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SPECIAL ARTICLE

International Myeloma Working Group Recommendations for the Diagnosis and Management of Myeloma-Related Renal Impairment

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ABSTRACT

Purpose

The aim of the International Myeloma Working Group was to develop practical recommendations for the diagnosis and management of multiple myeloma–related renal impairment (RI).

Methods

Recommendations were based on published data through December 2015, and were developed using the system developed by the Grading of Recommendation, Assessment, Development, and Evaluation Working Group.

Recommendations

All patients with myeloma at diagnosis and at disease assessment should have serum creatinine, estimated glomerular filtration rate, and electrolytes measurements as well as free light chain, if available, and urine electrophoresis of a sample from a 24-hour urine collection (grade A). The Chronic Kidney Disease Epidemiology Collaboration, preferably, or the Modification of Diet in Renal Disease formula should be used for the evaluation of estimated glomerular filtration rate in patients with stabilized serum creatinine (grade A). International Myeloma Working Group criteria for renal reversibility should be used (grade B). For the management of RI in patients with multiple myeloma, high fluid intake is indicated along with antimyeloma therapy (grade B). The use of high-cutoff hemodialysis membranes in combination with antimyeloma therapy can be considered (grade B). Bortezomib-based regimens remain the cornerstone of the management of myeloma-related RI (grade A). High-dose dexamethasone should be administered at least for the first month of therapy (grade B). Thalidomide is effective in patients with myeloma with RI, and no dose modifications are needed (grade B). Lenalidomide is effective and safe, mainly in patients with mild to moderate RI (grade B); for patients with severe RI or on dialysis, lenalidomide should be given with close monitoring for hematologic toxicity (grade B) with dose reduction as needed. High-dose therapy with autologous stem cell transplantation (with melphalan 100 mg/m^2 to 140 mg/m^2) is feasible in patients with RI (grade C). Carfilzomib can be safely administered to patients with creatinine clearance $>$ 15 mL/min, whereas ixazomib in combination with lenalidomide and dexamethasone can be safely administered to patients with creatinine clearance $>$ 30 mL/min (grade A).

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INTRODUCTION

Renal impairment (RI) is one of the most common complications of multiple myeloma (MM). The incidence of RI at diagnosis ranges from 20% to 50%, according to how RI is defined, that is, either as serum creatinine (sCr) above the upper normal limit or $>$ 2 mg/dL or as estimated glomerular filtration rate (eGFR) $<$ 60 mL/min/1.73 m^2.[1-3] In the era of conventional chemotherapy (CC), RI was associated with a poor median survival time of approximately 2 years.[4] The use of novel antimyeloma agents resulted in a substantial increase in the survival of patients with MM with RI, although, severe RI is associated with as increased risk of early death.[5-7] During the last years, several studies reported data on the management of patients with MM with RI. The International Myeloma Working Group (IMWG) reviewed the available evidence and here provides recommendations for the diagnosis and management of myeloma-related RI.

METHODS

An interdisciplinary panel of experts on MM and RI developed these recommendations on the basis of the review of all available evidence reported in randomized clinical studies, systematic reviews, meta-analyses, and prospective and observational studies through December 2015. Expert consensus was introduced for recommendations for issues for which there were not sufficient published data. We used the system developed by the Grading of Recommendation, Assessment, Development, and Evaluation Working Group to grade recommendations for the development of this article (Appendix Table A1, online only).[8] A draft paper with all recommendations was initially circulated among panel members and subsequently underwent several rounds of revision until consensus was reached by all authors.

PATHOPHYSIOLOGY OF RI IN PATIENTS WITH MM

RI in patients with MM is caused mainly by the toxic effects of the monoclonal light chains on basement membranes of the glomeruli and/or the renal tubule.[9] The most common form of renal injury in patients with MM is cast nephropathy (CN), which often leads to acute kidney injury (AKI; see AKI criteria in Table 1).[9-11] CN develops when light chain production overcomes the capacity of tubular cells to endocytose and to catabolize the filtered free light chains. As a result, excess light chains form aggregates and casts with uromodulin in the distal nephron, leading to tubular obstruction and concomitant inflammation.[11-13] Hypercalcemia, dehydration, nephrotoxic drugs (aminoglycoside antibiotics and/or nonsteroidal anti-inflammatory agents), and contrast agents contribute to the development of or exacerbate existing RI by aggravating the toxic effect of light chains.[9,10,14]

Monoclonal immunoglobulin deposition disease (MIDD), amyloidosis, and rarely, kidney infiltration by myeloma cells or acquired adult Fanconi syndrome represent other renal pathologies in patients with MM.[15-17] In a review of 190 renal biopsies of patients with MM, MIDD and amyloidosis accounted for 22% and 21% of the total pathology, respectively.[15] The terminology of monoclonal gammopathy of renal significance has recently been introduced to describe B-cell monoclonal disorders that do not meet the criteria for the diagnosis of lymphoma or myeloma but produce monoclonal proteins that cause permanent renal injury. These entities are described in Table 2, and treatment options are suggested.[18,19]

DIAGNOSIS OF RI IN PATIENTS WITH MM

The definition of RI, according to the novel IMWG criteria for symptomatic MM, is based on either elevated sCr (> 2 mg/dL) or reduced creatinine clearance (CrCl; < 40 mL/min), which have to be the result of myeloma.[20] For evaluation of CrCl, eGFR as assessed by either the Modification of Diet in Renal Disease (MDRD) formula or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation seems to give accurate results that are close to those obtained with the inulin-based GFR estimation in cases of stable sCr.[21,22] In such patients, classification of RI can be performed by using the five stages of the CKD classification (Appendix Table A2, online only).[23]

CKD-EPI seems to more accurately reflect GFR than does MDRD, mostly in higher levels of GFR.[24,25] The two equations were evaluated in 1,937 newly diagnosed patients with MM: 9.7% of patients were allocated in different CKD stages by the two methods, mainly because CKD-EPI resulted in lower eGFR.[26] The CKD-EPI group has also suggested that an equation on the basis of both sCr and cystatin-C (CysC), which also reflects tumor burden, is more accurate than other eGFR formulae[21,27,28]. However, CysC is not available in all centers; thus, larger studies with health economics data are needed before recommending the wider use of this method for eGFR. β_2-Microglobulin is another marker that reflects both renal function and tumor burden in patients with MM and is thus also included in the new revised International Staging System.[29] eGFR, however, should be used only in patients with stable renal function. Thus, in cases of acute RI, RIFLE (Risk, Injury, Failure, Loss and End-Stage Kidney Disease) criteria and AKIN (Acute Kidney Injury Network) classification can be used (Table 1).[30] These criteria are more sensitive for the determination and evaluation of AKI but only limited data exist in the literature for the use of these criteria in MM. In 249 patients with hematologic malignancies who underwent allogeneic or autologous stem cell transplantation (ASCT), RIFLE showed greater sensitivity than did AKIN to identify patients with AKI post-transplant.[31] In another small study of 78 patients with myeloma with AKI, the severity of RI as staged by RIFLE was associated with long-term outcomes.[32] The use of RIFLE and AKIN is encouraged in myeloma studies to define their role in the management of myeloma-related RI.

