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.[5,7,8]

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 recommendations[17] 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

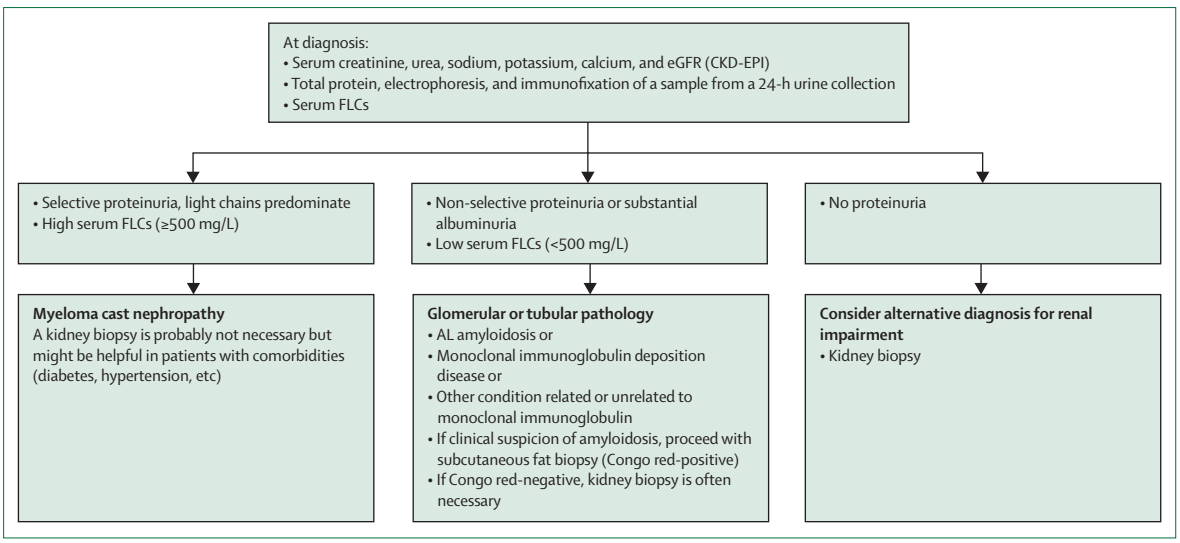

Figure: **Algorithm for the differential diagnosis of renal impairment in patients with multiple myeloma**
CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration. eGFR=estimated glomerular filtration rate. FLCs=free light chains.

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, β2-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 β2-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.

	Description	eGFR (mL/min per 1·73m²)
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**

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 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 β2-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 ≥50% or eGFR decrease of >25%	Serum creatinine increase of ≥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 ≥100% or eGFR decrease of >50%	Serum creatinine increase of ≥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 ≥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 ≥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 m²)*	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 alkalisation has not shown its efficacy in the reversibility of renal impairment.[53] The restoration of calcium homoeostasis 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 anti-biotics (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 alkalisation 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 MYRE[49] and the EuLITE[63] 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/m² intravenously	Reduction by 25% orally; high dose: 140 mg/m² intravenously	Reduction by 25% orally; high dose: 140 mg/m² intravenously	Reduction by 50% orally; high dose: 140 mg/m² intravenously	Reduction by 50% orally; high dose: 140 mg/m² 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/m²	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/m² or 20/56 mg/m² or 20/70 mg/m²	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 × 10⁶ CAR-positive, viable T cells	Not determined yet	Not determined yet	Not determined yet	Not determined yet
Ciltacabtagene autoleucel (intravenously)	0·5–1·0 × 10⁶ 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 trial[73] 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 haemato-poietic 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 study[89] 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
OPTIMISMM[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)

	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 m²	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 m²	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 m²	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 m²	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**

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 1·73m²	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 1·73m²	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 1·73m²	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 1·73m² 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 1·73m²	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 50mL/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 1·73m² 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 study[125] 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]

CAR T-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. Registrational 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 higher[154] 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, Cellectis, 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, Oncopeptides, 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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References

1 Ho PJ, Moore EM, McQuilten ZK, et al. Renal impairment at diagnosis in myeloma: patient characteristics, treatment, and impact on outcomes. Results from the Australia and New Zealand myeloma and related diseases registry. *Clin Lymphoma Myeloma Leuk* 2019; **19:** e415–24.

2 Hari P, Romanus D, Luptakova K, et al. The impact of age and comorbidities on practice patterns and outcomes in patients with relapsed/refractory multiple myeloma in the era of novel therapies. *J Geriatr Oncol* 2018; **9:** 138–44.

3 Abbott KC, Agodoa LY. Multiple myeloma and light chain-associated nephropathy at end-stage renal disease in the United States: patient characteristics and survival. *Clin Nephrol* 2001; **56:** 207–10.

