



Management of multiple myeloma-related renal impairment: recommendations from the International Myeloma Working Group

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Here, the International Myeloma Working Group (IMWG) updates its clinical practice recommendations for the management of multiple myeloma-related renal impairment on the basis of data published until Dec 31, 2022. All patients with multiple myeloma and renal impairment should have serum creatinine, estimated glomerular filtration rate, and free light chains (FLCs) measurements together with 24-h urine total protein, electrophoresis, and immunofixation. If non-selective proteinuria (mainly albuminuria) or involved serum FLCs value less than 500 mg/L is detected, then a renal biopsy is needed. The IMWG criteria for the definition of renal response should be used. Supportive care and high-dose dexamethasone are required for all patients with myeloma-induced renal impairment. Mechanical approaches do not increase overall survival. Bortezomib-based regimens are the cornerstone of the management of patients with multiple myeloma and renal impairment at diagnosis. New quadruplet and triplet combinations, including proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies, improve renal and survival outcomes in both newly diagnosed patients and those with relapsed or refractory disease. Conjugated antibodies, chimeric antigen receptor T-cells, and T-cell engagers are well tolerated and effective in patients with moderate renal impairment.

Introduction

Renal impairment is among the cardinal features of multiple myeloma; up to 50% of patients with multiple myeloma present with renal impairment (defined as estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m²) at the time of diagnosis, and 2–4% require dialysis.^{1–5} The differences in the reported incidence of renal impairment among studies might be partly attributed to different definitions of renal impairment, including serum creatinine concentrations higher than 2 mg/dL or higher than the upper normal limit,^{2,5} and eGFR less than 60 mL/min per 1.73 m²,¹ or less than 40 mL/min per 1.73 m².^{2,6}

Renal impairment has been linked to decreased overall survival and increased risk of early death for people with multiple myeloma.^{2,5,7–10} A meta-analysis of 11 randomised controlled trials done between 2005 and 2019 found that patients with multiple myeloma and renal impairment had a greater relative risk of myeloma progression or mortality than those without renal impairment, for both newly diagnosed patients (relative risk 1.07, 95% CI 1.001–1.046; $p=0.05$) and patients with relapsed or refractory disease (1.20, 1.003–1.431; $p=0.05$).¹¹ New therapies, such as proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies, improved both overall survival and kidney function, especially when compared with standard chemotherapy.^{7,8,12–15} Despite the fact that improved renal function has been associated with prolonged survival, overall survival was still lower in patients presenting with renal impairment than patients without renal impairment at the time of multiple myeloma diagnosis.^{3,7,8}

The introduction of new agents against multiple myeloma has enhanced the therapeutic choices for patients with multiple myeloma both at diagnosis and at relapsed or refractory disease.¹⁶ However, special considerations have to be made for patients with renal impairment. The International Myeloma Working Group (IMWG) aimed to review all currently available evidence and update previous recommendations¹⁷ for the management of renal impairment in patients with multiple myeloma.

Methods

Search strategy and selection criteria

An interdisciplinary panel of clinical experts on multiple myeloma and renal impairment reviewed available evidence published in randomised clinical studies, meta-analyses, systematic reviews of published clinical studies, observational studies, and case reports, and developed these recommendations on behalf of the IMWG. The panel included myeloma and nephrologist specialists who are members of the IMWG. The recommendations were initially circulated in draft form to each panel member, who had an opportunity to comment on the levels of evidence as well as the systematic grading of clinical data supporting each recommendation. The manuscript subsequently underwent rounds of revision until consensus was reached by all authors. MEDLINE, Embase, and Cochrane bibliographic databases, along with abstract lists from major haematology–oncology conferences including the American Society of Hematology, the American Society of Clinical Oncology, the European Hematology Association, and the European

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See Online for appendix

Society for Medical Oncology were searched from conception to Dec 31, 2022, for studies written in English, French, German, or Spanish. Search terms included a combination of the following: “multiple myeloma”, “myeloma”, “creatinine clearance”, “eGFR”, “renal”, “renal impairment”, “renal dysfunction”, “renal insufficiency”, “renal response”, “acute kidney injury”, “chronic kidney disease”, “cast nephropathy”, “dialysis”, “plasmapheresis”, and “renal biopsy”.

Levels of evidence, grade recommendations, and consensus formation

Levels of evidence and grades of recommendations were assigned using established criteria in line with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system and in accordance with the previously published recommendations from the IMWG (appendix p 1).^{18,19} When published clinical data were deemed insufficient to make clear conclusions, an expert panel consensus provided further recommendations. We did not receive any external support. The first draft was distributed to each panel member for critical review and input. The paper was revised three times by the panel members before reaching consensus by all authors and formulating the final recommendations. Compared with the recommendations on diagnosis and staging, the main updates of the current recommendations pertain to the therapeutic approach to multiple myeloma-related renal impairment.

Pathophysiology of renal impairment in patients with multiple myeloma

Renal damage in patients with multiple myeloma is primarily attributed to the toxic effects of monoclonal free light chains (FLCs) on the glomeruli and renal tubules.^{17,20} Under physiological conditions, FLCs are freely filtered through the glomerulus, endocytosed by proximal tubule cells through the megalin-cubulin receptor complex, and catabolised. In patients with multiple myeloma, the overproduction of monoclonal FLCs can surpass the absorptive and catabolic capacity of proximal tubule cells.²⁰ Residual FLCs in the proximal tubules might activate apoptotic molecular cascades and induce inflammation, which leads to fibrosis. Unabsorbed FLCs that reach the distal nephron can interact with Tamm-Horsfall protein and form aggregates, which precipitate and result in cast formation and subsequent tubular obstruction and inflammation.²⁰ These are the main pathophysiological mechanisms that lead to light-chain cast nephropathy, which is found in most patients with multiple myeloma and might lead to acute kidney injury.²¹ When light-chain cast nephropathy occurs in the setting of a plasma cell disorder, it is called myeloma cast nephropathy.

Other renal diseases that might co-exist and are associated with the deposition or precipitation of the entire monoclonal immunoglobulin or its fragments include immunoglobulin-related amyloidosis, monoclonal immunoglobulin

deposition disease, light-chain proximal tubulopathy, Fanconi syndrome, cryoglobulinaemic glomerulonephritis (type I and II), proliferative glomerulonephritis with monoclonal immunoglobulin deposits, cryocrystalglobulinaemia or crystalglobulin-induced nephropathy, crystal-storing histiocytosis, immunotactoid glomerulonephritis, and C3 glomerulopathy with monoclonal gammopathy.²¹ The presence of at least one of these entities associated with the production of nephrotoxic monoclonal immunoglobulin in the absence of otherwise symptomatic multiple myeloma lies in the spectrum of monoclonal gammopathy of renal significance.^{21,22}

Non-immunoglobulin related factors could also lead to renal impairment in patients with multiple myeloma, including dehydration, hypercalcaemia, infections, tumour lysis syndrome, nephrotoxic drugs, such as non-steroidal anti-inflammatory drugs, contrast media, antibiotics, diuretics, and renin-angiotensin-aldosterone system blockers, and anti-myeloma treatment, including bisphosphonates and possibly carfilzomib.^{17,20} Taking into consideration that the median age at multiple myeloma diagnosis is approximately 70 years,²³ normal age-related decline in renal function and the presence of comorbidities, such as diabetes, atherosclerotic vascular disease, and heart failure, might predispose for renal impairment in these patients.

Diagnosis and staging of renal impairment in patients with multiple myeloma

Early identification and prompt management of renal impairment both at diagnosis and at relapse is of utmost importance to optimise patient outcomes.²⁴ The IMWG defines renal impairment in people with multiple myeloma as serum creatinine higher than 2 mg/dL (170 µmol/L) or impaired creatinine clearance (<40 mL/min) due to multiple myeloma.^{6,17} An algorithmic approach should be followed to differentiate between the potential causes of renal impairment in patients with multiple myeloma (figure). More than one immunoglobulin-related or immunoglobulin-unrelated kidney disease might be present in the same patient concomitantly. The pattern of 24-h urine protein electrophoresis and serum FLC concentrations might lead to the diagnosis.^{25,26} Renal biopsy might be required for patients with inconclusive results (figure). Therefore, collaboration with the nephrologist should be promptly initiated for diagnostic evaluation and treatment.