Table 1. RIFLE and AKIN Definitions of Acute Renal Injury

Creatinine and GFR Criteria		Urine Output Criteria
RIFLE	AKIN	RIFLE and AKIN
Stage R: sCr increase ≥ 50%; or GFR decrease > 25%	Stage I: sCr increase > 50%; or > 0.3 mg/dL	< 0.5 mg/kg/h for 6 h
Stage I: sCr increase ≥ 100%; or GFR decrease > 50%	Stage II: sCr increase ≥ 100%	< 0.5 mg/kg/h for 12 h
Stage F: sCr increase ≥ 200%; GFR decrease > 75%; or sCr ≥ 4.0 mg/dL with an increase ≥ 0.5 mg/dL	Stage III: sCr increase ≥ 200%; or sCr ≥ 4.0 mg/dL with an increase ≥ 0.5 mg/dL	< 0.3 mg/kg/h for 24 h or anuria for 12 h
Stage L: Complete loss of kidney function (need for RRT) > 4 weeks	Stage III: Or RRT	
Stage E: End-stage kidney disease (need for RRT) > 3 months		

Abbreviations: AKIN, Acute Kidney Injury Network classification; GFR, glomerular filtration rate; RIFLE, Risk, Injury, Failure, Loss and End-Stage Kidney Disease criteria; RRT, renal replacement therapy; sCr, serum creatinine.

Table 2. Monoclonal Gammopathy of Renal Significance Disorders: Main Characteristics

Disease	Renal Symptoms	Extrarenal Involvement	Identification of M-Protein
Glomerular disorders			
With organized Ig deposits			
AL amyloidosis AH amyloidosis AHL amyloidosis	Proteinuria, nephrotic syndrome, and CKD; hypertension and hematuria uncommon	Frequent: heart, liver, peripheral nerve, and gastrointestinal tract	Serum EP/immunofixation: 66%-80% in AL, 85%-90% in AH/AHL; urine EP/immunofixation: 65%-70% in AL, 80% in AH/AHL; FLC: 75%-90% in AL, 80% in AH/AHL
Immunotactoid glomerulonephritis/GOMMID	Proteinuria, nephrotic syndrome, CKD, microhematuria, hypertension	Uncommon: peripheral nerve and skin	Serum EP/immunofixation: 35%-70%; Urine EP/immunofixation: 20%-55%; FLC: 20%
Type I cryoglobulinemic glomerulonephritis	Proteinuria, nephrotic syndrome, CKD, microhematuria, and hypertension; possible nephritic syndrome, AKI, and anuria	Frequent: skin, peripheral nerve, and joints	Serum EP/immunofixation: 75%; Urine EP/immunofixation: UN; FLC: UN
With nonorganized Ig deposits			
MIDD	Proteinuria, nephrotic syndrome, CKD, microhematuria, and hypertension	Common, often asymptomatic: heart, liver, and lung	Serum EP/immunofixation: 25%-75% in LCDD, 80%-100% in LHCDD, 67%-100% in HCDD; urine EP/immunofixation: 42%-90% in LCDD, 80%-100% in LHCDD, 50%-100% in HCDD; FLC: 100% in LCDD, LHCDD, HCDD
Proliferative glomerulonephritis with monoclonal immunoglobulin deposits	Proteinuria, nephrotic syndrome, CKD, microhematuria, and hypertension	None	Serum EP/immunofixation: 30%; urine EP/immunofixation: 10%; FLC: UN
C3 glomerulopathy with monoclonal gammopathy	Proteinuria, nephrotic syndrome, CKD, microhematuria, and hypertension	None	Serum EP/immunofixation: 100%; urine EP/immunofixation: 100%; FLC: 75%-100%
Tubular disorders			
Light chain Fanconi syndrome	Hypouricemia, hypophosphatemia, normoglysemic glycosuria, generalized aminoaciduria, low-molecular-weight proteinuria, proximal (type 2) renal tubular acidosis, and slowly progressive CKD	Bone: osteomalacia	
Proximal tubulopathy without crystals	Tubular proteinuria and progressive CKD	None	
Crystal-storing histiocytosi	Proximal tubule dysfunction and CKD	Bone marrow, liver, spleen, lymph nodes, lung, skin, and cornea	

Abbreviations: AH, immunoglobulin heavy chain; AHL, immunoglobulin heavy and light chain; AL, immunoglobulin ligh chain; AKI, acute kidney injury; CKD, chronic kidney disease; EP, electrophoresis; FLC, free light chain; GOMMID, glomerulonephritis with organized microtubular immunoglobulin deposits; HCDD, heavy chain deposition disease; Ig, immunoglobulin; LCDD, light chain deposition disease; LHCDD, light and heavy chain deposition disease; MIDD, monoclonal immunoglobulin deposition disease; UN, unknown (adapted by Bridoux et al[18]).

Another important issue is the cause of RI in MM. In > 15% of patients with myeloma with RI, renal biopsy indicated that the cause of RI had no association with the monoclonal gammopathy; RI was a result of arterionephrosclerosis (6%), diabetic glomerulosclerosis (5%), postinfectious glomerulonephritis (2%), or even smoking-related glomerulopathy (0.5%).[15] Furthermore, the presence of MIDD or amyloidosis must be excluded. As an aid to diagnostic work-up, 24-hour urine protein electrophoresis may reveal patterns of protein excretion that may provide clues to the etiology of RI. Predominantly selective proteinuria, consisting of light chains, with limited albumin excretion is most likely a result of CN, whereas larger amounts of albumin or nonselective patterns of proteinuria suggest an alternative pathology.[33] Serum free light chain (sFLC) > 500 mg/L to 1,500 mg/L may be more suggestive of CN.[10,19] Thus, all patients with symptomatic myeloma should have in their diagnostic work-up sCr, electrolytes measurements, and eGFR but also sFLC measurement and electrophoresis of a sample from a 24-hour urine collection. If proteinuria consists predominantly of light chains, a renal biopsy may not be necessary, and the cause of RI may be attributed to myeloma CN. On the contrary, amyloidosis, MIDD, or another underlying condition should be excluded and a renal biopsy could be considered in patients with nonselective proteinuria or albuminuria (Fig 1).[33-35] In cases in which amyloidosis is suspected, a subcutaneous fat aspirate may reveal the diagnosis in approximately 70% of patients[35]; if the fat biopsy is negative, a renal biopsy is required.