4 Tsakiris DJ, Stel VS, Finne P, et al. Incidence and outcome of patients starting renal replacement therapy for end-stage renal disease due to multiple myeloma or light-chain deposit disease: an ERA-EDTA Registry study. *Nephrol Dial Transplant* 2010; **25:** 1200–06.

5 Eleutherakis-Papaiakovou V, Bamias A, Gika D, et al. Renal failure in multiple myeloma: incidence, correlations, and prognostic significance. *Leuk Lymphoma* 2007; **48:** 337–41.

6 Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014; **15:** e538–48.

7 Chen X, Luo X, Zu Y, et al. Severe renal impairment as an adverse prognostic factor for survival in newly diagnosed multiple myeloma patients. *J Clin Lab Anal* 2020; **34:** e23416.

8 Gonsalves WI, Leung N, Rajkumar SV, et al. Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma. *Blood Cancer J* 2015; **5:** e296.

9 Augustson BM, Begum G, Dunn JA, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002—Medical Research Council Adult Leukaemia Working Party. *J Clin Oncol* 2005; **23:** 9219–26.

10 Bladé J, Fernández-Llama P, Bosch F, et al. Renal failure in multiple myeloma: presenting features and predictors of outcome in 94 patients from a single institution. *Arch Intern Med* 1998; **158:** 1889–93.

11 Mohyuddin GR, Koehn K, Shune L, et al. Renal insufficiency in multiple myeloma: a systematic review and meta-analysis of all randomized trials from 2005–2019. *Leuk Lymphoma* 2021; **62:** 1386–95.

12 Mikhael J, Singh E, Rice MS. Real-world renal function among patients with multiple myeloma in the United States. *Blood Cancer J* 2021; **11:** 99.

13 Dimopoulos MA, Delimpasi S, Katodritou E, et al. Significant improvement in the survival of patients with multiple myeloma presenting with severe renal impairment after the introduction of novel agents. *Ann Oncol* 2014; **25:** 195–200.

14 Uttervall K, Duru AD, Lund J, et al. The use of novel drugs can effectively improve response, delay relapse and enhance overall survival in multiple myeloma patients with renal impairment. *PLoS One* 2014; **9:** e101819.

15 van de Donk NWCJ, Richardson PG, Malavasi F. CD38 antibodies in multiple myeloma: back to the future. *Blood* 2018; **131:** 13–29.

16 Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *HemaSphere* 2021; **5:** e528.

17 Dimopoulos MA, Sonneveld P, Leung N, et al. International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. *J Clin Oncol* 2016; **34:** 1544–57.

18 Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004; **328:** 1490.

19 Terpos E, Zamagni E, Lentzsch S, et al. Treatment of multiple myeloma-related bone disease: recommendations from the Bone Working Group of the International Myeloma Working Group. *Lancet Oncol* 2021; **22:** e119–30.

20 Bridoux F, Leung N, Belmouaz M, et al. Management of acute kidney injury in symptomatic multiple myeloma. *Kidney Int* 2021; **99:** 570–80.

21 Leung N, Bridoux F, Batuman V, et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. *Nat Rev Nephrol* 2019; **15:** 45–59.

22 Gozzetti A, Guarnieri A, Zamagni E, et al. Monoclonal gammopathy of renal significance (MGRS): real-world data on outcomes and prognostic factors. *Am J Hematol* 2022; **97:** 877–84.

23 Zhou L, Yu Q, Wei G, et al. Measuring the global, regional, and national burden of multiple myeloma from 1990 to 2019. *BMC Cancer* 2021; **21:** 606.

24 Bladé J, Rosiñol L, Cibeira MT, Fernández de Larrea C. Treatment of relapsed myeloma in a patient with renal insufficiency. *J Clin Oncol* 2018; **36:** 2012–16.

25 Leung N, Gertz M, Kyle RA, et al. Urinary albumin excretion patterns of patients with cast nephropathy and other monoclonal gammopathy-related kidney diseases. *Clin J Am Soc Nephrol* 2012; **7:** 1964–68.

26 Yadav P, Sathick IJ, Leung N, et al. Serum free light chain level at diagnosis in myeloma cast nephropathy—a multicentre study. *Blood Cancer J* 2020; **10:** 28.

27 Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; **367:** 20–29.

28 Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150:** 604–12.

29 Delgado C, Baweja M, Crews DC, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN Task Force on reassessing the inclusion of race in diagnosing kidney disease. *Am J Kidney Dis* 2022; **79:** 268–88.

30 Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clin J Am Soc Nephrol* 2010; **5:** 1003–09.

31 Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; **67:** 2089–100.

32 Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145:** 247–54.

33 Terpos E, Christoulas D, Kastritis E, et al. The Chronic Kidney Disease Epidemiology Collaboration cystatin C (CKD-EPI-CysC) equation has an independent prognostic value for overall survival in newly diagnosed patients with symptomatic multiple myeloma; is it time to change from MDRD to CKD-EPI-CysC equations? *Eur J Haematol* 2013; **91:** 347–55.

