization, prompt treatment of infection, management of anemia, avoidance of nephrotoxic agents (NSAIDs, aminoglycoside, contrast dyes) are all equally important. Management of hypercalcemia in patients with renal failure includes only hydration for mild, asymptomatic hypercalcemia. For moderate to severe hypercalcemia, steroid antimyeloma regimens are recommended and calcitonin administration; when

renal function improves, patients can receive biphosphonate: Zoledronic acid and Pamidronate.

DIURETICS

One of the most important parts in the management of the MM patient with AKI is hydration and alkalisation of the urine (the most common cause of AKI being cast nephropathy), in order to increase tubular flow and urine pH. If the patient is oliguric, it requires diuretics in order to increase urinary flow.

Loop diuretics are not a good choice in this case, because they raise urinary sodium concentration, favouring tubular cast formation (the mechanism for this probably being the enhancement of Tam-Horsfall glycoprotein production) (21-23). They should therefore be used only in cases of severe fluid overload. Mannitol is an osmotic diuretic which acts in the proximal and distal tubules, resulting in an important water diuresis and washout effect. It also has antioxidative property, by reducing the damage of tubular cells and by enhancing local production of prostaglandins and lowering rennin levels, thus improving renal blood flow (24-26).

For patients with CKD stage 1 and 2, KDIGO recommends using any type of diuretics, according to the patient's clinical features: thiazide diuretics: Chlortalidone, Hydrochlorothiazide (risk of hyperuricemia), Indapamid, Metozolone; loop diuretics: Furosemide, Bumetanide, Torsemide; their advantages are the bioavailability is not affected by the presence of CKD, can be used in advanced CKD: eGFR < 30 ml/min, although they might contribute to myeloma cast nephropathy; potassium sparing diuretics: Triamterene, Amiloride, Spironolactone, Eplerenone, with caution at the risk of hyperpotasemia (greater if eGFR < 60ml/min). For patients with stage 3 CKD, thiazide and loop diuretics are suitable and for stage 4, loop diuretics are the main diuretic agent used. In case of nephritic syndrome, the best approach is to use a combination of diuretic agents: thiazide, loop and potassium sparing diuretics. Rojas et al. found in an experimental study in 2017 a potential therapeutic effect of amilorid in MM, discovering that it may have a synergistic effect when combined with dexamethasone, melphalan and lenalidomide (27).

MECHANICAL MEANS

Plasma exchange

Plasmapheresis or plasma exchange is a procedure that involves separation and removal of certain substances and cells such as lipoproteins, paraproteins, immune complexes, autoreactive antibodies and inflammatory mediators such as cytokines.

Current chemotherapy, especially Bortezomib, may induce a rapid and sustained myeloma response and

rapid decrease of FLCs production, but high levels of toxic FLCs may still circulate, especially in patients with reduced renal clearance, resulting in prolonged exposure of the kidney to the toxic FLCs. In normal renal function half life of FLCs is 3 to 6 h; in RF half life is 2-3 days.

Plasmapheresis has been tested for removal of FLCs in patients with MM and renal damage in order to improve kidney function. Data in literature regarding the role of plasmapheresis in MM patients with cast nephropathy and renal failure is conflicting. Johnson et al. concluded in a systemic review that PF doesn't affect overall survival or need for dialysis in MM patients with AKI (28). Burnette et al. showed that plasma exchange in combination with bortezomib-based chemotherapy, is associated, in a limited number of patients, with high rates of renal recovery (29). Another study by Hutchison et al. on patients with histological diagnosis of cast nephropathy and severe renal failure, highlighted that early PF treatment correlates with improvement of renal function as well as in median survival (30). In general, plasma therapy is combined with chemotherapy for almost a 60% reduction in FLC, but it remains unclear if this reflects the PF efficacy or that of bortezomib (31,32).

Other mechanical means – use of specific dialysis filters

High cutoff hemodialysis (HCO-HD) is currently used as an adjuvant to chemotherapy in patients with MM and AKI. It can remove an important quantity of sFLC, but the effect on clinical evolution is uncertain. The most recent meta-analysis by Tarragon et al. suggests that HCO-HD can reduce significantly sFLCs but has no effect on all-cause mortality. Renal outcomes apparently are the same as in conventional HD for patients with cast nephropathy, though the trend is towards a better renal function with HCO-HD (33).

In the EULITE trial (phase 2), newly diagnosed patients with MM and cast nephropathy, having AKI which required dialysis, were randomly treated (1:1) with HCO-HD and standard HF-HD and they all received chemotherapy (Bortezomib-doxorubicin-dexamethasone), on a 2-year follow-up. The results showed that HCO-HD didn't reach better clinical outcomes in comparison with HF-HD (34).

On the opposite side, in a study on 67 patients with ESRD and MM, dialysis dependent, treated with chemotherapy and HCO-HD, Hutchison et al. showed that 76% had a sustained reduction in sFLC concentration, of which 71% eventually became dialysis independent (35). The same authors reported a number of 14 out of 19 patients became dialysis independent after extended HCO-HD associated chemotherapy, with a reduction in FLCs of 50% (36).

A systematic review, including the Eulite trial, and 4 other studies, this time on patients receiving either pF or HCO-HD, conclusions were the same – no improvement in survival, nor in clinical outcome using neither of the mechanical means (37).