Recommendations

CKD-EPI, preferably, or MDRD should be used for the evaluation of renal function in patients with MM with stabilized sCr (grade A). The five stages of CKD should be used to classify these patients (grade A). For patients with acute renal injury, RIFLE and AKIN are more appropriate (grade C); however, these criteria need to be evaluated prospectively in patients with MM. Other formulae, such as the CKD-EPI-sCr-CysC equation, can be used in clinical trials to assess its value in the MM setting.

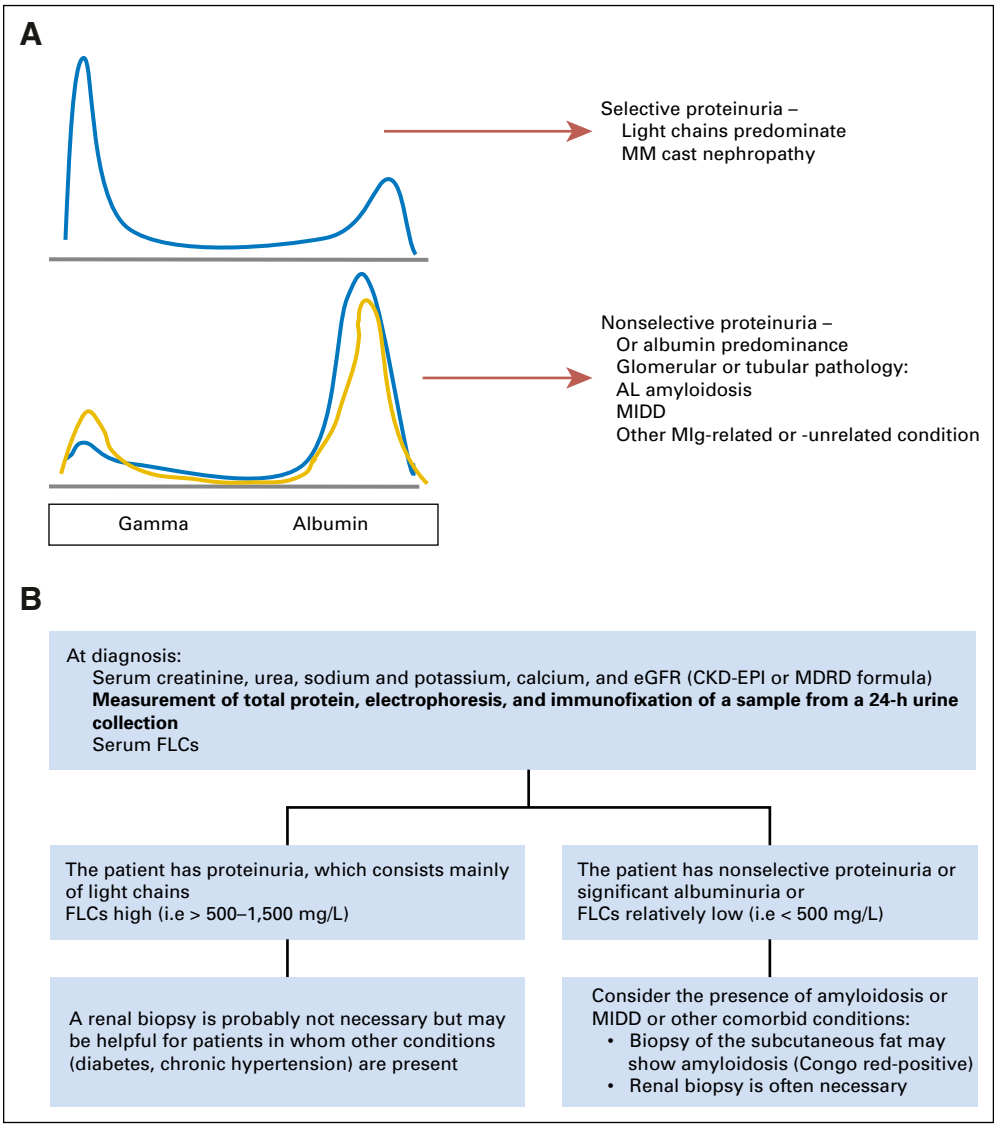

Fig 1. (A) Diagnosis of multiple myeloma (MM)–related renal impairment (RI): urinary protein electrophoresis. (B) Algorithm for the evaluation of patients with myeloma with RI. If the patient does not have proteinuria, an alternative diagnosis for RI should be considered. AL, amyloid light chain; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FLC, free light chain; MDRD, Modification of Diet in Renal Disease formula; MIDD, monoclonal immunoglobulin deposition disease; MIg, monoclonal immunoglobulin.

All patients with myeloma at diagnosis and at disease assessment should have sCr and electrolytes measurements as well as urine electrophoresis of a sample from a 24-hour urine collection (grade A). sFLC should be also measured if available (grade A). If nonselective proteinuria or significant albuminuria is detected, a renal biopsy should be performed for the establishment of the cause of the RI (grade B).

CRITERIA FOR THE DEFINITION OF RENAL RESPONSE TO TREATMENT

The definition of reversibility of renal dysfunction is an important issue, and it affects the choice of therapy and the evaluation of patient outcomes. In the case of patients on dialysis, independence from dialysis is a strong indication of improvement. For all other patients, the IMWG had suggested criteria for the definition of renal response to therapy (Table 3).[36] These criteria have been widely accepted and have been used worldwide for the evaluation of renal response in several studies.[37-41] Simplified criteria of renal response have also been proposed but must be tested in larger studies before their recommendation (Fig 2).[42]

Recommendations

IMWG criteria for the definition of renal response should be used in both clinical trials and every day clinical practice (grade B). MDRD or CKD-EPI equations can both be used for the eGFR used in these criteria (grade C).

MANAGEMENT OF PATIENTS WITH MM WITH RI

Acute RI is a myeloma emergency. Diagnosis should be established as fast as possible, and antimyeloma therapy should be started immediately after confirmation of diagnosis to rapidly restore renal function. For patients who require dialysis, the goal of therapy should be independence from dialysis.