34 Cepeda-Piorno F-J, González-García E, Méndez-Gallego A, et al. Cystatin C-based equations detect hidden kidney disease and poor prognosis in newly diagnosed patients with multiple myeloma. *Adv Hematol* 2022; **2022:** 4282226.

35 Pottel H, Björk J, Rule AD, et al. Cystatin C-based equation to estimate GFR without the inclusion of race and sex. *N Engl J Med* 2023; **388:** 333–43.

36 Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol* 2015; **33:** 2863–69.

37 Koeze J, Keus F, Dieperink W, van der Horst IC, Zijlstra JG, van Meurs M. Incidence, timing and outcome of AKI in critically ill patients varies with the definition used and the addition of urine output criteria. *BMC Nephrol* 2017; **18:** 70.

38 Ando M, Mori J, Ohashi K, et al. A comparative assessment of the RIFLE, AKIN and conventional criteria for acute kidney injury after hematopoietic SCT. *Bone Marrow Transplant* 2010; **45:** 1427–34.

39 Shi H, Zhang W, Li X, Ren H, Pan X, Chen N. Application of RIFLE criteria in patients with multiple myeloma with acute kidney injury: a 15-year retrospective, single center, cohort study. *Leuk Lymphoma* 2014; **55:** 1076–82.

40 Dimopoulos MA, Terpos E, Chanan-Khan A, et al. Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group. *J Clin Oncol* 2010; **28:** 4976–84.

41 Kastritis E, Terpos E, Symeonidis A, et al. Prospective phase 2 trial of daratumumab with dexamethasone in patients with relapsed/refractory multiple myeloma and severe renal impairment or on dialysis: the DARE study. *Am J Hematol* (in press).

42 Dimopoulos MA, Roussou M, Gavriatopoulou M, et al. Bortezomib-based triplets are associated with a high probability of dialysis independence and rapid renal recovery in newly diagnosed myeloma patients with severe renal failure or those requiring dialysis. *Am J Hematol* 2016; **91:** 499–502.

43 Sharma R, Jain A, Jandial A, et al. Lack of renal recovery predicts poor survival in patients of multiple myeloma with renal impairment. *Clin Lymphoma Myeloma Leuk* 2022; **22:** 626–34.

44 Kim Y, Park S-S, Jeon Y-W, et al. Response and dynamics of renal function in transplantation-eligible multiple myeloma patients treated with a novel agent: the CAREMM-2201 study. *Transplant Cell Ther* 2023; **29:** 55.e1–e9.

45 Bachmann F, Schreder M, Engelhardt M, et al. Kinetics of renal function during induction in newly diagnosed multiple myeloma: results of two prospective studies by the German Myeloma Study Group DSMM. *Cancers (Basel)* 2021; **13:** 1322.

46 Ramasamy K, Iqbal G, Brouwer R, et al. Bortezomib, bendamustine and dexamethasone *vs* thalidomide, bendamustine and dexamethasone in myeloma patients presenting with renal failure (OPTIMAL): a randomised, multi-centre phase II trial. *Blood Cancer J* 2022; **12:** 162.

47 Kumar S, Fu A, Niesvizky R, Jagannath S, Boccia R, Raje N. Renal response in real-world carfilzomib- *vs* bortezomib-treated patients with relapsed or refractory multiple myeloma. *Blood Adv* 2021; **5:** 367–76.

48 Palladini G, Hegenbart U, Milani P, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. *Blood* 2014; **124:** 2325–32.

49 Bridoux F, Carron P-L, Pegourie B, et al. Effect of high-cutoff hemodialysis *vs* conventional hemodialysis on hemodialysis independence among patients with myeloma cast nephropathy: a randomized clinical trial. *JAMA* 2017; **318:** 2099–110.

50 Bridoux F, Arnulf B, Karlin L, et al. Randomized trial comparing double versus triple bortezomib-based regimen in patients with multiple myeloma and acute kidney injury due to cast nephropathy. *J Clin Oncol* 2020; **38:** 2647–57.

51 Royal V, Leung N, Troyanov S, et al. Clinicopathologic predictors of renal outcomes in light chain cast nephropathy: a multicenter retrospective study. *Blood* 2020; **135:** 1833–46.

52 Dimopoulos MA, Roussou M, Gavriatopoulou M, et al. Outcomes of newly diagnosed myeloma patients requiring dialysis: renal recovery, importance of rapid response and survival benefit. *Blood Cancer J* 2017; **7:** e571.

53 MRC Working Party on Leukaemia in Adults. Analysis and management of renal failure in fourth MRC myelomatosis trial. *Br Med J (Clin Res Ed)* 1984; **288:** 1411–16.

54 Sawyer N, Newstead C, Drummond A, Newland A, Cunningham J. One-shot high-dose pamidronate disodium (APD): effective, simple treatment for hypercalcaemia in haematological malignancy. *Clin Lab Haematol* 1989; **11:** 179–84.

