Renal Impairment in Patients With Multiple Myeloma: A Consensus Statement on Behalf of the International Myeloma Working Group


Renal impairment is a common complication of multiple myeloma (MM). The estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula is the recommended method for the assessment of renal function in patients with MM with stabilized serum creatinine. In acute renal injury, the RIFLE (risk, injury, failure, loss and end-stage kidney disease) and Acute Renal Injury Network criteria seem to be appropriate to define the severity of renal impairment. Novel criteria based on eGFR measurements are recommended for the definition of the reversibility of renal impairment. Rapid intervention to reverse renal dysfunction is critical for the management of these patients, especially for those with light chain cast nephropathy. Bortezomib with high-dose dexamethasone is considered as the treatment of choice for such patients. There is limited experience with thalidomide in patients with myeloma with renal impairment. Thus, thalidomide can be carefully administered, mainly in the context of well-designed clinical trials, to evaluate if it can improve the rapidity and probability of response that is produced by the combination with bortezomib and high-dose dexamethasone. Lenalidomide is effective in this setting and can reverse renal insufficiency in a significant subset of patients, when it is given at reduced doses, according to renal function. The role of plasma exchange in patients with suspected light chain cast nephropathy and renal impairment is controversial. High-dose melphalan (140 mg/m²) and autologous stem-cell transplantation should be limited to younger patients with chemosensitive disease.

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ABSTRACT

Renal impairment is a common complication of multiple myeloma (MM). The estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula is the recommended method for the assessment of renal function in patients with MM with stabilized serum creatinine. In acute renal injury, the RIFLE (risk, injury, failure, loss and end-stage kidney disease) and Acute Renal Injury Network criteria seem to be appropriate to define the severity of renal impairment. Novel criteria based on eGFR measurements are recommended for the definition of the reversibility of renal impairment. Rapid intervention to reverse renal dysfunction is critical for the management of these patients, especially for those with light chain cast nephropathy. Bortezomib with high-dose dexamethasone is considered as the treatment of choice for such patients. There is limited experience with thalidomide in patients with myeloma with renal impairment. Thus, thalidomide can be carefully administered, mainly in the context of well-designed clinical trials, to evaluate if it can improve the rapidity and probability of response that is produced by the combination with bortezomib and high-dose dexamethasone. Lenalidomide is effective in this setting and can reverse renal insufficiency in a significant subset of patients, when it is given at reduced doses, according to renal function. The role of plasma exchange in patients with suspected light chain cast nephropathy and renal impairment is controversial. High-dose melphalan (140 mg/m²) and autologous stem-cell transplantation should be limited to younger patients with chemosensitive disease.

INTRODUCTION

Renal impairment (RI) is a common feature of multiple myeloma (MM).1,2 A review of the United States Renal Data System showed that renal morbidity from MM is a considerable burden.3 Of the 375,152 patients in the registry who initiated therapy for end-stage renal disease (ESRD) between January 1992 and June 1997, 3,298 (0.88%) had MM. The 2-year all-cause mortality of patients with ESRD due to MM was 58% versus 31% in all other patients (P < .01).3 Similarly, a recent update of the European Renal Association-European Dialysis and Transplant Association registry showed that from 1985 to 2005 1.5% (2,453) of the 159,637 patients placed on renal replacement therapy had MM. The incidence of renal replacement therapy for ESRD due to MM increased from 0.70 per million people (1986 to 1990) to 2.52 per million people (2001 to 2005). The unadjusted median overall survival (OS) on renal replacement therapy was 0.91 years in patients with MM and 4.46 years in non-MM patients.4 Several studies in the era of conventional chemotherapy have confirmed that RI was associated with poor prognosis in MM, with a median survival of shorter than 2 years.5-7 The introduction of novel agents has led to an improved survival of patients with MM,6,9 even in those with RI. Some studies have also indicated that reversibility of RI is associated with improved survival.10-12 In this consensus statement, we focus on the clinical implications and management of RI in patients with MM. Depending on the definition of RI, this complication is reported in 15% to 40% of patients with MM. At diagnosis, 30% to 40% of patients with MM have
a serum creatinine above the upper limit of normal and the majority have a serum creatinine lower than 4 mg/dL. In several series from tertiary hospitals, up to 10% of patients present with RI severe enough to require dialysis. RI can also evolve over time and an estimated 25% to 50% of patients are affected during the course of their disease.