The eGFR could be calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)^{27,28} equation without the race variable,²⁹ to measure creatinine clearance in patients with stable renal function.³⁰ The CKD classification can be used for the staging of stable renal impairment (table 1).³¹ The addition of cystatin C in the CKD-EPI equation outperforms the Modification of Diet in Renal Disease formula,³² in terms of both sensitivity for renal impairment detection and prognostic value for overall survival in newly diagnosed patients with

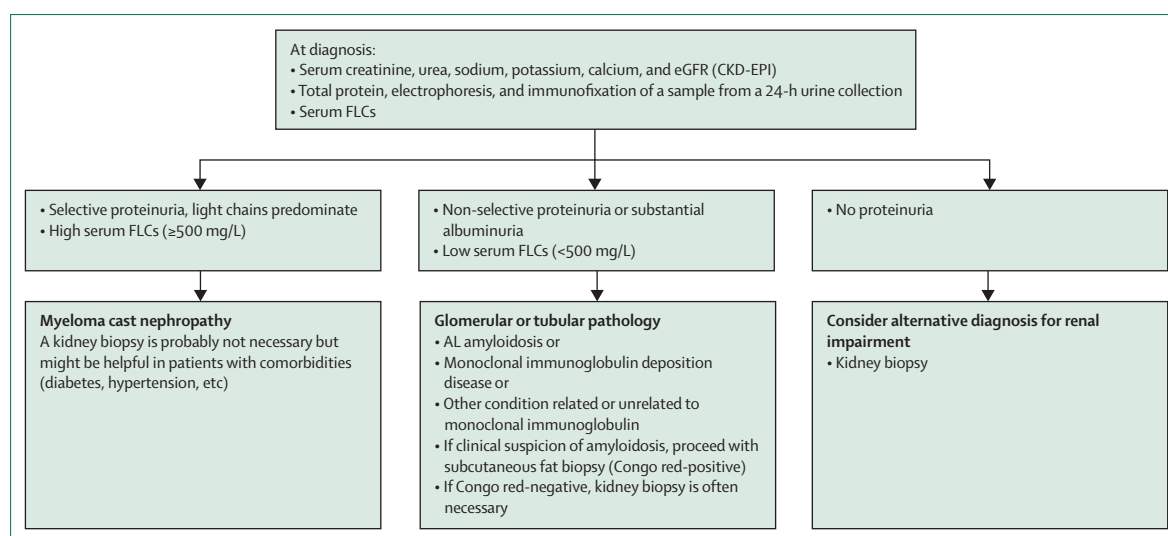


Figure: Algorithm for the differential diagnosis of renal impairment in patients with multiple myeloma

CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration. eGFR=estimated glomerular filtration rate. FLCs=free light chains.

multiple myeloma.^{33,34} The National Kidney Foundation and the American Society of Nephrology Task Force recommend national efforts to facilitate increased, routine, and timely use of cystatin C, especially to confirm eGFR in adults who are at risk for or have chronic kidney disease, because combining filtration markers (creatinine and cystatin C) is more accurate and would support better clinical decisions than either marker alone.²⁹ However, continuous refinement of the equation to estimate GFR is still ongoing.³⁵ Furthermore, β_2 -microglobulin concentrations are increased in patients with multiple myeloma and renal impairment and this parameter is included in the revised International Staging System for multiple myeloma.³⁶ The differential prognostic impact of increased β_2 -microglobulin concentrations from tumour load versus renal impairment is not known.

In cases of acute kidney injury, the Kidney Disease: Improving Global Outcomes (KDIGO), the Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE), and the Acute Kidney Injury Network (AKIN) criteria can be used (table 2).³⁷ KDIGO and AKIN might be more sensitive for the detection of acute kidney injury in critically ill patients.³⁷ However, RIFLE might identify more patients with haematological malignancies and acute kidney injury after transplantation than AKIN,³⁸ and it might predict long-term outcomes in patients with multiple myeloma.³⁹ Prospective studies are encouraged to establish the optimal method of evaluation of acute kidney injury in patients with multiple myeloma.

Recommendations

All patients with multiple myeloma and renal impairment should have serum creatinine, eGFR, electrolytes, and FLCs measurements together with total protein, urine electrophoresis, and immunofixation of a sample from

Description		eGFR (mL/min per 1.73m ²)
1	Normal or elevated eGFR	≥90
2	Mild reduction in eGFR	60–89
3	Moderate reduction in eGFR	30–59
4	Severe reduction in eGFR	15–29
5	Renal failure or end-stage renal disease	<15 or RRT

eGFR=estimated glomerular filtration rate. RRT=renal replacement therapy

Table 1: Staging of chronic kidney disease

a 24-h urine collection at diagnosis and at disease assessment (grade A recommendation). If non-selective proteinuria (mainly albuminuria) or involved serum FLCs value less than 500 mg/L is detected, and in the absence of other known causes of exacerbation of renal impairment, such as nephrotoxic medications, hypercalcaemia, infection, and dehydration, then a renal biopsy should be done to identify the cause of renal impairment, especially in the absence of amyloid material in subcutaneous fat or in other tissues (grade B recommendation).

The CKD-EPI formula without the race variable should be used for the evaluation of renal function and the CKD staging should be used for the classification of patients with multiple myeloma with stabilised serum creatinine concentrations (grade B recommendation). If available, the addition of cystatin C as a variable might improve the CKD-EPI calculations (grade B recommendation). Baseline β_2 -microglobulin concentrations should be measured in all patients with multiple myeloma (grade A recommendation). For patients with acute kidney injury, the KDIGO, RIFLE, and AKIN criteria should be used (grade C recommendation).

	KDIGO	RIFLE	AKIN	KDIGO, RIFLE, and AKIN
Stage 1 (AKIN and KDIGO) or Risk (RIFLE)	Serum creatinine increase to 1.5–1.9 times baseline or increase of ≥ 0.3 mg/dL	Serum creatinine increase of $\geq 50\%$ or eGFR decrease of $>25\%$	Serum creatinine increase of $\geq 50\%$ or increase of ≥ 0.3 mg/dL	Urine output <0.5 mg/kg per h for 6 h
Stage 2 (AKIN and KDIGO) or Injury (RIFLE)	Serum creatinine increase to 2.0–2.9 times baseline	Serum creatinine increase of $\geq 100\%$ or eGFR decrease of $>50\%$	Serum creatinine increase of $\geq 100\%$	Urine output <0.5 mg/kg per h for 12 h
Stage 3 (AKIN and KDIGO) or Failure (RIFLE)	Serum creatinine increase to ≥ 3.0 times baseline, or increase to ≥ 4 mg/dL, or renal replacement therapy	Serum creatinine increase of $\geq 200\%$, or eGFR decrease of $>75\%$, or serum creatinine increase to ≥ 4.0 mg/dL with an acute increase of ≥ 0.5 mg/dL from baseline	Serum creatinine increase of $\geq 200\%$, or increase to ≥ 4.0 mg/dL with an acute increase of ≥ 0.5 mg/dL from baseline, or renal replacement therapy	Urine output <0.3 mg/kg per h for 24 h or anuria for 12 h
Loss (RIFLE)	..	Complete loss of kidney function (need for renal replacement therapy) for >4 weeks	..	..
End-stage kidney disease (RIFLE)	..	End stage kidney disease (need for renal replacement therapy) for >3 months	..	..

AKIN=Acute Kidney Injury Network. eGFR=estimated glomerular filtration rate. KDIGO=Kidney Disease: Improving Global Outcomes. RIFLE=Risk, Injury, Failure, Loss, and End-stage kidney disease.

Table 2: Staging of acute kidney injury

	Baseline eGFR (mL/min per 1.73 m ²)*	Best creatinine clearance response (mL/min)
Complete response	<50	≥ 60
Partial response	<15	30–59
Minor response	<15	15–29
Minor response	15–29	30–59

eGFR=estimated glomerular filtration rate. *eGFR calculated with the Chronic Kidney Disease Epidemiology Collaboration equation.

Table 3: Criteria for renal response to anti-myeloma treatment

Criteria for renal response

The primary aim of treatment of patients with multiple myeloma and renal impairment is the reversibility of renal impairment, which is associated with improved patient outcomes.⁸ The IMWG criteria for renal response to anti-myeloma treatment (table 3)⁴⁰ are well established and have been used in several studies internationally to assess renal response.^{41–47} In the presence of biopsy-proven AL amyloidosis, specific renal response criteria should be used.⁴⁸

Almost all studies have highlighted that renal response depended on early, substantial reduction of the involved FLCs. In the MYRE study, serum FLC concentrations less than 500 mg/L after the first cycle of chemotherapy were independently associated with renal response in patients needing dialysis.⁴⁹ In patients who did not require dialysis, haematological response in terms of FLCs reduction (at least partial response) within the first 6 months, AKIN stage 3, and pre-existing mild-to-moderate CKD (eGFR 30–59 mL/min per 1.73 m²) were independent predictors of renal outcome.⁵⁰

However, FLC response is not the sole determinant of renal response, which also depends on several conditions, such as pre-existing CKD and histological parameters, particularly the mean number of cortical

casts per square millimetre on kidney biopsy, as highlighted in a large multicentre cohort of patients with biopsy-proven myeloma cast nephropathy.⁵¹ Because of the necessity of rapidly decreasing the production and serum concentrations of nephrotoxic FLCs, any interruption of anti-myeloma therapy, side-effects such as pre-existing infections, or haemodynamic instability can be highly deleterious for renal recovery in these patients and lead to definitive end stage kidney disease. Notably, patients with myeloma cast nephropathy are particularly frail and thus careful evaluation of the efficacy and toxicity of chemotherapy is of paramount importance in these patients. For patients requiring dialysis, independence from dialysis has been associated with prolonged survival.^{42,52}

Recommendations

The IMWG criteria for the definition of renal response should be used in both clinical trials and daily clinical practice (grade B recommendation).