Table 3. Criteria for the Definition of Renal Response to Antimyeloma Therapy

Renal Response	Baseline eGFR, mL/min/1.73 m^2*	Best CrCl Response
Complete response	< 50	≥60 mL/min
Partial response	< 15	30-59 mL/min
Minor response	< 15	15-29 mL/min
	15-29	30-59 mL/min

Abbreviations: CrCl, creatinine clearance; eGFR, estimate glomerular filtration rate.
*eGFR is based on the Modification of Diet in Renal Disease formula, or the Chronic Kidney Disease Epidemiology Collaboration equation.

Supportive Care

For all patients in whom myeloma-induced RI is suspected, adequate supportive care is mandatory. This includes adequate hydration with fluids (≥ 3 L/d, approximately 2 L/m^2/d), which is particularly important in patients with fluid depletion resulting from concomitant hypercalcemia.[43,44] Careful monitoring of fluid balance is recommended for all patients and mainly for those with congestive heart failure. A fluid challenge should be attempted in patients who present with anuria in an attempt to reverse it. Patients with established anuria need fluid monitoring during dialysis.

Urine alkalization is used in several centers; however, data from randomized clinical trials have not proven its value in the reversibility of RI.[44] Management of factors that contribute to RI is crucial; rapid reversal of hypercalcemia may result in improvement of RI in several cases. Bisphosphonates (BPs) or denosumab are licensed for the management of hypercalcemia of malignancy; however, according to current guidelines, BPs (both pamidronate and zoledronic acid) are not indicated for patients with CrCl < 30 mL/min.[45] Denosumab was safe for treatment of patients with solid tumors and RI; caution and close monitoring is needed to guard against the development of hypocalcemia.[46] High-dose steroids and calcitonin can be used safely for treatment of hypercalcemia and RI.

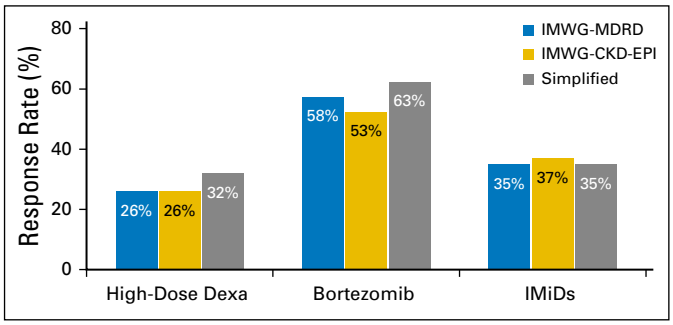

Fig 2. Simplified criteria of renal response have been proposed: Patients who presented with stage 5 renal impairment (RI) should double their estimate glomerular filtration rate (eGFR) and improve to at least stage 4 to be defined as responders, whereas patients with stage 4 RI must increase their eGFR by at least 50% and improve to at least stage 3 (GFR ≥ 60 mL/min) to be considered as having renal response. These criteria were evaluated in 105 unselected patients with newly diagnosed multiple myeloma with severe RI who received treatment on the basis of high-dose dexamethasone (Dexa; 19%), bortezomib (38%) or immunomodulatory drugs (IMiDs; 43%). There were no differences in renal responses with the use of the standard International Myeloma Working Group (IMWG) criteria versus the simplified criteria.[42] CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; MDRD, Modification of Diet in Renal Disease formula.

Furosemide is not recommended as it may enhance cast formation in the renal tubules.[47] BPs for myeloma-related bone disease should be delayed until GFR has improved.

Recommendations

High fluid intake (≥ 3 L/d or approximately 2 L/m^2/d) can be started with antimyeloma therapy (grade B). Urine alkalization seems not to offer advantage in the reversal of RI in myeloma (grade B). Bisphosphonates can reduce calcium levels in the case of hypercalcemia but neither pamidronate nor zoledronic acid should be used in patients with severe RI (CrCl < 30 mL/min; grade A). Denosumab may be useful in patients with hypercalcemia and RI but calcium levels must be closely monitored (grade C). Avoidance of nephrotoxic agents, such as aminoglycoside antibiotics, furosemide, and contrast agents, is highly recommended for patients with MM with RI (grade A).

Mechanical Approaches

Plasma exchange. Two studies in the CC era suggested that plasma exchange was able to reverse RI in patients with myeloma,[48,49] whereas a prospective study with a low number of patients (n = 21) reported only a trend in favor of plasma exchange,[50] and a larger randomized trial (n = 104) failed to show a clear advantage of plasma exchange regarding dialysis independence.[51] However, the latter study was limited by the lack of histologic confirmation of CN. The combination of bortezomib-based chemotherapy and plasma exchange offered a dramatic reduction of free light chain (FLC; 75% to 96%) in a small Mayo Clinic study (n = 14).[52] A recent meta-analysis that included three randomized studies with patients who received chemotherapy only (n = 63) or both chemotherapy and plasmapheresis (n = 84) showed that the 6-month dialysis dependency ratio was significantly lower in patients treated with both chemotherapy and plasmapheresis than in chemotherapy alone (15.6% *v* 37.2%; risk ratio, 2.02; P = .04). However, there was no difference in overall survival (OS) between the two groups.[53]

High-cutoff hemodialysis. The use of the high-cutoff hemodialysis (HCO-HD) membranes, which allow the removal of FLCs through their larger pores (molecules ≤ 60 kD to 65 kD can be removed), has produced encouraging results in the reduction of FLCs and the reversal of RI. In a study of 67 patients with myeloma with dialysis-dependent RI, the use of HCO-HD in combination with antimyeloma therapy produced a sustained reduction of FLCs in 67% of patients by day 12 and caused dialysis independency in 63%. The most important factors that predicted independence from dialysis were the degree of FLC reduction on days 12 (P = .002) and 21 (P = .005) and the time to initiation of HCO-HD (P = .006).[54] Similar results were confirmed in smaller studies.[55,56] Currently, two prospective randomized studies, the European multicenter, randomized controlled EuLITE study (European Trial of Free Light Chain Removal by Extended Hemodialysis in Cast Nephropathy; NCT00700531) and the French MYRE study (Studies in Patients With MM and Renal Failure Due To Myeloma Cast Nephropathy; NCT01208818) are evaluating the role of HCO-HD in the recovery of RI in patients with MM who receive bortezomib-based antimyeloma therapy.