Serum creatinine is easily assessed and in several trials it is used to define RI in MM. A serum creatinine higher than 2.0 mg/dL represents one of the Hypercalcemia, Renal Impairment, Anemia, and Bone Disease (CRAB) diagnostic criteria for symptomatic MM requiring therapy. However, serum creatinine may depend on factors such as age, sex, and muscle mass. GFR is a more accurate parameter, providing a true reflection of renal function. GFR in healthy subjects is considered to be in the range of 90 to 130 mL/min/1.73 m^2. The inulin infusion method with concomitant urine collection is considered the gold standard method to measure GFR. However, this method is unsuitable for clinical practice due to the need for continuous infusion, multiple blood samples, and expense. Radiolabeled and nonradioactive tracers, such as technetium-99–labeled diethylene-triamine-pentacetic acid, chromium-51–labeled ethylenediamine tetraacetic acid, and 125I-Iothalamate require only a single injection and blood sample, and their use would appear to be more practical than the inulin infusion method. However, due to expense and practical limitations, neither inulin nor radiotracers are widely used in clinical practice and mainly serve as reference standards to validate other methods.

Clearance of creatinine (CrCl) is defined as the volume of plasma which is completely cleared of creatinine per time unit (usually mL/min). This volume of plasma is not an actual but a virtual volume. In contrast to mass removal, which is largely dependent on the concentration of the solute, the clearance is, under given circumstances, concentration independent. In the assessment of renal function, the CrCl by timed (24-hour) urine collections has long been a mainstay in diagnostics. However, CrCl may overestimate GFR due to the additional tubular secretion of creatinine, a mechanism which becomes relatively more important when renal function declines. Timed urine collections to assess CrCl may also have a role in the estimation of GFR in less advanced renal failure. However, a potential drawback is that timed collections are often incomplete and the collection process may be cumbersome for the patient. Therefore, CrCl has been largely replaced by the prediction formulas of GFR.

Prediction equations of GFR based on serum creatinine values are often used for the definition of renal impairment: the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) study equations are the most commonly used (Table 1). The MDRD equation generally outperforms the Cockcroft-Gault equation, but may still have a high level of bias, depending on creatinine assay calibration, and low precision with at best approximately 80% of estimated GFR in the accuracy range of 70% to 130% of measured GFR even in patients with known CKD. Because Cockcroft-Gault and MDRD equations have limitations, especially in the normal or near-normal GFR range and in kidney transplant recipients, other prediction equations based on serum cystatin-C values were also considered as possibly more sensitive GFR surrogate markers. Estimating GFR based on both serum cystatin-C and serum creatinine seems to be more accurate than estimations based only on serum creatinine. A novel classification of CKD, based on CrCl, has been recently produced (Table 2). The Chronic Kidney Disease Epidemiology Collaboration formula for estimation of GFR has not been categorically evaluated in patients with MM.

However, we have to distinguish between acute and chronic RI in MM. Both the MDRD equation and the five stages of the CKD classification have been validated only in patients with CKD, and not in

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**Table 1. Prediction Equations for GFR Currently Used or Proposed For Use in Clinical Practice**

<table>
<thead>
<tr>
<th>Name</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft-Gault*</td>
<td>CrCl (ml/min) = [([140–age (years)] × body weight (kg) × constant)/Scr (micromol/L) + constant] × 0.85 if female × 1.212 if African-American</td>
</tr>
</tbody>
</table>
| MDRD†               | Original equation GFR (ml/min)/1.73 m^2 = 186 × (Scr/88.4) – 1.105 × age – 0.203 × (0.742 if female) × 1.212 if African-American
|                     | IDMS traceable GFR (ml/min)/1.73 m^2 = 175 × (Scr/1.154) – 1.105 × age – 0.203 × (0.742 if female) × 1.212 if African-American |
|                     | Equation based on both serum creatinine and CysC‡ GFR (ml/min)/1.73 m^2 = 177.6 × Scr – 0.85 × CysC^0.57 × age – 0.20 × (0.92 if female) × (1.11 if black) |