Supportive care

Renal impairment due to multiple myeloma is a medical emergency, and immediate initiation of effective anti-myeloma treatment is of utmost importance. Additionally, adequate supportive care is required for all patients with a suspicion of myeloma-induced renal impairment. Supportive care involves appropriate fluid hydration (at least 3 L/day or 2 L/m² per day), which is crucial in individuals with fluid depletion due to hypercalcaemia.⁵³ Fluid balance should be carefully monitored, especially in patients with congestive heart failure. A fluid challenge is appropriate for patients presenting with anuria. Urine alkalinisation has not shown its efficacy in the reversibility of renal impairment.⁵³ The restoration of calcium homeostasis might be crucial for reversing renal impairment. Bisphosphonates and denosumab are approved for the treatment of myeloma-associated hypercalcaemia;

however, bisphosphonates (both pamidronate and zoledronic acid) are not recommended in patients with a creatinine clearance of less than 30 mL/min and treatment with these agents should be started only upon GFR improvement, due to risk of renal injury.¹⁹ In patients on chronic dialysis, with no option of GFR reversal to rates higher than 30 mL/min per 1.73m², bisphosphonates might be used for the management of myeloma-related bone disease. However, a single dose of pamidronate for the management of hypercalcaemia does not increase the risk for nephrotoxicity, provided that dose and infusion methods are adapted to GFR value.⁵⁴ Denosumab is safe in patients with multiple myeloma and in patients with solid cancer and renal impairment; nevertheless, the development of hypocalcaemia and hypophosphataemia requires close monitoring.^{19,55} High-dose steroids and calcitonin can be administered safely. Furosemide is not advised, because it might promote cast formation in the renal tubules.⁵⁶ Nephrotoxic agents, including contrast agents, renin-angiotensin-aldosterone system blockers, non-steroidal anti-inflammatory drugs, and some antibiotics (eg, aminoglycosides), should be avoided or discontinued in patients with multiple myeloma and renal impairment.⁵⁷ Bacterial infection should be ruled out, or if confirmed, treated with antibiotic therapy. Polypharmacy is common for patients with multiple myeloma, especially when comorbidities are present; therefore, special attention should be given to appropriate dose adjustments for both anti-myeloma drugs (table 4) and concomitant medications.

Recommendations

High-fluid administration (at least ≥ 3 L/day or 2 L/m² per day) should be initiated together with anti-myeloma therapy (grade B recommendation). Urine alkalinisation seems not to offer an advantage in the reversal of renal impairment in patients with multiple myeloma (grade B recommendation). Bisphosphonates can reduce calcium concentrations in patients with hypercalcaemia, but neither pamidronate nor zoledronic acid should be used in patients with multiple myeloma and severe renal impairment (creatinine clearance <30 mL/min; grade A recommendation). In patients on chronic dialysis, with no option of GFR reversal to rates higher than 30 mL/min per 1.73m², bisphosphonates might be used for the management of myeloma-related bone disease (grade D recommendation). Denosumab might be useful in patients with hypercalcaemia and renal impairment, but calcium and phosphate concentrations should be closely monitored (grade B recommendation). Avoidance of nephrotoxic agents, such as aminoglycoside antibiotics, renin-angiotensin-aldosterone system blockers, furosemide, non-steroidal anti-inflammatory drugs, and contrast agents, is highly recommended in patients with multiple myeloma and renal impairment (grade A recommendation).

Mechanical approaches

Mechanical approaches have been used in patients with multiple myeloma and renal impairment to rapidly reduce serum FLCs concentrations. The concomitant administration of anti-myeloma treatment is crucial to reduce monoclonal FLC production from malignant plasma cells. The additive value of plasmapheresis in improving patient outcomes has been inconclusive in the era of conventional chemotherapy; however, the efficacy of plasmapheresis seems to be reduced due to the total volume exchanged per session.^{58,59} High-cutoff haemodialysis is more effective in FLC removal because it allows for the removal of molecules up to 65 000 daltons. The combination of high-cutoff membranes with modern anti-myeloma treatments has led to more than double haemodialysis independence rates compared with plasma exchange.⁶⁰⁻⁶² Two randomised controlled trials compared high-cutoff haemodialysis with standard high-flux haemodialysis in patients receiving bortezomib-based regimens.^{49,63} Both the MYRE⁴⁹ and the EuLITE⁶³ studies did not show a significant improvement with high-cutoff membranes in the rate of dialysis independence at 3 months on study. However, a benefit was noted in the MYRE study at 6 months and 12 months after study entry for patients with anuric renal failure. However, in the EuLITE study, overall survival was inferior in patients undergoing high-cutoff haemodialysis compared with patients undergoing standard high-flux haemodialysis.

Treatment discontinuation is primarily due to infections.⁶³ Other mechanical approaches yet to be evaluated in prospective studies include haemodialysis with adsorptive polymethyl-methacrylate dialysers,⁶⁴ haemodiafiltration with ultrafiltrate regeneration,⁶⁵ supra-haemodiafiltration with endogenous reinfusion after FLC adsorption,⁶⁶ or continuous venovenous haemofiltration with high-cutoff filters.⁶⁷ Patients with irreversible end-stage renal impairment require long-term dialysis and have a poor prognosis.⁸

In addition to the questionable efficacy, the optimal timing of applying an extracorporeal approach is debatable. In the MYRE study,⁴⁹ patients initiated treatment after a preinclusion period of up to 15 days that included symptomatic measures and high-dose steroids. In the EuLITE study,⁶³ patients initiated treatment upfront, immediately after inclusion. Dialysis should be initiated in all patients with an indication to treat acute kidney injury due to severe volume overload and electrolyte disorders, irrespective of the underlying myeloma. Otherwise, monoclonal cast nephropathy should be highly suspected or histologically confirmed to proceed with the mechanical removal of FLCs.⁶⁸ Initial intensive supportive measures and correction of precipitating factors of acute kidney injury, such as low hydration and hypercalcaemia, might be feasible for patients with stage 1 (AKIN and KDIGO) or Risk (RIFLE) acute kidney injury and for patients with stage 2

	Creatinine clearance				On dialysis
	≥60 mL/min	30–59 mL/min	15–29 mL/min	<15 mL/min	
Dexamethasone (orally or intravenously)	20–40 mg	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Melphalan	0.15–0.25 mg/kg per day orally; high dose: 200 mg/m ² intravenously	Reduction by 25% orally; high dose: 140 mg/m ² intravenously	Reduction by 25% orally; high dose: 140 mg/m ² intravenously	Reduction by 50% orally; high dose: 140 mg/m ² intravenously	Reduction by 50% orally; high dose: 140 mg/m ² intravenously
Doxorubicin (intravenously)	According to regimen	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Cyclophosphamide (orally or intravenously)	According to regimen	No dose modification needed	No dose modification needed	No dose modification needed*	No dose modification needed
Bortezomib (subcutaneously)	1.3 mg/m ²	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Carfilzomib (intravenously)	Loading dose/full dose: 20/27 mg/m ² or 20/56 mg/m ² or 20/70 mg/m ²	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed, after dialysis
Ixazomib (orally)	4 mg	4 mg	3 mg	3 mg	3 mg
Thalidomide (orally)	50–200 mg	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Lenalidomide (orally)	25 mg per day	10 mg per day, can be increased to 25 mg per day if no toxicity occurs	15 mg every other day or 10 mg per day, can be increased to 15 mg per day if no toxicity occurs	5 mg per day, can be increased to 15 mg per day if no toxicity occurs	5 mg per day after dialysis, can be increased to 15 mg per day if no toxicity occurs
Pomalidomide (orally)	4 mg per day	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed, after dialysis
Daratumumab	16 mg/kg intravenously or 1800 mg subcutaneously	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Isatuximab (intravenously)	10 mg/kg	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Elotuzumab (intravenously)	10 mg/kg	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Belantamab mafodotin (intravenously)	2.5 mg/kg	No dose modification needed	Not determined yet	Not determined yet	Not determined yet
Selinexor (orally)	80 mg	No dose modification needed	No dose modification needed	Not determined yet	Not determined yet
Idecabtagene vicleucel (intravenously)	260–500 × 10 ⁶ CAR-positive, viable T cells	Not determined yet	Not determined yet	Not determined yet	Not determined yet
Ciltacabtagene autoleucel (intravenously)	0.5–1.0 × 10 ⁶ CAR-positive, viable T cells	Not determined yet	Not determined yet	Not determined yet	Not determined yet
Teclistamab (subcutaneously)	1.5 mg/kg	No dose modification needed with creatinine clearance >40 mL/min	Not determined yet	Not determined yet	Not determined yet
Venetoclax: off-label for patients with t(11;14)(q13;q32)	800 mg per day orally	No dose modification needed	No dose modification needed	Not determined yet	Not determined yet

There are several treatment regimens for each drug in terms of frequency and schedule, depending also on the treatment phase. CAR=chimeric antigen receptor. *Monitor patients with severe renal impairment for toxicity. Decreased renal excretion in these patients might result in increased plasma concentrations of this drug and its metabolites, which could lead to increased toxicity.