55 Cicci JD, Buie L, Bates J, van Deventer H. Denosumab for the management of hypercalcemia of malignancy in patients with multiple myeloma and renal dysfunction. *Clin Lymphoma Myeloma Leuk* 2014; **14:** e207–11.

56 Sanders PW, Booker BB. Pathobiology of cast nephropathy from human Bence Jones proteins. *J Clin Invest* 1992; **89:** 630–39.

57 Stacul F, Bertolotto M, Thomsen HS, et al. Iodine-based contrast media, multiple myeloma and monoclonal gammopathies: literature review and ESUR Contrast Media Safety Committee guidelines. *Eur Radiol* 2018; **28:** 683–91.

58 Yu X, Gan L, Wang Z, Dong B, Chen X. Chemotherapy with or without plasmapheresis in acute renal failure due to multiple myeloma: a meta-analysis. *Int J Clin Pharmacol Ther* 2015; **53:** 391–97.

59 Clark WF, Stewart AK, Rock GA, et al. Plasma exchange when myeloma presents as acute renal failure: a randomized, controlled trial. *Ann Intern Med* 2005; **143:** 777–84.

60 Curti A, Schwarz A, Trachsler J, Tomonaga Y, Ambühl PM. Therapeutic efficacy and cost effectiveness of high cut-off dialyzers compared to conventional dialysis in patients with cast nephropathy. *PLoS One* 2016; **11:** e0159942.

61 Gerth HU, Pohlen M, Görlich D, et al. Impact of high-cut-off dialysis on renal recovery in dialysis-dependent multiple myeloma patients: results from a case-control study. *PLoS One* 2016; **11:** e0154993.

62 Zannetti BA, Zamagni E, Santostefano M, et al. Bortezomib-based therapy combined with high cut-off hemodialysis is highly effective in newly diagnosed multiple myeloma patients with severe renal impairment. *Am J Hematol* 2015; **90:** 647–52.

63 Hutchison CA, Cockwell P, Moroz V, et al. High cutoff versus high-flux haemodialysis for myeloma cast nephropathy in patients receiving bortezomib-based chemotherapy (EuLITE): a phase 2 randomised controlled trial. *Lancet Haematol* 2019; **6:** e217–28.

64 Hudier L, Decaux O, Haddj-Elmrabet A, et al. Intensive haemodialysis using PMMA dialyser does not increase renal response rate in multiple myeloma patients with acute kidney injury. *Clin Kidney J* 2018; **11:** 230–35.

65 Pendón-Ruiz de Mier MV, Ojeda R, Álvarez-Lara MA, et al. Hemodiafiltration with ultrafiltrate regeneration reduces free light chains without albumin loss in multiple myeloma patients. *BMC Nephrol* 2020; **21:** 227.

66 Pasquali S, Iannuzzella F, Corradini M, et al. A novel option for reducing free light chains in myeloma kidney: supra-hemodiafiltration with endogenous reinfusion (HFR). *J Nephrol* 2015; **28:** 251–54.

67 Mehta S, Shtaynberg N, Goldman M, Asti D, Kiroycheva M, Pepe J. Use of continuous venovenous hemofiltration for acute renal failure due to multiple myeloma cast nephropathy. *Hematology* 2012; **17:** 229–31.

68 Fabbrini P, Finkel K, Gallieni M, et al. Light chains removal by extracorporeal techniques in acute kidney injury due to multiple myeloma: a position statement of the Onconephrology Work Group of the Italian Society of Nephrology. *J Nephrol* 2016; **29:** 735–46.

69 Bayraktar UD, Warsch S, Pereira D. High-dose glucocorticoids improve renal failure reversibility in patients with newly diagnosed multiple myeloma. *Am J Hematol* 2011; **86:** 224–27.

70 Kastritis E, Anagnostopoulos A, Roussou M, et al. Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone-containing regimens and the impact of novel agents. *Haematologica* 2007; **92:** 546–49.

71 Dimopoulos MA, Roussou M, Gkotzamanidou M, et al. The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma. *Leukemia* 2013; **27:** 423–29.

72 Gertz MA, Garton JP, Greipp PR, Witzig TE, Kyle RA. A phase II study of high-dose methylprednisolone in refractory or relapsed multiple myeloma. *Leukemia* 1995; **9:** 2115–18.

73 Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med* 2003; **348:** 2609–17.

74 Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005; **352:** 2487–98.

75 Bladé J, Sonneveld P, San Miguel JF, et al. Pegylated liposomal doxorubicin plus bortezomib in relapsed or refractory multiple myeloma: efficacy and safety in patients with renal function impairment. *Clin Lymphoma Myeloma* 2008; **8:** 352–55.

76 Dimopoulos MA, Roussou M, Gavriatopoulou M, et al. Reversibility of renal impairment in patients with multiple myeloma treated with bortezomib-based regimens: identification of predictive factors. *Clin Lymphoma Myeloma* 2009; **9:** 302–06.