Long-term dialysis. End-stage RI requires long-term dialysis. Patients on dialysis have an increased risk of death of approximately 15% to 30% within the first months of diagnosis.[5,57] The

response rate to antimyeloma therapy is between 40% and 60%, whereas the median survival time of patients on long-term dialysis is approximately 2 years, with 30% surviving for > 3 years.[5,57-59]

Recommendations

Current data supports the use of HCO-HD in combination with antimyeloma therapy for patients with myeloma with acute RI as a result of CN (grade B). In the case that HCO-HD is unavailable, plasma exchange may be of benefit in select patients with proven acute RI or that which is strongly suspected to be related to light chain CN (grade C).

Antimyeloma Therapy

Systemic antimyeloma therapy must start immediately to reduce the load of toxic FLCs and thus improve renal function.

CC and high-dose corticosteroids. CC has been used in the past mainly for the management of patients with myeloma with RI. In a large study (the Medical Research Council IV trial; n = 554), approximately one half of patients with acute RI died within 3 months of CC initiation, whereas 44% of patients (39 of 80) who were alive for > 100 days experienced a complete reversal of RI, which was defined as sCr < 1.5 mg/dL.[60] CC with standard-dose corticosteroids produces 25% to 50% of renal recovery.[61] In the VISTA trial, 34% of patients with RI (CrCl < 50 mL/min, mostly moderate RI) who received MP managed to achieve a renal complete response (CR) at a median of 2.4 months.[62] High-dose corticosteroids (equivalent to dexamethasone ≥ 160 mg over 4 days; in the majority of studies, dexamethasone 40 mg, 4 days on and 4 days off, for 3 pulses in a 28-day cycle) are effective in improving RI, with renal responses ≤ 65%, compared with conventional doses of corticosteroids.[63-66] The administration of high-dose dexamethasone—≥ 160mg in the first month of therapy—was associated with a more rapid renal response, even in patients treated with immunomodulatory drugs (IMiDs) or bortezomib, in a retrospective analysis of 133 patients with newly diagnosed myeloma (NDMM) with RI (1.6 *v* 46 months for doses of < 160 mg; $P = .008$).[38] Table 4 includes possible dose modifications of most common antimyeloma drugs according to renal function.

IMiD-based regimens. Thalidomide is not excreted by the kidneys and thus does not need dose modification. The renal recovery expected with thalidomide-based regimens (usually in combination with high-dose corticosteroids) ranges from 55% to 75% in patients wth NDMM and is approximately 60% in patients with relapsed/refractory (RR) disease (Table 5).[38,67-69,78] Special concern is needed for patients on dialysis in whom an unexplained hyperkalemia has been observed.[67,79]

Lenalidomide is excreted through the kidneys and thus requires dose adjustments according to the degree of RI.[80] In the major phase III trials that evaluated the combination of lenalidomide and high-dose dexamethasone in RR MM, 82 patients had moderate RI (CrCl < 60 mL/min) and 16 had severe RI (CrCl < 30 mL/min). Lenalidomide 25 mg was administered without dose adjustment for RI. There were no differences in response rates, response quality, time to progression, or progression-free survival (PFS) among patients with different stages of RI, whereas there was a trend toward decreased OS in patients with moderate or severe RI. Importantly, 72% of patients with RI experienced improved renal function by at least one level (from severe to moderate or from moderate to mild or no RI).[71] In a recent phase II study, dose-adjusted lenalidomide with high-dose dexamethasone was administered to 35 patients with acute RI. Myeloma responses were observed in 69% of patients (CR, 20%), whereas renal response was observed in 45% of patients (CR, 14%; partial response, 11%; minor response, 20%). Five of 13 patients requiring dialysis at baseline became dialysis independent. The

Table 4. Dose Modifications for Drugs Used for the Management of Patients With Multiple Myeloma With Renal Impairment

Drug	CrCl > 60 mL/min	CrCl, 30-59 mL/min	CrCl, 15-29 mL/min	CrCl < 15 mL/min	On Dialysis
Dexamethasone	20-40 mg	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Melphalan	Oral melphalan 0.15 to 0.25 mg/kg/d for 4-7 days High-dose melphalan 200 mg/m^2	Oral melphalan reduced 25% (0.11-0.19 mg/kg/d for 4-7 days High-dose melphalan 140 mg/m^2	Oral melphalan reduced 25% (0.11-0.19 mg/kg/d for 4-7 days High-dose melphalan 140 mg/m^2	Oral melphalan reduced 50% (0.0175-0.125 mg/kg/d for 4-7 days). High-dose melphalan 140 mg/m^2	Oral melphalan reduced 50% (0.0175-0.125 mg/kg/d for 4-7 days). High-dose melphalan 140 mg/m^2
Bortezomib	1.3 mg/m^2 on days 1, 4, 8, and 11, or weekly regimens	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Thalidomide	50-200 mg/d	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Lenalidomide	25 mg/d	10 mg per d, can be increased to 15 mg/d if no toxicity occurs	15 mg once every other d, can be adjusted to 10 mg/d	5 mg/d	5 mg/d
Carfilzomib	20 mg/m^2 cycle 1; 27 mg/m^2 cycle 2 and on	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Doxorubicin	According to regimen	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Cyclophosphamide	According to regimen	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Pomalidomide	4 mg/d	No dose modification needed for CrCl ≥ 45 mL/min	Ongoing studies will clarify if modification is needed	Ongoing studies will clarify if modification is needed	Ongoing studies will clarify if modification is needed

Abbreviation: CrCl, creatinine clearance.

Table 5. Summary of the More Important Studies With Immunomodulatory Drugs–Based Regimens in Patients With Myeloma With RI