Bottomline, larger RCTs, with longer follow-up periods need to be performed to further assess the clinical outcomes of HCO-HD.

HEMODIALYSIS

Renal replacement therapy is required in a large number of patients with myeloma and ESRD. When e-GFR reaches values smaller than 15 ml/min/1,73m², RRT must be taken into consideration. KDIGO recommends dialysis initiation when there are clinical manifestations related to CKD, such as electrolyte or acid-base disorders (hyperkalemia, acidosis), serositis, pruritus, when fluid overload can't be managed only with medication, uncontrollable AH, poor nutritional status unresponsive to dietary measures, cognitive disorders, peripheral neuropathy, rapidly progressive renal failure. Often, these signs and symptoms appear at GFR of 5-10 ml/min.

The absolute HD contraindication is the absence of a viable vascular access and relative contraindications are: advanced malignancies, major psychiatric disorders, coagulation disorders, decompensated systemic disorders, CCF class IV NYHA, haemorrhagic acute stroke, liver cirrhosis with encephalopathy or HRS.

An ERA-EDTA registry study showed that the number of patients with MM or LCDD increased in the passed 20 years in Europe, with a median survival for patients on RRT of 0,91 years (non-MM patients had a 4,46 years median survival) (38).

A population-based study in Taiwan showed high mortality rates in MM patients on HD in the first year. It is suggested though that prompt initiation of HD in addition to chemotherapy may be beneficial to patient outcome (39).

Peritoneal dialysis may be a good alternative for patients who need to preserve their vascular bed or for those who don't have a vascular access or is difficult to create one (diabetes mellitus patients), for patients with CKD over 60 years old, children, patients waiting for renal transplant or a functioning arterio-venous fistula, patients with heparin allergy, recent hemorrhagic stroke or gastro-intestinal bleeding.

Peritoneal dialysis contraindications are absolute (peritonitis, peritoneal carcinomatosis, ascites, peritoneal fibrosis; recent abdominal surgery or abdominal trauma, inflammatory bowel diseases) and relative (abdominal wall infections, intraabdominal malformations, severe lung and cardiovascular disease, colostoma, nephrostoma, ADPKD, physical and psychological handicaps).

CAPD is being used only in limited number of patients with renal failure due to multiple myeloma, despite the fact it is not associated with circulatory stress, it grants better preservation of hemoglobin, higher clearance of paraproteins, and higher chances of recovery of renal function than maintenance hemodialysis.

STEM CELL TRANSPLANTATION

Despite novel therapies, stem cell transplantation is a very important part of MM patients management, especially for those younger who qualify. The right moment for initiation is still debatable.

High dose therapy (HDT) and autologous stem cell transplantation (ASCT) is recommended and feasible in MM patients with renal impairment, including patients on dialysis. It has, though, a risk of toxicity (40) and is contraindicated in patients with severe systemic involvement due to high mortality (4).

A reduced dose of Melphalan 140 mg/m² is used in MM patients with low eGFR or undergoing dialysis (41). Transplant-related mortality is 4-29% vs. < 1% in patients who recovered a normal renal function after initial therapy (42-44).

RENAL TRANSPLANTATION (RT) IN MM PATIENTS WITH END-STAGE RENAL DISEASE (ESRD)

Renal transplantation is rare due to the nature of the disease: MM patients die in median of 3-5 years after diagnosis. There is high risk of infections and MM several relapses often expose the renal graft to toxic light chains. Use of specific immunosuppression therapy is difficult in these patients (45,46). RT could be considered in MM patients who attain long-lasting responses or who may have complete response for several years (47-49). A combination of ASCT with RT might also be considered (50).

PROGNOSIS OF MM PATIENTS WITH RENAL IMPAIRMENT

Infection and renal failure are the main direct causes of early mortality in MM patients (51). Early death risk increases more than fourfold for MM patients with severe renal damage (52). Also, MM patients who present with AKI have increased early mortality (30% in the first 2 months) (53). Patients with renal failure also have increased infection susceptibility, they require prolonged hospitalization and have greater risk of developing acute tubular necrosis due to drugs nephrotoxicity, all of this contributing to a poorer prognosis. Knudsen et al. concluded that reversibility of renal fail-

ure improves long term survival, being more easy to achieve in patients with moderate renal impairment, hypercalcemia and low BJ protein excretion. RF, stage 3, old age and hyprecalcemia were independent survival prognostic factors (54). In another analysis, median survival of patients with renal failure was 19.5 months, compared with 40.4 months for those without RF. Independent variables associated with survival were poor performance status, advanced age, high LDH, thrombocytopenia and elevated B2-microglobulin, but not the high values of sCr (55). Improvement of prognosis began to show when novel agents and therapies emerged.

CONCLUSIONS

Renal disease is one of the major end-organ impairments in multiple myeloma, being triggered by FLCs ne-

phrotoxicity through a variety of mechanisms. Multiple myeloma should always be considered in patients with renal impairment and proteinuria without any other apparent, identifiable cause, as early diagnosis and prompt treatment administration improves renal outcomes and survival. Prognosis has improved since the discovery of novel agents. Utilisation of HCO-HD is promising but larger RCTs, with longer follow-up periods need to be performed to further assess the clinical outcomes of HCO-HD. ASCT is feasible for patients with moderate renal impairment and low systemic involvement and patients with long-lasting remission periods or complete response for several years, may qualify for renal transplantation.

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