77 Jagannath S, Barlogie B, Berenson JR, et al. Bortezomib in recurrent and/or refractory multiple myeloma. Initial clinical experience in patients with impared renal function. *Cancer* 2005; **103:** 1195–200.

78 Ludwig H, Adam Z, Hajek R, et al. Light chain-induced acute renal failure can be reversed by bortezomib–doxorubicin–dexamethasone in multiple myeloma: results of a phase II study. *J Clin Oncol* 2010; **28:** 4635–41.

79 Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous bortezomib in patients with relapsed multiple myeloma: subanalysis of patients with renal impairment in the phase III MMY-3021 study. *Haematologica* 2015; **100:** e207–10.

80 Pönisch W, Moll B, Bourgeois M, et al. Bendamustine and prednisone in combination with bortezomib (BPV) in the treatment of patients with relapsed or refractory multiple myeloma and light chain-induced renal failure. *J Cancer Res Clin Oncol* 2013; **139:** 1937–46.

81 San-Miguel JF, Richardson PG, Sonneveld P, et al. Efficacy and safety of bortezomib in patients with renal impairment: results from the APEX phase 3 study. *Leukemia* 2008; **22:** 842–49.

82 Dimopoulos MA, Richardson PG, Schlag R, et al. VMP (bortezomib, melphalan, and prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: cohort analysis of the phase III VISTA study. *J Clin Oncol* 2009; **27:** 6086–93.

83 Oortgiesen BE, Azad R, Hemmelder MH, et al. The impact of the introduction of bortezomib on dialysis independence in multiple myeloma patients with renal impairment: a nationwide Dutch population-based study. *Haematologica* 2018; **103:** e311–14.

84 Zhu W, Chen W. Bortezomib-based treatment for multiple myeloma patients with renal impairment: a systematic review and meta-analysis of observational studies. *Medicine (Baltimore)* 2016; **95:** e5202.

85 Scheid C, Sonneveld P, Schmidt-Wolf IG, et al. Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/GMMG-HD4 trial. *Haematologica* 2014; **99:** 148–54.

86 Salwender H, Elmaagacli A, Merz M, et al. Long-term follow-up of subcutaneous versus intravenous bortezomib during induction therapy for newly diagnosed multiple myeloma treated within the GMMG-MM5 Phase III trial. *Leukemia* 2021; **35:** 3007–11.

87 Quach H, White D, Spencer A, et al. Pharmacokinetics and safety of carfilzomib in patients with relapsed multiple myeloma and end-stage renal disease (ESRD): an open-label, single-arm, phase I study. *Cancer Chemother Pharmacol* 2017; **79:** 1067–76.

88 Badros AZ, Vij R, Martin T, et al. Carfilzomib in multiple myeloma patients with renal impairment: pharmacokinetics and safety. *Leukemia* 2013; **27:** 1707–14.

89 Dimopoulos M, Siegel D, White DJ, et al. Carfilzomib *vs* bortezomib in patients with multiple myeloma and renal failure: a subgroup analysis of ENDEAVOR. *Blood* 2019; **133:** 147–55.

90 Cavo M, Dimopoulos MA, San-Miguel J, et al. Impact of baseline renal function on efficacy and safety of daratumumab plus bortezomib-melphalan-prednisone (VMP) in patients (Pts) with newly diagnosed multiple myeloma (NDMM) ineligible for transplantation (ALCYONE). *J Clin Oncol* 2018; **36:** e20024.

91 Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. *Lancet* 2019; **394:** 29–38.

92 Usmani SZ, Kumar S, Plesner T, et al. Efficacy of daratumumab, lenalidomide, and dexamethasone in transplant-ineligible patients with newly diagnosed multiple myeloma and impaired renal function from the phase 3 MAIA study based on lenalidomide starting dose. *Blood* 2021; **138** (suppl 1)**:** 1646.

93 Siegel DS, Dimopoulos MA, Ludwig H, et al. Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. *J Clin Oncol* 2018; **36:** 728–34.

94 Weisel KC, Dimopoulos MA, Moreau P, et al. Analysis of renal impairment in MM-003, a phase III study of pomalidomide + low-dose dexamethasone versus high-dose dexamethasone in refractory or relapsed and refractory multiple myeloma. *Haematologica* 2016; **101:** 872–78.

95 Schjesvold F, Dimopoulos MA, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone (PVd) in lenalidomide (LEN)-pretreated relapsed refractory multiple myeloma: subanalysis of patients with renal impairment in OPTIMISMM. *J Clin Oncol* 2020; **38:** e20562.

96 Bahlis NJ, Dimopoulos MA, White DJ, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. *Leukemia* 2020; **34:** 1875–84.

97 Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; **375:** 754–66.

98 Dimopoulos MA, Terpos E, Boccadoro M, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2021; **22:** 801–12.

99 Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. *Lancet* 2020; **396:** 186–97.