Study	No. of Patients With RI	Patients On Dialysis	Disease Status	Myeloma Response	Renal Response	Safety and Survival
Thalidomide-based regimens						
Fakhouri et al[67]	7	1	Rel/Ref	3 of 7 CR; 1 PR; 3 MR	NE	One patient presented with severe hyperkalaemia (> 8 mmol/l) on two occasions during therapy with thalidomide 400 mg/d
Tosi et al[68]	20 with sCr > 1.5 mg/dL and CrCl < 60 mL/min	3	Rel/Ref	PR, 45%	60% achieved sCr < 1.5 mg/dL	
Kastritis et al[66]	13 with sCr > 2 mg/dL	4	Newly diagnosed	65%	77% sCr < 1.5 mg/dL; three of four dialysis patients became dialysis independent	
Tosi et al[69]	31 with CrCl < 50 mL/min	7	Newly diagnosed	74% (10% CR)	55% CrCl > 50 mL/min; two of seven patients became dialysis independent	10% developed DVT; one patient developed extensive skin rash
Dimopoulos et al[38]	62 with eGFR < 60 mL/min	4	Newly diagnosed	ORR, 63%	Major renal response (≥ renal PR), 55%; renal CR, 53%; two of four dialysis patients became dialysis independent	Median time to renal response, 2.7 months (82 days)
Lenalidomide and dexamethasone						
Niesvizky et al[70]	14 with CrCl < 40 mL/min	0	Newly diagnosed	NR	Three of 14 patients had an increase of CrCl to > 70 mL/min	Baseline CrCl<40 mL/min was associated with grade ≥ 3 myelosuppression and the need to reduce lenalidomide dosage
Dimopoulos et al[71]	98 (82 patients with CrCl between 30 and 59 mL/min, and 16 with CrCl < 30 mL/min)	0	Rel/Ref	ORR, quality of response, TTP and PFS similar to patients without RI	Improvement of renal dysfunction by at least one level in 72%	Trend for shorter survival in patients with moderate or severe RI Thrombocytopenia was significantly more common and dose reductions were required more often in patients with moderate or severe RI
De la Rubia et al[72]	15	15	Rel/Ref	4 CR; 1 VGPR; 4 PR	1 patient became dialysis independent	Len adjusted to RI (15 mg 3 x week or 5 mg QD) 4 patients died from infectious complications
Dimopoulos et al[73]	12	1	Rel/Ref	61%	In 40% of patients with RI improved	Lenalidomide dose was adjusted according to renal function; no excessive toxicity
Klein et al[74]	33	5	Rel/Ref	3% CR; 12% VGPR; 49% ORR	27% showed an improvement of RI	OS was similar for patients with or without RI
Dimopoulos et al[38]	28 (eGFR < 60 mL/min)	0	Newly diagnosed	ORR, 82%	Major renal response (≥ renal PR), 43%; renal CR, 36%; increase of median eGFR from 49 to 85 mL/min/1.73 m^2	Len adjusted to RI; manageable and no excess toxicity

(continued on following page)

Table 5. Summary of the More Important Studies With Immunomodulatory Drugs–Based Regimens in Patients With Myeloma With RI (continued)

Study	No. of Patients With RI	Patients On Dialysis	Disease Status	Myeloma Response	Renal Response	Safety and Survival
Ludwig et al[41]	35	13	28 newly diagnosed and 7 Rel/Ref	ORR, 68.6% (CR, 20%; VGPR, 8.6%; PR, 40%)	45.7% (renal CR, 14.2%; renal PR, 11.4%; renal MR, 20%)	Len adjusted to RI; high-dose dexamethasone only in the 1st cycle; four patients died within the first two cycles, and five discontinued therapy; infections, cardiotoxicity, anemia, and thrombocytopenia were the most frequent toxicities
Zhou et al[75]	68 (54 patients with CrCl between 30-59 mL/min, and 14 with CrCl < 30 mL/min)	0	Rel/Ref	ORR, 48%; in mild or no RI, 50%; in moderate and severe RI, 42%	NR	Len adjusted to RI; low-dose dexamethasone was administered; median PFS was 9.3, 6.9, and 4.8 months for mild/no RI, moderate, and severe RI, respectively; median OS was 22.4, 16, and 11.1 months for mild/no RI, moderate, and severe RI, respectively; grade 3 and 4 neutropenia, anemia, and thrombocytopenia were higher in patients with severe RI
Dimopoulos et al[76]	Rd continuous; 169 in patients with CrCl < 50 mL/min (n = 45 with < 30 mL/min) Rd18; n = 166, (n = 47 with < 30 mL/min)	0	Newly diagnosed multiple myeloma		NR	Len adjusted to RI; low-dose dexamethasone was administered; for Rd continuous, PFS was 23 months for moderate RI and 11 months for CrCl < 30 mL/min; for Rd18, PFS was 18.7 months for moderate RI and 15.3 months for severe RI; for Rd continuous, OS was 43.7 months for moderate RI and 33.2 months for CrCl < 30 mL/min; for Rd18, OS was 41.8 months for moderate RI and 42.6 months for severe RI
Pomalidomide and low-dose dexamethasone						
Weisel et al[77]	215 with moderate RI (CrCl < 60 mL/min)	0	Rel/Ref	ORR, 37% in moderate RI and 33% in patients with CrCl ≥ 60 mL/min	NR	Median PFS was 3.7 months for patients with moderate RI *v* 4.6 months for patients without moderate RI (CrCl ≥ 60 mL/min; $P = .1142$).

Abbreviations: CR, complete response; CrCl, creatinine clearance; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; MR, minor response; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; sCr, serum creatinine; Rel/Ref, relapsed/refractory; RI, renal impairment; TTP, time to progression.

median times to best myeloma response and best renal response were 92 days and 157 days, respectively.[41] Increased toxicity, mainly neutropenia, thrombocytopenia, and infections, were observed in patients with RI in both studies.[41,71] Similar results for efficacy and toxicity have been observed in several studies with lenalidomide in patients with MM with RI (Table 5).[70,72-75]

Pomalidomide, the third-generation IMiD, is metabolized before excretion and only 2% of the parent drug is thus excreted in the urine. Results from phase III studies suggest that pomalidomide requires no dose adjustment in patients with CrCl ≥ 45 mL/min.[81] In a subanalysis of the phase IIIb STRATUS trial, pomalidomide at a dose of 4 mg produced similar objective response rate (ORR) and PFS in patients with and without moderate RI (CrCl < 60 mL/min and CrCl ≥ 60 mL/min, respectively), although there was a trend for prolonged PFS in the group with CrCl ≥ 60 mL/min (Table 5).[77] Pomalidomide is being further studied in patients with CrCl < 45 mL/min.

Proteasome inhibitor–based regimens. Combinations of bortezomib, which has a half-life independent of renal clearance, with dexamethasone (VD) or with melphalan and prednisone for elderly patients have been considered to date the standard of care for patients with MM with RI.[36] This has been confirmed by several studies in which the rapid reduction of tumor load by bortezomib along with its nonrenal metabolism had led to high ORR, renal responses, and dialysis independence rates (Table 6).[38,39,62,82-88] In a retrospective large analysis that included 133 patients with NDMM with RI, a significant improvement of renal function (≥ renal partial response) was observed in 77% of patients treated with bortezomib-based regimens versus 55% and 43% for patients treated with thalidomide- or lenalidomide-based regimens, respectively. Bortezomib was used more often in patients with severe RI or in patients requiring dialysis; however, higher doses of dexamethasone were used in combination with bortezomib.[38] The addition of a third drug to VD seems to improve renal outcomes.[89] In the prospective HOVON-65/GMMG-HD4 study, patients were randomly assigned to receive three cycles of VAD (vincristine, doxorubicin, dexamethasone) or PAD (bortezomib, doxorubicin, dexamethasone) followed by ASCT and maintenance with thalidomide (VAD arm) or bortezomib (PAD arm). Baseline sCr was ≥ 2 mg/dL in 81 patients who achieved a renal response rate of 63% in the VAD arm and 81% in the PAD arm. OS at 3 years for these patients was 34% in the VAD arm and 74% in the PAD arm ($P < .001$).[88] Response at 8 years was 12% and 47%, respectively.[90] Two randomized studies have shown that the subcutaneous use of bortezomib produced results similar to intravenous administration in patients with RI.[91,92]