Table 4: Dose modifications for anti-myeloma drugs in patients with renal impairment

(AKIN and KDIGO) or Injury (RIFLE) acute kidney injury (table 2); however, close patient monitoring is crucial to start dialysis in non-responders early. Prompt diagnosis and treatment initiation is essential because delayed intervention might not reverse kidney damage, which would thus become irreversible.

Recommendations

Mechanical approaches alone do not improve overall survival or haemodialysis independence even in patients with multiple myeloma and acute kidney injury AKI because of monoclonal cast nephropathy (grade B recommendation). Mechanical approaches in combination with anti-myeloma therapy might

improve the rate of dialysis independence (grade C recommendation). There is no difference in the rates of dialysis independence between high-cutoff haemodialysis and conventional high-flux haemodialysis at 3 months (grade C recommendation).

Anti-myeloma therapy

Renal impairment in patients with multiple myeloma, especially upfront, is a potentially reversible condition and should be treated immediately. Newly diagnosed patients with multiple myeloma and renal impairment have a high chance of improvement, whereas patients with relapsed or refractory multiple myeloma and renal impairment are more challenging to manage.

Regimens based on high-dose steroids

Regimens with high-dose steroids include steroid doses equivalent to at least 160 mg of dexamethasone for 4 days. A common regimen consists of 40 mg of dexamethasone administered 4 days on and 4 days off for three pulses in a 28-day cycle and lead to renal responses in up to 65% of patients.^{69,70} High-dose dexamethasone in the first month of therapy has been associated with a more rapid renal response in newly diagnosed patients with multiple myeloma and renal impairment treated with proteasome inhibitors or immunomodulatory drugs.^{70,71} Intravenous methylprednisolone at equivalent dose to dexamethasone can be helpful, especially in patients with severe acute kidney injury, as an alternative to dexamethasone.⁷² However, patients should be carefully monitored, because this treatment is associated with increased risk of infections. In patients with acute renal impairment attributed to the underlying multiple myeloma, steroids can be initiated before all investigations are reported and before the administration of specific anti-myeloma treatment (panel opinion).

Recommendations

The recommended dose for high-dose dexamethasone (orally or intravenously) is 40 mg/day (20 mg for patients aged ≥ 75 years), 4 days on and 4 days off for three pulses during the first cycle of therapy, and then according to the treatment protocol (grade B recommendation).

Regimens based on proteasome inhibitors

Bortezomib-based combinations are the mainstay of first-line treatment combinations in patients with multiple myeloma. Bortezomib has long been regarded as the gold standard of therapy for patients with multiple myeloma and renal impairment, owing to its non-renal metabolism, favourable effects on the kidney (improved kidney function), and the accumulating data supporting its effectiveness in this patient population, which was first observed in the SUMMIT trial⁷³ and then in the APEX study.⁷⁴ Bortezomib-based regimens generate rapid and deep haematological and renal responses, with possible reversal of renal impairment and dialysis independence.^{46,71,75–84} Bortezomib-based induction and high-dose melphalan therapy with autologous haematopoietic stem-cell transplantation (HSCT) improve the prognosis of patients with multiple myeloma presenting with renal impairment at baseline.⁸⁵ In randomised controlled trials, the subcutaneous administration of bortezomib provided similar results to the intravenous injection in patients with multiple myeloma and renal impairment, although intravenous administration with hydration in patients with severe acute kidney injury might be a suitable option, due to a possible more rapid effect.^{79,86} Bortezomib-based triplet combinations might improve renal response and dialysis discontinuation rates compared with the bortezomib–dexamethasone combination.^{42,45} However, a randomised controlled trial did not show any

additive benefit of cyclophosphamide in the bortezomib–dexamethasone regimen among patients with multiple myeloma and established acute kidney injury without the need for dialysis.⁵⁰ A tailored approach based on patient frailty is encouraged to optimise the balance between efficacy and toxicity.

Carfilzomib is a second-generation proteasome inhibitor and its combinations are highly effective in patients with relapsed or refractory multiple myeloma. Intravenous carfilzomib clearance, efficacy, and toxicity do not differ among patients with normal renal function and those with varying degrees of renal impairment.^{87,88} A post-hoc exploratory subgroup analysis of the ENDEAVOR randomised phase 3 study⁸⁹ assessed the effectiveness and safety of carfilzomib–dexamethasone compared with bortezomib–dexamethasone in patients with varying degrees of renal impairment at baseline (table 5). Progression-free survival, overall survival, and overall response rate improved in the carfilzomib–dexamethasone group across renal subgroups. Approximately 15% of patients with a creatinine clearance of 15–50 mL/min had complete renal response.⁸⁹ A subgroup analysis of the phase 3 ARROW trial showed that once weekly administration of carfilzomib–dexamethasone (70 mg/m²) improved progression-free survival and overall response rate across all renal subgroups (creatinine clearance 30–49 mL/min, 50–79 mL/min, and ≥ 80 mL/min) compared with twice per week carfilzomib–dexamethasone (27 mg/m²).¹⁰³ A large real-world study compared renal response rates among patients with relapsed or refractory multiple myeloma and renal impairment (eGFR ≤ 50 mL/min per 1.73m²) treated with carfilzomib–dexamethasone (n=543) or bortezomib–dexamethasone (n=1005) in the second through fourth line of therapy.⁴⁷ Patients undergoing second-line therapy who received carfilzomib–dexamethasone had substantially higher rates of renal overall response (51.4% vs 39.6%; $p < 0.0001$) and renal complete response (26.6% vs 22.2%; $p = 0.0229$) than patients receiving bortezomib–dexamethasone. The results were similar for patients with an eGFR of 15 mL/min per 1.73m² or less and for patients receiving third-line and fourth-line treatments.⁴⁷ However, carfilzomib-related renal complications including thrombotic microangiopathy, albuminuria, and grade 3 acute kidney injury have been reported.¹⁰⁴ Furthermore, in the FOCUS study, renal failure was more frequently observed in patients receiving carfilzomib monotherapy who had low GFR and proteinuria than in patients receiving cyclophosphamide.¹⁰⁵ Therefore, carfilzomib should be administered with caution in patients with impaired renal function and bortezomib remains the first choice of proteasome inhibitor in patients with multiple myeloma and renal impairment in the absence of disease refractoriness to bortezomib.

Ixazomib is an oral proteasome inhibitor for patients with relapsed or refractory multiple myeloma.

Additionally, patients with mild-to-moderate renal impairment (creatinine clearance 30–59 mL/min) comprised 25% of the patients receiving ixazomib–lenalidomide–dexamethasone in the phase 3 TOURMALINE-MM1 trial.¹⁰⁶ Although subgroup analyses were not done, the study results show that the safety and efficacy profile of the regimen can be safely extended to this patient group. Despite ixazomib having

a low renal clearance,¹⁰⁷ a lower starting dose (3 mg) is indicated for individuals with a creatinine clearance of less than 30 mL/min.¹⁰⁸

Recommendations

Bortezomib-based regimens remain the cornerstone of the management of myeloma-related renal impairment (grade A recommendation). Bortezomib should be