100 Dimopoulos MA, Leleu X, Moreau P, et al. Isatuximab plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma patients with renal impairment: ICARIA-MM subgroup analysis. *Leukemia* 2021; **35:** 562–72.

101 Capra M, Martin T, Moreau P, et al. Isatuximab plus carfilzomib and dexamethasone versus carfilzomib and dexamethasone in relapsed multiple myeloma patients with renal impairment: IKEMA subgroup analysis. *Haematologica* 2022; **107:** 1397–409.

102 Delimpasi S, Mateos MV, Auner HW, et al. Efficacy and tolerability of once-weekly selinexor, bortezomib, and dexamethasone in comparison with standard twice-weekly bortezomib and dexamethasone in previously treated multiple myeloma with renal impairment: subgroup analysis from the BOSTON study. *Am J Hematol* 2022; **97:** E83–86.

103 Dimopoulos MA, Niesvizky R, Weisel K, et al. Once- versus twice-weekly carfilzomib in relapsed and refractory multiple myeloma by select patient characteristics: phase 3 A.R.R.O.W. study subgroup analysis. *Blood Cancer J* 2020; **10:** 35.

104 Fotiou D, Roussou M, Gakiopoulou C, et al. Carfilzomib-associated renal toxicity is common and unpredictable: a comprehensive analysis of 114 multiple myeloma patients. *Blood Cancer J* 2020; **10:** 109.

105 Hájek R, Masszi T, Petrucci MT, et al. A randomized phase III study of carfilzomib *vs* low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS). *Leukemia* 2017; **31:** 107–14.

106 Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; **374:** 1621–34.

107 Gupta N, Zhang S, Pusalkar S, et al. A phase I study to assess the mass balance, excretion, and pharmacokinetics of [^{14}C]-ixazomib, an oral proteasome inhibitor, in patients with advanced solid tumors. *Invest New Drugs* 2018; **36:** 407–15.

108 Gupta N, Hanley MJ, Harvey RD, et al. A pharmacokinetics and safety phase 1/1b study of oral ixazomib in patients with multiple myeloma and severe renal impairment or end-stage renal disease requiring haemodialysis. *Br J Haematol* 2016; **174:** 748–59.

109 Tosi P, Zamagni E, Cellini C, et al. Thalidomide alone or in combination with dexamethasone in patients with advanced, relapsed or refractory multiple myeloma and renal failure. *Eur J Haematol* 2004; **73:** 98–103.

110 Chen N, Lau H, Kong L, et al. Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. *J Clin Pharmacol* 2007; **47:** 1466–75.

111 Quach H, Fernyhough L, Henderson R, et al. Upfront lower dose lenalidomide is less toxic and does not compromise efficacy for vulnerable patients with relapsed refractory multiple myeloma: final analysis of the phase II RevLite study. *Br J Haematol* 2017; **177:** 441–48.

112 Mikhael J, Manola J, Dueck AC, et al. Lenalidomide and dexamethasone in patients with relapsed multiple myeloma and impaired renal function: PrE1003, a PrECOG study. *Blood Cancer J* 2018; **8:** 86.

113 Dimopoulos M, Alegre A, Stadtmauer EA, et al. The efficacy and safety of lenalidomide plus dexamethasone in relapsed and/or refractory multiple myeloma patients with impaired renal function. *Cancer* 2010; **116:** 3807–14.

114 Ludwig H, Rauch E, Kuehr T, et al. Lenalidomide and dexamethasone for acute light chain-induced renal failure: a phase II study. *Haematologica* 2015; **100:** 385–91.

115 Zhou DB, Yu L, Du X, et al. Lenalidomide plus low-dose dexamethasone in Chinese patients with relapsed or refractory multiple myeloma and renal impairment. *Int J Hematol* 2015; **101:** 569–77.

116 de la Rubia J, Roig M, Ibáñez A, et al. Activity and safety of lenalidomide and dexamethasone in patients with multiple myeloma requiring dialysis: a Spanish multicenter retrospective study. *Eur J Haematol* 2010; **85:** 363–65.

117 Dimopoulos MA, Christoulas D, Roussou M, et al. Lenalidomide and dexamethasone for the treatment of refractory/relapsed multiple myeloma: dosing of lenalidomide according to renal function and effect on renal impairment. *Eur J Haematol* 2010; **85:** 1–5.

118 Klein U, Neben K, Hielscher T, Heiss C, Ho AD, Goldschmidt H. Lenalidomide in combination with dexamethasone: effective regimen in patients with relapsed or refractory multiple myeloma complicated by renal impairment. *Ann Hematol* 2011; **90:** 429–39.

119 Specter R, Sanchorawala V, Seldin DC, et al. Kidney dysfunction during lenalidomide treatment for AL amyloidosis. *Nephrol Dial Transplant* 2011; **26:** 881–86.