Carfilzomib is a second-generation proteasome inhibitor that has been licensed for the management of RR MM. In a recent study, there were no differences in carfilzomib clearance among patients with normal renal function and with various degrees of RI. Similarly, there was no difference in ORR and toxicity among the different RI groups.[93] In a recent, phase III randomized trial, treatment with carfilzomib plus dexamethasone (n = 464) was compared with treatment with bortezomib plus dexamethasone (n = 465) in 929 patients with RRMM who had received one to three prior lines of therapy. Inclusion criteria included CrCl ≥ 15 mL/min. Carfilzomib was found to be superior to bortezomib for median PFS (18.7 *v* 9.4 months), which supported previous observations that carfilzomib can be also administered to patients with RI. Acute renal failure (grade 3 and 4) was noted in 7% of patients in the carfilzomib arm versus 4% in the bortezomib arm.[94]

Ixazomib is the first oral proteasome inhibitor recently approved by the US Food and Drug Administration in combination with lenalidomide and dexamethasone for patients with RR MM, who have received one to three prior lines of therapy. The phase III randomized study that led to the approval of the combination included patients with CrCl ≥ 30 mL/min.[95] On the basis of the results of the study, this combination can be safely administered to patients with myeloma with CrCl ≥ 30 mL/min.

ASCT. High-dose therapy (HDT) with ASCT remains the treatment of choice for eligible patients with NDMM, and is feasible even in patients who require dialysis.[96] RI does not to affect the $CD34^+$ yield or their engraftment.[97] Melphalan dose needs to be adjusted (100 to 140 mg/m^2), but seems to be as effective as the 200 mg/m2 dose[98]; however, the procedure is associated with an increased risk of transplant-related mortality for patients with RI (> 4%) compared with patients without RI at the time of transplantation (< 1%).[96-98] Retrospective analyses have reported a ≥ 25% improvement in RI in one third of patients, a 15% to 20% probability of dialysis independence, and a 5-year OS of nearly 35%.[98,99] Novel agents may further improve these results. In a recent study, 27 patients on dialysis received induction therapy with either bortezomib or CC (mainly VAD) followed by HDT with ASCT. ORR was higher after bortezomib-based induction (83% *v* 36%; $P = .02$) and at day > 100 post-ASCT (100% *v* 58%; $P = .01$). Bortezomib also prolonged PFS and produced a trend toward a decreased time on hemodialysis (6 *v* 17 months in patients who received CC).[100]

Kidney transplantation in patients with myeloma with end-stage renal disease. There are some case reports and small case studies in which kidney transplantation has been offered to patients with MM who have sustained CR for several years[101]; however, the data are limited in the literature.

Recommendations

Bortezomib-based regimens remain the cornerstone of the management of myeloma-related RI (grade A). Bortezomib should be started at the standard dosage of 1.3 mg/m^2 on days 1, 4, 8, and 11 of a 3-week cycle (grade A), and high-dose dexamethasone should be administered for at least the first month of therapy (grade B). Subcutaneous administration of bortezomib has efficacy similar to intravenous administration (grade A). The recommended dosage of high-dose dexamethasone is 40 mg/d (20 mg/d for patients age ≥ 75 years), 4 days on and 4 days off, for the first cycle of therapy, then by treatment protocol. The addition of a third drug to VD seems to be beneficial. In patients eligible for ASCT, bortezomib could be administered in combination with CC (doxorubicin or cyclophosphamide) or thalidomide and dexamethasone (grade A). In patients who are ineligible for ASCT, bortezomib with melphalan and prednisone can also be administered (grade B), but no data exist for this regimen in patients on dialysis. Thalidomide is effective in patients with myeloma with RI (grade B) and should be administered without dose modification (grade A). Lenalidomide is also effective and safe, mainly in patients with mild to moderate RI (grade B), and should be administered with dose adjustments according to patient CrCl level (grade A). Lenalidomide can be also administered to patients with severe RI or to

Table 6. Summary of Major Studies With Bortezomib-Based Regimens in Patients With Myeloma With RI

Study	No. of Patients With RI	Patients On Dialysis	Disease Status	Regimen	Myeloma Response	Renal Response	Safety and Survival
Jagannath et al[82]	52 with CrCl < 50 mL/min	0	Rel/Ref	Bor alone	25%	NR	Manageable toxicities
San Miguel et al[83]	58 with CrCl < 50 mL/min (15 with CrCl < 30 mL/min)	0	Rel/Ref	Bor± Dexa (VD)	47%	NR	Trend for shorter OS in patients with moderate/severe RI compared with no/mild RI
Bláde et al[84]	193 patients with renal insufficiency (CrCl < 60 mL/min; no patient with CrCl < 30 mL/min)	0	Rel/Ref	Bor+PLD *v* Bor alone	49% in Bor+PLD; 39% in Bor alone	Statistically significant improvement in renal function (increase in CrCl)	Median TTP in patients with renal insufficiency; Bor+PLD, 10.9 months; Bor alone, 6.5 months; grade 3 and 4 anemia, diarrhea and pneumonia more common in patients with RI
Dimopoulos et al[85]	46	9	Newly diagnosed (n = 10); Rel/Ref (n = 36)	VD (n = 17); VMDT (n = 14); PAD (n = 6); VTD (n = 5); VRD (n = 4)	76%	Reversal of renal failure in 59%; two of nine became dialysis independent	Light chain myeloma was associated with a shorter time to renal response; four of nine patients who were rated as having stable disease achieved a renal response as well as one of eight patients who had progressive disease
Dimopoulos et al[62]	227 (34 with CrCl < 30 mL/min)	0	Newly diagnosed, ineligible for autologous stem cell transplantation	VISTA trial; VMP, 111; MP, 116	VMP, 74% in patients with CrCl < 30 mL/min; MP, 47% in patients with CrCl < 30 mL/min	Renal impairment reversal (baseline GFR < 50 improving to > 60 mL/min) was seen in 49 (44%) of 111 patients receiving VMP *v* 40 (34%) of 116 patients receiving MP	Response rates with VMP and TTP in both arms did not seem significantly different between patients with GFR ≤ 50 or > 50 mL/min, but they were higher compared with MP
Ludwig et al[86]	68	9	Newly diagnosed (n = 50); Rel/Ref (n = 18)	PAD	ORR 72% (38% CR/nCR; 15% VGPR; 13% PR)	62% had a renal response; median GFR increased from 20.5 mL/min to 48.4 mL/min; three of nine became dialysis independent	Significant improvement in renal function (renal CR) correlated with baseline GFR and myeloma response
Morabito et al[87]	117 (82 had CrCl < 30 mL/min)	14	Newly diagnosed (n = 27); Rel/Ref (n = 90)	VD (54); VD+CC (63)	ORR, 73% (19% CR; 8% nCR; 17% VGPR)	>80 mL/min in 41%; three of 14 discontinued dialysis	RI improvement more frequently in previously untreated patients and in those with mild to moderate RI; ORR was similar across renal subgroups (severe *v* moderate *v* mild RI)
Dimopoulos et al[38]	43 (eGFR < 60 mL/min)	6 (14%)	Newly diagnosed	VD, VTD or VCD	ORR, 81%	Major renal response (≥ renal PR), 77%; renal CR, 67%; three of six patients became independent of dialysis	Median time to renal response 41 days