Cutoff for renal impairment*		Median progression-free survival		Median overall survival		Overall response rate (%)	Complete renal response (%)	Median time to complete renal response (weeks)	Grade ≥3 adverse events (%)
		Months	Hazard ratio (95% CI)	Months	Hazard ratio (95% CI)				
Newly diagnosed patients with multiple myeloma									
ALCYONE ⁹⁰									
DaraVMp (n=150)	≥30 to <60	NR	0.36 (0.24–0.56)	NR	NA	89%	NA	NA	47%
VMp (n=145)	≥30 to <60	16.9	1 (ref)	NA	NA	73%	NA	NA	42%
CASSIOPEIA ⁹¹									
DaraVTd (n=212)	≥40 to <90	NA	0.37 (0.21–0.66)	NA	NA	NA	NA	NA	NA
VTd (n=226)	≥40 to <90	NA	1 (ref)	NA	NA	NA	NA	NA	NA
MAIA (lenalidomide 25 mg) ⁹²									
DaraRd (n=60)	≥30 to <60	NR	0.42 (0.24–0.72)	NR	0.37 (0.19–0.73)	NA	NA	NA	NA
Rd (n=62)	≥30 to <60	35.4	1 (ref)	NR	1 (ref)	NA	NA	NA	NA
MAIA (lenalidomide <25 mg) ⁹²									
DaraRd (n=98)	≥30 to <60	49.1	0.56 (0.38–0.83)	62.8	0.81 (0.52–1.26)	NA	NA	NA	NA
Rd (n=75)	≥30 to <60	24.9	1 (ref)	54.8	1 (ref)	NA	NA	NA	NA
Patients with relapsed or refractory multiple myeloma									
ASPIRE ⁹³									
KRd (n=79)	≥30 to <60	NA	NA	NA	0.72 (0.51–1.02)	NA	NA	NA	NA
Rd (n=82)	≥30 to <60	NA	NA	NA	1 (ref)	NA	NA	NA	NA
ENDEAVOR ⁸⁹									
Kd (n=85)	≥15 to <50	14.9	0.49 (0.32–0.76)	42.1	0.66 (0.44–0.99)	74.1%	15.3%	8.1	87%
Vd (n=99)	≥15 to <50	6.5	1 (ref)	23.7	1 (ref)	49.5%	14.1%	6.4	79%
MM-003 ⁹⁴									
Pd (n=93)	≥30 to <60	4.0	0.48 (0.33–0.70)	10.4	0.65 (0.44–0.96)	28%	32%	NA	NA
Plowd (n=56)	≥30 to <60	1.9	1 (ref)	4.9	1 (ref)	11%	43%	NA	NA
OPTIMISM ⁹⁵									
PVd (n=35)	≥30 to <60	15.1	0.67 (0.34–1.34)	NA	NA	91.4%	NA	3.1†	NA
Vd (n=28)	≥30 to <60	9.5	1 (ref)	NA	NA	53.6%	NA	4.6†	NA
POLLUX ⁹⁶									
DaraRd (n=80)	≥30 to <60	33.6	0.41 (0.26–0.65)	NR	NA	91%	NA	NA	NA
Rd (n=65)	≥30 to <60	11.3	1 (ref)	NR	NA	68%	NA	NA	NA
CASTOR ⁹⁷									
DaraVd (n=57)	≥20 to ≤60	NR	0.55 (0.30–1.02)	NA	NA	NA	NA	NA	NA
Vd (n=70)	≥20 to ≤60	6.5	1 (ref)	NA	NA	NA	NA	NA	NA
APOLLO ⁹⁸									
DaraPd (n=40)	≥30 to ≤60	12.1	0.59 (0.35–0.99)	NA	NA	NA	NA	NA	NA
Pd (n=47)	≥30 to ≤60	6.1	1 (ref)	NA	NA	NA	NA	NA	NA
CANDOR ⁹⁹									
DaraKd (n=38)	≥15 to <50	NA	0.44 (0.19–1.00)	NA	NA	NA	NA	NA	NA
Kd (n=27)	≥15 to <50	NA	1 (ref)	NA	NA	NA	NA	NA	NA

(Table 5 continues on next page)

(Table 5 continues on next page)

Cutoff for renal impairment*		Median progression-free survival		Median overall survival		Overall response rate (%)	Complete renal response (%)	Median time to complete renal response (weeks)	Grade ≥3 adverse events (%)
		Months	Hazard ratio (95% CI)	Months	Hazard ratio (95% CI)				
(Continued from previous page)									
ICARIA-MM ¹⁰⁰									
IPd (n=55)	eGFR ≥30 to <60 mL/min per 1.73 m ²	9.5	0.50 (0.30–0.85)	NR	0.53 (0.30–0.96)	56.4%	71.9%	3.4	91%
Pd (n=49)	eGFR ≥30 to <60 mL/min per 1.73 m ²	3.7	1 (ref)	11.6	1 (ref)	24.5%	38.1%	7.3	79%
IKEMA ¹⁰¹									
IKd (n=43)	eGFR ≥15 to <60 mL/min per 1.73 m ²	NR	0.27 (0.11–0.66)	NA	NA	93.1%	52.0%	7.8	79.1%
Kd (n=18)	eGFR ≥15 to <60 mL/min per 1.73 m ²	13.4	1 (ref)	NA	NA	61.1%	30.8%	NA	77.8%
BOSTON ¹⁰²									
XVd (n=21; n=35)	≥20 to <40; ≥40 to <60	7.6; 16.6	0.62 (p=0.13); 0.49 (p=0.028)	NR; NR	0.74 (p=0.26); 0.55 (p=0.080)	81.0%; 80.0%	NA	NA	66.7%; 42.9%
Vd (n=26; n=44)	≥20 to <40; ≥40 to <60	4.3; 7.6	1 (ref); 1 (ref)	19.1; 21.2	1 (ref); 1 (ref)	53.8%; 59.1%	NA	NA	40.0%; 47.6%
DaraKd=daratumumab plus Kd. DaraRd=daratumumab plus Rd. DaraVd=daratumumab plus Vd. DaraVMp=daratumumab plus VMp. DaraVTd=daratumumab plus VTd. eGFR=estimated glomerular filtration rate. IPd=isatuximab–pomalidomide–dexamethasone. IKd=isatuximab–carfilzomib–dexamethasone. Kd=carfilzomib–dexamethasone. KRd=carfilzomib–lenalidomide–dexamethasone. NA=not available. NR=not reached. Pd=pomalidomide–dexamethasone. Plowd=pomalidomide–low-dose dexamethasone. PVD=pomalidomide–bortezomib–dexamethasone. Rd=lenalidomide–dexamethasone. Vd=bortezomib–dexamethasone. VMp=bortezomib–melphalan–prednisone. VTd=bortezomib–thalidomide–dexamethasone. XVd=selinexor–bortezomib–dexamethasone. *Creatinine clearance cutoff (mL/min), unless otherwise stated. †Time to first improvement in renal function.									
Table 5: Subgroup analyses of patients with multiple myeloma and renal impairment in selected phase 3 studies									

Table 5: Subgroup analyses of patients with multiple myeloma and renal impairment in selected phase 3 studies

initiated at the standard dose of 1.3 mg/m² on days 1, 4, 8, and 11 of a 3-week cycle (grade A recommendation) and high-dose dexamethasone should be administered at least for the first month of therapy (grade B recommendation). Subcutaneous administration of bortezomib has similar efficacy to intravenous use (grade A recommendation). Bortezomib-based triplet combinations might improve renal outcomes in some patients to ensure an optimal balance between efficacy and toxicity (grade C recommendation). Carfilzomib is safe and effective in patients with relapsed or refractory multiple myeloma and renal impairment (grade A recommendation for creatinine clearance ≥15 mL/min; grade B recommendation for creatinine clearance <15 mL/min) without the need for dose adjustments. Close monitoring is important for early identification and prompt management of carfilzomib-related renal complications. Ixazomib can be safely administered in combination with lenalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma and a creatinine clearance of 30 mL/min or higher (grade A recommendation). A lower starting dose of 3 mg is indicated for individuals with a creatinine clearance of less than 30 mL/min (grade B recommendation).

Regimens based on immunomodulatory drugs

Thalidomide is one of the first anti-myeloma drugs and it is still used in combination with other agents (eg, bortezomib–thalidomide–dexamethasone) in newly diagnosed patients with multiple myeloma and in patients with relapsed or refractory multiple myeloma.

Because thalidomide is not eliminated by the kidneys, no dosage adjustments are required. The anticipated renal recovery with thalidomide-based regimens ranges from up to 75% in newly diagnosed patients with multiple myeloma and 60% in patients with relapsed or refractory multiple myeloma.^{71,109}

Lenalidomide is a second-generation immunomodulatory drug that has been incorporated into the whole treatment continuum of multiple myeloma both in the first and in the subsequent lines of therapy. Lenalidomide is eliminated unaltered in the urine and should be dosed according to renal function.¹¹⁰ Dose modifications do not compromise efficacy and ensure safety for both newly diagnosed patients with multiple myeloma and patients with relapsed or refractory multiple myeloma.^{109,111} The phase 1/2 PrECOG study showed the feasibility of administering lenalidomide at full dose (25 mg) to patients with a creatinine clearance of 30 mL/min or higher and up to a maximum of 15 mg daily to patients with a creatinine clearance of less than 30 mL/min, including patients on dialysis.¹¹² A retrospective analysis of registrational studies of lenalidomide–dexamethasone showed that the majority of patients with multiple myeloma and moderate-to-severe renal impairment improved by at least one level in creatinine clearance (table 3).¹¹³ However, patients with severe renal impairment had an increased incidence of toxic effects and shorter overall survival. The efficacy and safety of lenalidomide–dexamethasone have been shown in phase 2 trials,^{114,115} and in real-world studies of patients with multiple myeloma and renal impairment