120 Hoffmann M, Kasserra C, Reyes J, et al. Absorption, metabolism and excretion of [^{14}C]pomalidomide in humans following oral administration. *Cancer Chemother Pharmacol* 2013; **71:** 489–501.

121 Li Y, Wang X, O'Mara E, et al. Population pharmacokinetics of pomalidomide in patients with relapsed or refractory multiple myeloma with various degrees of impaired renal function. *Clin Pharmacol* 2017; **9:** 133–45.

122 Siegel DS, Weisel KC, Dimopoulos MA, et al. Pomalidomide plus low-dose dexamethasone in patients with relapsed/refractory multiple myeloma and moderate renal impairment: a pooled analysis of three clinical trials. *Leuk Lymphoma* 2016; **57:** 2833–38.

123 Maciocia N, Melville A, Cheesman S, et al. Real-world use of pomalidomide and dexamethasone in double refractory multiple myeloma suggests benefit in renal impairment and adverse genetics: a multi-centre UK experience. *Br J Haematol* 2017; **176:** 908–17.

124 Dimopoulos M, Weisel K, van de Donk NWCJ, et al. Pomalidomide plus low-dose dexamethasone in patients with relapsed/refractory multiple myeloma and renal impairment: results from a phase II trial. *J Clin Oncol* 2018; **36:** 2035–43.

125 Lee HC, Cohen AD, Chari A, et al. DREAMM-2: Single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) and renal impairment. *J Clin Oncol* 2020; **38:** 8519.

126 Vogl DT, Nooka A, Gavriatopoulou M, et al. Improvements in renal function with selinexor in relapsed/refractory multiple myeloma: post-hoc analyses from the STORM study. *Clin Lymphoma Myeloma Leuk* 2019; **19:** e118–19.

127 Cheng Y, Xue Y, Chen L, et al. Model-based analysis for the population pharmacokinetics of iberdomide and its major active metabolite in healthy subjects and patients with relapsed and refractory multiple myeloma. *Br J Clin Pharmacol* 2023; **89:** 316–29.

128 van de Donk NWCJ, Raab MS, Besemer B, et al. P-279: efficacy, safety, and pharmacokinetics of iberdomide plus dexamethasone in patients with relapsed/refractory multiple myeloma by renal function: a subgroup analysis of the CC-220-MM-001 trial. *Clin Lymphoma Myeloma Leuk* 2022; **22:** S191–92.

129 Sidana S, Kumar S, Fraser R, et al. Impact of induction therapy with VRD versus VCD on outcomes in patients with multiple myeloma in partial response or better undergoing upfront autologous stem cell transplantation. *Transplant Cell Ther* 2022; **28:** 83.e1–9.

130 Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood* 2010; **116:** 679–86.

131 Richardson PG, Oriol A, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2019; **20:** 781–94.

132 Jeyaraman P, Bhasin A, Dayal N, Pathak S, Naithani R. Daratumumab in dialysis-dependent multiple myeloma. *Blood Res* 2020; **55:** 65–67.

133 Mizuno S, Kitayama C, Yamaguchi K, Sanada S, Sato T. Successful management of hemodialysis-dependent refractory myeloma with modified daratumumab, bortezomib and dexamethasone regimen. *Int J Hematol* 2020; **112:** 860–63.

134 Rocchi S, Tacchetti P, Pantani L, et al. Safety and efficacy of daratumumab in dialysis-dependent renal failure secondary to multiple myeloma. *Haematologica* 2018; **103:** e277–78.

135 Smyth E, Glavey S, Melotti D, et al. Dialysis independence following single-agent daratumumab in refractory myeloma with renal failure. *Ir J Med Sci* 2019; **188:** 1079–80.

136 Cejalvo MJ, Legarda M, Abella E, et al. Single-agent daratumumab in patients with relapsed and refractory multiple myeloma requiring dialysis: results of a Spanish retrospective, multicentre study. *Br J Haematol* 2020; **190:** e289–92.

137 Kuzume A, Tabata R, Terao T, et al. Safety and efficacy of daratumumab in patients with multiple myeloma and severe renal failure. *Br J Haematol* 2021; **193:** e33–36.

138 Monge J, Solomon RS, Flicker K, et al. Daratumumab in patients with multiple myeloma and renal impairment—real-world data from a single-center institution. *Blood* 2019; **134** (suppl 1)**:** 5563.

139 Usmani SZ, Nahi H, Plesner T, et al. Daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma: final results from the phase 2 GEN501 and SIRIUS trials. *Lancet Haematol* 2020; **7:** e447–55.

140 Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med* 2015; **373:** 1207–19.

141 Richardson PG, Perrot A, San-Miguel J, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): follow-up analysis of a randomised, phase 3 study. *Lancet Oncol* 2022; **23:** 416–27.

142 Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med* 2015; **373:** 621–31.

143 Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. *N Engl J Med* 2018; **379:** 1811–22.