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Table 6. Summary of Major Studies With Bortezomib-Based Regimens in Patients With Myeloma With RI (continued)

Study	No. of Patients With RI	Patients On Dialysis	Disease Status	Regimen	Myeloma Response	Renal Response	Safety and Survival
Ponisch et al[39]	36 (eGFR < 60 mL/min)	16 (eGFR < 15 mL/min)	Rel/Ref	BPV	ORR, 67%	Renal ORR, 87%; CR, 31%; PR, 14%; MR, 42%	With a median follow-up period of 22 months, median PFS and OS for patients with CrCl 15-59 mL/min were 10 and 25 months, respectively; median PFS and OS for patients with CrCl < 15 mL/min were 3 and 7 months, respectively
Scheid et al[88]	81 (sCr ≥ 2 mg/dL)	0	Newly diagnosed	PAD, 36; VAD, 45	ORR: PAD, 89%; VAD, 64%; CR: PAD, 36%; VAD, 13%	Renal response rate was 63% in the VAD arm and 81% in the PAD arm	OS at 3 years: PAD, 74% *v* VAD, 34% ($P < .001$); PFS at 3 y: PAD, 48% *v* VAD, 16% ($P = .004$)

Abbreviations: Bor, bortezomib; BPV, bendamustine, prednisone, and bortezomib; CC, conventional chemotherapy; CR, complete response; CrCl, creatinine clearance; Dexa, dexamethasone; eGFR, estimate glomerular filtration rate; GFR, glomerular filtration rate; MP, melphalan and prednisone; MR, minor response; nCR, near complete response; NR, not reported; ORR, objective response rate; OS, overall survival; PAD, bortezomib, doxorubicin, and dexamethasone; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PR, partial response; sCr, serum creatinine; TTP, time to progression; VAD, vintristine, doxorubicin, dexamethasone; VCD, bortezomib, cyclophosphamide, and dexamethasone; VD, bortezomib and dexamethasone; VGPR, very good partial response; VMP, bortezomib, melphalan, prednisone; VTD, bortezomib, thalidomide, dexamethasone.

patients on dialysis but patients should be closely monitored for hematologic toxicity (grade B). HDT with ASCT is feasible in patients with myeloma with RI; the dose of melphalan should be restricted to 100 to 140 mg/m^2 (grade C). Pomalidomide should be administered in a dosage of 4 mg/d in patients with CrCl $\geq$ 45 mL/min (grade A); additional studies will reveal if the dose should be reduced for more severe RI. Carfilzomib is another option for patients with RR MM and RI and it needs no dose modification and produces similar results in patients with and without RI (grade A for patients with CrCl $\geq$ 15 mL/min; grade B for patients with CrCl $<$ 15 mL/min). More data are needed regarding its renal safety. Ixazomib can be safely administered in combination with lenalidomide and dexamethasone in patients with RR MM and CrCl $\geq$ 30 mL/min (grade A).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

International Myeloma Working Group Recommendations for the Diagnosis and Management of Myeloma-Related Renal Impairment

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186. David Vesole, Hackensack University Medical Center, Hackensack, NJ.
187. Ravi Vij, Washington University School of Medicine, St. Louis, MO.
188. Peter Voorhees, University of North Carolina, Chapel Hill, NC.
189. Anders Waage, University Hospital, Trondheim, Norway.
190. Michael Wang, MD Anderson Cancer Center, Houston, TX.
191. Donna Weber, MD Anderson Cancer Center, Houston, TX.
192. Brendan M. Weiss, Abramson Cancer Center, Philadelphia, PA.
193. Jan Westin, Sahlgrenska University Hospital, Gothenburg, Sweden.
194. Keith Wheatley, University of Birmingham, Birmingham, United Kingdom.
195. Elena Zamagni, University of Bologna, Bologna, Italy.
196. Jeffrey Zonder, Karmanos Cancer Institute, Detroit, MI.
197. Sonja Zweegman, VU Medical Center, Amsterdam, The Netherlands.

Table A1. Levels of Evidence and Grades of Recommendations

	Type of Evidence
Level	
Ia	Evidence obtained from meta-analysis of multiple well-designed, randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed, nonrandomized study, including phase II trials and case-control trials
IIb	Evidence obtained from at least one other type of well-designed, quasi-experimental study (ie, studies without planned intervention, including observational studies)
III	Evidence obtained from well-designed, nonexperimental descriptive studies, such as nonrandomized, controlled single-group, prepost, cohort, time, or matched case-control series, or randomized controlled trials or phase II studies only published in abstract form
IV	Expert committee reports or opinion and/or clinical experience of respective authorities
Grade	
A	There is evidence of type Ia and Ib
B	There is evidence of types IIa, IIb, and III
C	There is evidence of type IV

Table A2. Classification of Chronic Renal Disorders

Stage of Renal Impairment	Description	GFR, mL/min/1.73 m^2
1	Kidney damage with normal or elevated GFR	$\geq$ 90
2	Kidney damage with mild reduction of GFR	60-89
3	Moderate reduction of GFR	30-59
4	Severe reduction of GFR	15-29
5*	Renal failure	$<$ 15 or on dialysis

Abbreviation: GFR, glomerular filtration rate.
*Stages 5 is also defined as end-stage renal disease.