	Cutoff for renal impairment*	Median (range) previous lines of therapy	Median (range) eGFR, mL/min per 1.73m ²	Median (95% CI) progression-free survival, months	Median (95% CI) overall survival, months	Overall response rate (%)	Renal response rate (%)	Adverse events	
								Grade ≥3 (%)	Serious (%)
MM-013 ¹²⁴									
Pomalidomide-dexamethasone (n=33)	eGFR 30 to <45 mL/min per 1.73m ²	3 (2–8)	38.8 (31.0–47.0)	6.5 (4.60–10.62)	16.4 (7.79–25.18)	39.4%	18.2%	NA	54.5%
Pomalidomide-dexamethasone (n=34)	eGFR <30 mL/min per 1.73m ²	4 (1–10)	22.2 (8.0–33.5)	4.2 (2.79–6.51)	11.8 (6.35–13.45)	32.4%	35.3%	NA	61.8%
Pomalidomide-dexamethasone (n=14)	eGFR <30 mL/min per 1.73m ² requiring haemodialysis	4 (2–5)	8.9 (4.0–21.0)	2.4 (0.95–6.41)	5.2 (1.81–9.67)	14.3%	7.1%	NA	85.7%
DARE ⁴¹									
Daratumumab-dexamethasone (n=38)	eGFR <30 mL/min per 1.73m ²	3 (2–6)	12 (4–58)	11.8 (2.8–20.8)	24.5 (5.5–NR)	47.4%	18.4%	63.2%	28.9%
DREAMM-2 ¹²⁵									
Belantamab mafodotin 2.5 mg/kg (n=24)	≥30 to <60	7 (3–21)	NA	3.7 (1.0–NR)	NA	33%	NA	NA	50%
Belantamab mafodotin 3.4 mg/kg (n=22)	≥30 to <60	6 (4–21)	NA	3.4 (0.8–6.4)	NA	27%	NA	NA	50%
STORM ¹²⁶									
Selinexor-dexamethasone (n=14)	≥20 to <40	7 (3–18)	NA	NR	6.1	35.7%	43%†	73%	73%
Selinexor-dexamethasone (n=25)	≥40 to <60	7 (3–18)	NA	4.7	5.8	16.0%	38%†	60%	68%

eGFR=estimated glomerular filtration rate. NA=not available. NR=not reached. *Creatinine clearance cutoff (mL/min), unless otherwise stated. †Increase in creatinine clearance by at least one category level from baseline.

Table 6: Selected phase 2 studies reporting outcomes of patients with relapsed or refractory multiple myeloma and renal impairment

including end-stage renal impairment.^{116–118} Lenalidomide should be avoided in patients with AL amyloidosis and proteinuria.¹¹⁹ Of note, lenalidomide dose adaptation is possible only in patients with stable renal function. In patients with acute kidney injury, whose serum creatinine concentrations can rise every day, dose adaptation is more difficult, because the eGFR cannot be easily estimated, except for patients requiring dialysis.

Pomalidomide is a third-generation immunomodulatory drug that is administered to patients with relapsed or refractory multiple myeloma after exposure to lenalidomide. Pomalidomide is extensively metabolised by the liver, with only minimal renal clearance of the active drug.¹²⁰ No dose modification is necessary for patients with renal impairment, in whom it should be administered after dialysis.¹²¹ A post-hoc analysis of the MM-003 trial showed that pomalidomide plus low-dose dexamethasone resulted in similar progression-free survival, overall survival, renal response rates, and toxicity in patients with a creatinine clearance of 30–59 mL/min (table 5) and in those with a creatinine clearance of 60 mL/min or higher.⁹⁴ A pooled analysis of three clinical trials including patients with relapsed or refractory multiple myeloma and moderate renal impairment showed similar results.¹²² A real-world study showed no differences in survival outcomes and toxicity with pomalidomide plus low-dose dexamethasone between patients with an eGFR of less than 45 mL/min per 1.73 m² and those with an eGFR of

45 mL/min per 1.73 m² or higher.¹²³ The phase 2 MM-013 trial prospectively evaluated pomalidomide plus low-dose dexamethasone in 81 patients with relapsed or refractory multiple myeloma and moderate renal impairment (eGFR 30–45 mL/min per 1.73 m²), severe renal impairment (eGFR <30 mL/min per 1.73 m²), or on dialysis. All patients had substantial rates of disease control with a manageable safety profile, although the patients with severe renal impairment had a shorter overall survival (table 6).¹²⁴

Iberdomide is a new, potent cereblon E3 ligase modulator with enhanced tumoricidal and immune-stimulatory effects compared with immunomodulatory drug. Iberdomide is extensively metabolised, constituting only 16% of intact drug in urine.¹²⁷ In a sub-analysis from the phase 1/2 study CC-220-MM-001 (NCT02773030), the combination of iberdomide plus dexamethasone produced similar efficacy, safety, and pharmacokinetics results in patients with relapsed or refractory multiple myeloma with no renal impairment, mild renal impairment, or moderate renal impairment. Thus, iberdomide dose modifications are not required for patients with mild-to-moderate renal impairment. In the CC-220-MM-001 trial, no patient had a creatinine clearance of less than 30 mL/min and, thus, iberdomide dosing in patients with severe renal impairment or kidney failure requires further study.¹²⁸ Iberdomide is not approved yet for use in patients with multiple myeloma.

Recommendations

Thalidomide is effective in patients with multiple myeloma and renal impairment (grade B recommendation) and should be given without dose modifications (grade A recommendation). Lenalidomide with dexamethasone is effective and safe in patients with multiple myeloma and renal impairment (grade B recommendation). Lenalidomide should be administered with dose adjustments according to creatinine clearance (grade B recommendation). Patients with a creatinine clearance of less than 30 mL/min, whether on dialysis or not, can receive up to 15 mg daily (grade B recommendation). Pomalidomide with dexamethasone is safe and effective in patients with relapsed or refractory multiple myeloma and renal impairment, including patients on dialysis (grade A recommendation for creatinine clearance ≥ 45 mL/min; grade B recommendation for creatinine clearance < 30 mL/min).

Regimens based on proteasome inhibitors and immunomodulatory drugs

Upfront treatment with bortezomib–lenalidomide–dexamethasone can improve renal function in up to 64% of patients presenting with an eGFR of less than 60 mL/min and in patients not requiring autologous HSCT.^{129,130} Bortezomib–thalidomide–dexamethasone is an efficacious and safe regimen in patients with multiple myeloma and renal impairment.⁷⁰ An analysis including 1772 newly diagnosed patients with multiple myeloma and an eGFR (with the Modification of Diet in Renal Disease formula) of less than 50 mL/min per 1.73 m² from a US nationwide electronic database showed that patients who received a regimen including a proteasome inhibitor and an immunomodulatory drug in the first and second line of treatment were significantly more likely to have a complete renal response and improved overall survival than those who did not receive either treatment.¹² A post-hoc analysis of the phase 3 OPTIMISMM study showed that pomalidomide–bortezomib–dexamethasone improved overall response rate, progression-free survival, and time to improvement in renal function with no new safety signals compared with bortezomib–dexamethasone in patients with relapsed or refractory multiple myeloma and a creatinine clearance of less than 60 mL/min (table 5).^{95,131} Carfilzomib–lenalidomide–dexamethasone improved overall survival compared with lenalidomide–dexamethasone in the final analysis of the phase 3 ASPIRE study in patients with relapsed or refractory multiple myeloma and a creatinine clearance of 30–59 mL/min or of 60 mL/min or higher.⁹³ Overall, triplet combinations are preferred over doublet combination because of superior outcomes, provided that the patient is fit enough to receive a triplet combination.

Recommendations

Triplet combinations including a proteasome inhibitor, an immunomodulatory drug, and a steroid in the

upfront setting and at first relapse in patients with a creatinine clearance of less than 50 mL/min improve complete renal response rates and survival outcomes (grade B recommendation). Triplet combinations (eg, pomalidomide–bortezomib–dexamethasone and carfilzomib–lenalidomide–dexamethasone) improve rates of haematological and renal response along with survival outcomes compared with doublet combinations (eg, bortezomib–dexamethasone and lenalidomide–dexamethasone) in patients with relapsed or refractory multiple myeloma and a creatinine clearance of 30–59 mL/min (grade B recommendation).