144 Berdeja J, Jagannath S, Zonder J, et al. Pharmacokinetics and safety of elotuzumab combined with lenalidomide and dexamethasone in patients with multiple myeloma and various levels of renal impairment: results of a phase Ib study. *Clin Lymphoma Myeloma Leuk* 2016; **16:** 129–38.

145 Richardson PG, Jagannath S, Moreau P, et al. Elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma: final phase 2 results from the randomised, open-label, phase 1b-2 dose-escalation study. *Lancet Haematol* 2015; **2:** e516–27.

146 Parikh GC, Amjad AI, Saliba RM, et al. Autologous hematopoietic stem cell transplantation may reverse renal failure in patients with multiple myeloma. *Biol Blood Marrow Transplant* 2009; **15:** 812–16.

147 Mahindra A, Hari P, Fraser R, et al. Autologous hematopoietic cell transplantation for multiple myeloma patients with renal insufficiency: a center for international blood and marrow transplant research analysis. *Bone Marrow Transplant* 2017; **52:** 1616–22.

148 Augeul-Meunier K, Chretien M-L, Stoppa A-M, et al. Extending autologous transplantation as first line therapy in multiple myeloma patients with severe renal impairment: a retrospective study by the SFGM-TC. *Bone Marrow Transplant* 2018; **53:** 749–55.

149 Kumar L, Chellapuram SK, Dev R, et al. Induction therapy with novel agents and autologous stem cell transplant overcomes the adverse impact of renal impairment in multiple myeloma. *Clin Hematol Int* 2019; **1:** 205–19.

150 Li AY, Atenafu EG, Bernard RS, et al. Toxicity and survival outcomes of autologous stem cell transplant in multiple myeloma patients with renal insufficiency: an institutional comparison between two eras. *Bone Marrow Transplant* 2020; **55:** 578–85.

151 Lee C-K, Zangari M, Barlogie B, et al. Dialysis-dependent renal failure in patients with myeloma can be reversed by high-dose myeloablative therapy and autotransplant. *Bone Marrow Transplant* 2004; **33:** 823–28.

152 Antlanger M, Dust T, Reiter T, et al. Impact of renal impairment on outcomes after autologous stem cell transplantation in multiple myeloma: a multi-center, retrospective cohort study. *BMC Cancer* 2018; **18:** 1008.

153 Raab MS, Breitkreutz I, Hundemer M, et al. The outcome of autologous stem cell transplantation in patients with plasma cell disorders and dialysis-dependent renal failure. *Haematologica* 2006; **91:** 1555–58.

154 Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med* 2021; **384:** 705–16.

155 Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet* 2021; **398:** 314–24.

156 He SL, Cheng YH, Wang D, et al. Anti-BCMA CAR-T cell therapy in relapsed or refractory multiple myeloma patients with impaired renal function. *Curr Med Sci* 2021; **41:** 474–81.

157 Li H, Yin L, Wang Y, et al. Safety and efficacy of chimeric antigen receptor T-cell therapy in relapsed/refractory multiple myeloma with renal impairment. *Bone Marrow Transplant* 2020; **55:** 2215–18.

158 Lichtman SM, Etcubanas E, Budman DR, et al. The pharmacokinetics and pharmacodynamics of fludarabine phosphate in patients with renal impairment: a prospective dose adjustment study. *Cancer Invest* 2002; **20:** 904–13.

159 Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med* 2022; **387:** 495–505.

160 Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N Engl J Med* 2022; **387:** 2232–44.

161 Domínguez-Pimentel V, Rodríguez-Muñoz A, Froment-Brum M, et al. Kidney transplantation after hematopoietic cell transplantation in plasma cell dyscrasias: case reports. *Transplant Proc* 2019; **51:** 383–85.

162 Shah S, Ibrahim M, Delaney M, et al. Risk of relapse of multiple myeloma following kidney transplantation. *Clin Kidney J* 2019; **12:** 216–23.

163 Lum EL, Kogut N, Pham T, Danovitch GM, Bunnapradist S. Kidney transplantation in patients with active multiple myeloma: case reports. *Transplant Direct* 2017; **3:** e200.

164 Le TX, Wolf JL, Peralta CA, Webber AB. Kidney transplantation for kidney failure due to multiple myeloma: case reports. *Am J Kidney Dis* 2017; **69:** 858–62.

165 Diamond B, Korde N, Lesokhin AM, et al. Dynamics of minimal residual disease in patients with multiple myeloma on continuous lenalidomide maintenance: a single-arm, single-centre, phase 2 trial. *Lancet Haematol* 2021; **8:** e422–32.

166 Munshi NC, Avet-Loiseau H, Anderson KC, et al. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. *Blood Adv* 2020; **4:** 5988–99.

167 Anderson KC, Auclair D, Adam SJ, et al. Minimal residual disease in myeloma: application for clinical care and new drug registration. *Clin Cancer Res* 2021; **27:** 5195–212.