Regimens based on monoclonal antibodies

The introduction of monoclonal antibodies for the treatment of multiple myeloma, as part of quadruplet combinations in newly diagnosed patients and as part of triplet combinations in patients with relapsed disease, have further enhanced patient outcomes. The anti-CD38 monoclonal antibody daratumumab with dexamethasone was administered to patients with relapsed or refractory multiple myeloma and severe renal impairment (eGFR < 30 mL/min per 1.73 m² or on dialysis) in the phase 2 DARE study (table 6).⁴¹ The study included 38 patients with eGFR < 30 mL/min per 1.73 m²; the overall response rate was 47% and the 6-month progression-free survival was 54%. The overall response rate among those requiring dialysis (n=17) was 47%. The renal response rate was 18% in patients with eGFR < 30 mL/min per 1.73 m².⁴¹ Case reports^{132–135} and case series^{136,137} of dialysis-dependent patients with relapsed or refractory multiple myeloma who received daratumumab-based treatment indicated consistent benefit with reduced dialysis frequency or dialysis independence. In a retrospective study, daratumumab-based regimens improved progression-free survival in patients with relapsed or refractory multiple myeloma regardless of renal function (eGFR < 30 mL/min per 1.73 m² vs 30–59 mL/min per 1.73 m² vs ≥ 60 mL/min per 1.73 m²), whereas 41% of patients with an eGFR of 30–59 mL/min per 1.73 m² had a renal response.¹³⁸ A pooled analysis of the pivotal phase 1/2 study and the supporting phase 2 trial that led to the approval of daratumumab monotherapy in patients with relapsed or refractory multiple myeloma reported similar overall response rates between patients with a creatinine clearance of 30–60 mL/min and those with a creatinine clearance higher than 60 mL/min.^{139,140}

Daratumumab-based triplet combinations and quadruplet combinations are efficacious and safe in patients with multiple myeloma and renal impairment (table 5). In the phase 3 ALCYONE study,⁹⁰ daratumumab–bortezomib–melphalan–prednisone improved overall response rates, minimal residual disease (MRD) negativity rates, and progression-free survival without safety issues compared with bortezomib–melphalan–prednisone in newly diagnosed patients with multiple myeloma and a creatinine clearance of 40–60 mL/min.

In the phase 3 CASSIOPEIA study,⁹¹ daratumumab–bortezomib–thalidomide–dexamethasone improved overall response rates and progression-free survival compared with bortezomib–thalidomide–dexamethasone in newly diagnosed patients with multiple myeloma and a creatinine clearance of 40–90 mL/min. In the phase 3 MAIA study,⁹² daratumumab–lenalidomide–dexamethasone improved survival outcomes compared with lenalidomide–dexamethasone in newly diagnosed patients with multiple myeloma and a creatinine clearance of 30–60 mL/min. In the phase 3 CASTOR trial,⁹⁷ daratumumab–bortezomib–dexamethasone improved progression-free survival compared with bortezomib–dexamethasone in patients with relapsed or refractory multiple myeloma and a creatinine clearance of 20–60 mL/min. In the phase 3 CANDOR trial,⁹⁹ daratumumab–carfilzomib–dexamethasone prolonged progression-free survival compared with carfilzomib–dexamethasone in patients with relapsed or refractory multiple myeloma and a creatinine clearance of 15–50 mL/min. In the phase 3 POLLUX trial,⁹⁶ daratumumab–lenalidomide–dexamethasone increased progression-free survival compared with lenalidomide–dexamethasone in patients with relapsed or refractory multiple myeloma and a creatinine clearance of 30–60 mL/min. In the phase 3 APOLLO trial,⁹⁸ daratumumab–pomalidomide–dexamethasone improved progression-free survival compared with pomalidomide plus low-dose dexamethasone in patients with relapsed or refractory multiple myeloma and a creatinine clearance of 30–60 mL/min. In general, the balance between efficacy and toxicity of quadruplet therapy in patients with multiple myeloma and severe acute kidney injury remains poorly documented, in the absence of dedicated studies that are needed. In newly diagnosed patients with multiple myeloma, daratumumab–bortezomib–dexamethasone, assessment of FLC response every week, and reinforcement at the second cycle with an immunomodulatory drug might offer the best results (panel opinion). This treatment has to be proven in prospective studies.

Isatuximab is another anti-CD38 monoclonal antibody with high efficacy and safety in triplet combinations for patients with relapsed or refractory multiple myeloma and renal impairment. In the phase 3 ICARIA-MM study,^{100,141} isatuximab–pomalidomide–dexamethasone improved overall response rate, MRD negativity rate, and progression-free survival compared with pomalidomide plus low-dose dexamethasone in patients with an eGFR of 30–60 mL/min per 1.73m², in addition to its efficacy in the intent-to-treat overall population. Complete renal response rates were 72% with isatuximab–pomalidomide–dexamethasone and 38% with pomalidomide plus low-dose dexamethasone, and isatuximab–pomalidomide–dexamethasone shortened the median time to renal response (table 5). Treatment-emergent toxicities were more frequent with

isatuximab–pomalidomide–dexamethasone, but they were manageable.¹⁰⁰ In the phase 3 IKEMA study,¹⁰¹ isatuximab–carfilzomib–dexamethasone improved overall response rate, MRD negativity rate, and progression-free survival compared with carfilzomib–dexamethasone in patients with relapsed or refractory multiple myeloma and an eGFR of 15–60 mL/min per 1.73m². Complete renal response rates were 52% with isatuximab–carfilzomib–dexamethasone and 31% with carfilzomib–dexamethasone (table 5).¹⁰¹

Elotuzumab is an anti-SLAMF7 monoclonal antibody approved with lenalidomide–dexamethasone or pomalidomide plus low-dose dexamethasone. Elotuzumab–lenalidomide–dexamethasone is administered to patients with relapsed or refractory multiple myeloma and a creatinine clearance of 30 mL/min or higher, whereas elotuzumab–pomalidomide–dexamethasone is given to patients with relapsed or refractory multiple myeloma and a creatinine clearance of 45 mL/min or higher.^{142,143} In a phase 1b study,^{144,145} elotuzumab–lenalidomide–dexamethasone was effective and well tolerated by patients with multiple myeloma and severe renal impairment including end-stage renal impairment.

Recommendations

Daratumumab with dexamethasone is safe and effective in patients with multiple myeloma and renal impairment, including those on dialysis (grade B recommendation). Daratumumab-based regimens are safe and effective for newly diagnosed patients with multiple myeloma and a creatinine clearance of 40 mL/min or higher (daratumumab–bortezomib–melphalan–prednisone and daratumumab–bortezomib–thalidomide–dexamethasone) or of 30 mL/min or higher (daratumumab–lenalidomide–dexamethasone; grade B recommendation). Anti-CD38-based triplet combinations are safe and effective in patients with relapsed or refractory multiple myeloma and moderate-to-severe renal impairment (proteasome inhibitors: daratumumab–bortezomib–dexamethasone, daratumumab–carfilzomib–dexamethasone, and isatuximab–carfilzomib–dexamethasone) or moderate renal impairment (immunomodulatory drugs: daratumumab–lenalidomide–dexamethasone, daratumumab–pomalidomide–dexamethasone, and isatuximab–pomalidomide–dexamethasone; grade B recommendation). Elotuzumab–lenalidomide–dexamethasone is well tolerated and effective in patients with relapsed or refractory multiple myeloma and renal impairment (grade C recommendation).

Autologous HSCT

High-dose melphalan followed by autologous HSCT remains a standard of care for eligible, newly diagnosed patients with multiple myeloma. Autologous HSCT is feasible in patients with stable renal impairment, but not in patients with acute kidney injury, with a potential

dose adjustment of melphalan from 200 mg/m² to 140 mg/m², although data show the safety of melphalan at 200 mg/m².^{146–148} All panellists would consider reducing the melphalan dose to 140 mg/m² when the eGFR is less than 30 mL/min per 1.73 m².

In the era of bortezomib-based and daratumumab-based induction regimens, mortality related to transplantation is similar to that of patients without renal impairment.^{148–150} Autologous HSCT might result in improvement in renal function in up to a third of patients and dialysis independence in more than a quarter of patients.^{146,147,151} Induction with new agents and subsequent autologous HSCT might overcome the adverse prognostic effect of renal impairment at diagnosis.^{149,152} In a small study with 34 patients undergoing haemodialysis,¹⁵³ high-dose melphalan was given on a single day in a dose of 100 mg/m² and showed equivalent efficacy with high-dose melphalan 200 mg/m² and manageable toxicity.

Recommendations

High-dose melphalan followed by autologous HSCT is safe and effective in eligible, newly diagnosed patients with multiple myeloma and stable renal impairment (grade B recommendation). A reduced (100 mg/m² or 140 mg/m²) or full (200 mg/m²) dose of melphalan can be administered depending on the severity of renal impairment (grade C recommendation).

Antibody-drug conjugates

Belantamab mafodotin is an antibody-drug conjugate targeting B-cell maturation antigen (BCMA) and has anti-myeloma activity in triple-class refractory patients after exposure to a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody. A post-hoc analysis of the DREAMM-2 study¹²⁵ showed that belantamab mafodotin resulted in similar overall response rate, progression-free survival, and toxicities across patient groups according to renal function (eGFR 90 mL/min per 1.73 m² vs 60–89 mL/min per 1.73 m² vs 30–59 mL/min per 1.73 m²). An ongoing study (DREAMM-12) will assess the pharmacokinetic profile and safety in patients with severe and end-stage renal impairment.

XPO1 inhibitors

Selinexor is an exportin 1 inhibitor for patients with relapsed or refractory multiple myeloma and is administered orally. A post-hoc analysis of the phase 2b STORM trial showed that selinexor–dexamethasone resulted in similar overall response rate regardless of baseline renal function of heavily pretreated (penta-refractory) patients with relapsed or refractory multiple myeloma (creatinine clearance 20 mL/min to <40 mL/min, 40 mL/min to <60 mL/min, and ≥60 mL/min), whereas an increase in creatinine clearance became evident in up to 67% of patients.¹²⁶ A sub-analysis

of the phase 3 BOSTON study showed that, compared with bortezomib–dexamethasone, selinexor–bortezomib–dexamethasone significantly improved the overall response rate in patients with relapsed or refractory multiple myeloma and different levels of renal function (creatinine clearance 20 mL/min to <40 mL/min, 40 mL/min to <60 mL/min, and ≥60 mL/min; table 5).¹⁰²

CART-cell therapy

Chimeric antigen receptor (CAR) T cells targeting BCMA on myeloma cells have been approved for relapsed or refractory multiple myeloma because of significantly improved outcomes in triple-class refractory patients after at least four previous lines of therapy. Registration studies of idecabtagene vicleucel (KarMMA)¹⁵⁴ and ciltacabtagene autoleucel (CARTITUDE-1)¹⁵⁵ included patients with adequate renal function and a creatinine clearance of 45 mL/min or higher¹⁵⁴ and of 40 mL/min or higher,¹⁵⁵ which is mainly due to the use of fludarabine as lymphodepletion agent. A post-hoc analysis of pooled data from two phase 1 studies of distinct anti-BCMA CAR T-cell treatments showed that patients with renal dysfunction (eGFR 30–89 mL/min per 1.73 m²) showed an improvement in eGFR; however, they had a worse prognosis compared with patients with normal renal function.¹⁵⁶ Another report including seven patients with relapsed or refractory multiple myeloma and an eGFR of 15–29 mL/min per 1.73 m² showed 100% overall response rate and 100% renal response rates.¹⁵⁷ Fludarabine should be reduced to 24 mg/m² for patients with an eGFR of 30–70 mL/min per 1.73 m² due to risk for nephrotoxicity.¹⁵⁸ No dosing recommendation is available for patients with an eGFR of less than 30 mL/min per 1.73 m².

Bispecific T-cell engagers

Bispecific T-cell engagers are new and promising anti-myeloma immunotherapy approaches that might result in deep and durable responses in patients with relapsed or refractory multiple myeloma. Teclistamab has been approved for the management of relapsed or refractory multiple myeloma, whereas others (eg, talquetamab or elranatamab) are near approval. All reported studies so far include patients with a creatinine clearance higher than 40 mL/min with no substantial renal toxicity.^{159,160} However, studies in patients with moderate-to-severe renal impairment are highly anticipated.¹⁵⁹

Recommendations

Belantamab mafodotin is well tolerated and effective in patients with relapsed or refractory multiple myeloma and moderate renal impairment (grade C recommendation). Selinexor-based regimens are well tolerated and effective in patients with relapsed or refractory multiple myeloma and moderate-to-severe renal impairment (grade C recommendation). Additional studies are needed to establish the safety of CAR T-cells and

bispecific T-cell engagers in patients with multiple myeloma and moderate-to-severe renal impairment. Ciltacabtagene autoleucel and idecabtagene vicleucel seem to be safe in patients with a creatinine clearance equal to or higher than 40 mL/min and 45 mL/min, respectively, whereas teclistamab is well tolerated in patients with a creatinine clearance higher than 40 mL/min (grade C recommendation).

Kidney transplantation

Kidney transplantation has been offered to a few eligible patients with long-term myeloma control and end-stage renal impairment who have previously undergone autologous HSCT and the results are encouraging.^{161–164} A multidisciplinary expert approach is essential to manage the adverse events from the combined immunosuppressive treatment and anti-myeloma therapy. The available data do not suggest the best time to transplantation or whether immunosuppression after kidney transplantation might increase the risk of myeloma relapse. All but one member of the panel suggest that, in eligible patients, the presence of sustained MRD negativity at 2 years might signify a suitable time point for kidney transplantation, if there is an available organ. Although this suggestion is not supported by data in patients with end-stage renal impairment, patients with multiple myeloma, who sustained MRD negativity for 2 years of lenalidomide maintenance after autologous HSCT, had no recorded disease progression at median follow-up of 19.8 months after the 2-year maintenance landmark.¹⁶⁵ We acknowledge that MRD testing might not be done in routine clinical practice in all settings; however, we encourage the introduction of MRD testing in the management of patients with multiple myeloma, as well as in patients with end-stage renal impairment, because it is the best predictor of prolonged progression-free survival and overall survival.^{166,167}

Recommendations

Kidney transplantation can be considered in some fit patients with end-stage renal impairment and sustained myeloma control (ie, MRD negativity for 2 years) in referral centres (grade D recommendation).

Conclusions

The diagnosis and management of renal impairment in patients with multiple myeloma is often challenging and requires a multidisciplinary approach. The updated clinical practice recommendations address the therapeutic advances in myeloma and the introduction of new agents and combinations in the management of patients with multiple myeloma and renal impairment. Several factors complicate the assessment of outcomes in patients with multiple myeloma and renal impairment and should be addressed in future studies to optimise clinical practice and patient outcomes. Limitations in the available studies pertain to the method of renal impairment definition and

evaluation, the exclusion of patients with severe renal impairment with an eGFR of less than 30 mL/min from clinical trials, the inappropriate use of equations developed for estimating renal function in CKD in patients with acute kidney injury, and the differential diagnosis of renal impairment in patients with multiple myeloma.¹¹ Prospective data on patients with renal impairment exploring renal outcomes are scarce, which are essential to formulate strong recommendations tailored for patients with severe renal impairment. Thus, we highly encourage future research in this field.

Several regimens offer both myeloma and renal responses and increase survival in patients with multiple myeloma and renal impairment. However, the optimal therapy, especially in patients with relapsed or refractory multiple myeloma, has not yet been established. Initiation of effective treatment is crucial; all new drugs including the new generation immunotherapy can be administered to patients with renal impairment. No patient with renal impairment should be prevented from effective treatment regimens.

Contributors

MAD and ET conceptualised and designed the study and wrote the first draft of the manuscript. All authors collected, assembled, analysed, and interpreted the data. All authors reviewed and edited the manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests

MAD has received honoraria from AbbVie, Amgen, Bristol Myers Squibb (BMS), GSK, Janssen, Karyopharm Therapeutics, Pharmacyclics, Pfizer, Sanofi, and Takeda Pharmaceuticals. FB holds consulting roles for Janssen, AstraZeneca, Attralus, and Prothena; and is part of the speakers' bureau for GSK, Janssen, and Sanofi. NL has received institutional research support for clinical trials from Omeros and holds stocks in AbbVie. JM holds consulting roles for Amgen, BMS, Janssen, Karyopharm Therapeutics, Sanofi, and Takeda Pharmaceuticals. SJH holds consulting roles for and has received honoraria from AbbVie, Amgen, BMS-Celgene, GSK, HaemaLogix, Janssen, Novartis, Roche-Genetec, Takeda Pharmaceuticals, Sanofi, EUSA Pharma, and Terumo; and research funding from Amgen, BMS-Celgene, GSK, HaemaLogix, Janssen, and Roche-Genetec. EK has received honoraria and research funding from Amgen, Janssen, GSK, and Pfizer. LG has received honoraria from BMS-Celgene, Janssen, Takeda Pharmaceuticals, Sanofi, and GSK. AG has received honoraria from Janssen, Amgen, and Sanofi. NWCJvdD has received research support from Janssen, Amgen, Celgene, Novartis, Collectis, and BMS, all paid to their institution; and serves in advisory boards for Janssen, Amgen, Celgene, BMS, Takeda Pharmaceuticals, Roche, Novartis, and Adaptive Biotechnologies. KCW has received honoraria from AbbVie, Amgen, Adaptive Biotechnologies, AstraZeneca, BMS-Celgene, BeiGene, GSK, Janssen, Karyopharm Therapeutics, Novartis, Oncoceptides, Pfizer, Roche, Sanofi, Stemline Therapeutics, and Takeda Pharmaceuticals; and research support (paid to their institution) from AbbVie, Amgen, BMS-Celgene, GSK, Janssen, and Sanofi. AZB has received research grants from Janssen, BMS, GSK, and Celgene. MB serves in advisory boards for Janssen, Takeda Pharmaceuticals, Sanofi, Menarini, and Pfizer; and is part of the speakers' bureau for Janssen, Takeda Pharmaceuticals, and Sanofi. JH has received honoraria for serving in advisory boards from Amgen, Angitia, Axxess Network, GSK, Janssen, and Sanofi; honoraria for talks from Amgen, BeiGene, Beijing Medical Award Foundation, Curio Science, Janssen, and Target Oncology; and is part of the Data Safety Monitoring Committee for Janssen. MM has received honoraria from Adaptive Biotechnologies, Amgen, Astellas Pharma, BMS, GSK, Janssen, Jazz Pharmaceuticals, Novartis, Pfizer, Sanofi, Stemline Therapeutics, and Takeda Pharmaceuticals; and research funding from Janssen and Sanofi. PJH is a member of advisory

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