**Table 2. A Novel Classification of CKD Based on CrCl**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Creatinine (mg/dL)</th>
<th>CrCl (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(&lt;2.0)</td>
<td>&gt;110</td>
</tr>
<tr>
<td>2</td>
<td>(2.0–4.0)</td>
<td>110–45</td>
</tr>
<tr>
<td>3a</td>
<td>(4.0–6.0)</td>
<td>45–15</td>
</tr>
<tr>
<td>3b</td>
<td>(6.0–8.0)</td>
<td>15–5</td>
</tr>
<tr>
<td>4</td>
<td>(&gt;8.0)</td>
<td>&lt;5.0</td>
</tr>
</tbody>
</table>

**Abbreviations:** GFR, glomerular filtration rate; CrCl, clearance of creatinine; Scr, serum creatinine; MDRD, Modification of Diet in Renal Disease; IDMS, isotope dilution mass spectrometry; CysC, cystatin-C; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula. The Cockcroft-Gault formula can also be expressed per 1.73 m^2 body surface area.
RI in MM results primarily from the toxic effects of monoclonal light chains on the kidney, as well as other contributing factors, such as dehydration, hypercalcemia, hyperuricemia, the use of nephrotoxic drugs (eg, nonsteroid anti-inflammatory drugs, antibiotics, and contrast media), and rarely myeloma cell infiltration or hyperviscosity.1-3 Cast nephropathy is the main cause of RI in MM (approximately 90% of cases) and is characterized by tubular atrophy and tubular-interstitial fibrosis.30-34 Proximal tubule cells may be also affected.35-38 Some patients with myeloma present with acute oliguric renal failure, which is often associated with significant dehydration, with massive cast deposition in distal and mainly in proximal tubules and with poor outcome.34

Amyloid deposit is another cause of RI in MM; the deposits are fibrillar and consequently show positive Congo red staining.39 In monoclonal immunoglobulin deposition disease (MIDD), the glomerular deposits of immunoglobulin light or heavy chains are nonfibrillar and Congo red negative.40,41 Diagnosis requires renal biopsy with ultrastructural studies. In amyloid light chain (AL) amyloidosis and MIDD, proteinuria is usually nonselective and albuminuria is usually predominant.

We recommend careful assessment of a sample from a 24-hour urine collection with urine protein electrophoresis and immunofixation. If significant albuminuria is detected, then AL amyloidosis or MIDD should be considered and further evaluation is needed.

## PROGNOSIS AND REVERSIBILITY OF RENAL FAILURE

RI reflects advanced disease and high tumor burden in patients with myeloma cast nephropathy, but not in those with light chain deposition disease or AL amyloidosis, who usually show mild or moderate marrow infiltration by plasma cells.11,42,43 In the recent years, prognosis of patients with MM with RI has improved due to the availability of more effective treatments for MM and improvements in supportive care. Prognosis, however, remains tied to the reversibility of RI, although this has not been confirmed in all series.10-12 When the reversal

### Table 2. Classification of Chronic Renal Disorders

<table>
<thead>
<tr>
<th>Stage of Renal Impairment</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or elevated GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild reduction of GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate reduction of GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe reduction of GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Renal failure</td>
<td>&lt; 15 or on dialysis</td>
</tr>
</tbody>
</table>

NOTE. Stage 5 is also defined as ESRD, while stage 4 is defined as pre-ESRD. Abbreviations: GFR, glomerular filtration rate; ESRD, end-stage renal disease.

### Table 3. RIFE and AKIN Definitions

<table>
<thead>
<tr>
<th>RIFE</th>
<th>AKIN</th>
<th>RIFE and AKIN Urine Output Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>Creatinine/GFR Criteria</td>
<td>Stage</td>
</tr>
<tr>
<td>R</td>
<td>Scr increase ≥ 50% or GFR decrease &gt; 50%</td>
<td>I</td>
</tr>
<tr>
<td>I</td>
<td>Scr increase ≥ 100% or GFR decrease &gt; 50%</td>
<td>II</td>
</tr>
<tr>
<td>F</td>
<td>Scr increase ≥ 200% or GFR decrease &gt; 75% or pCr ≥ 4.0 mg/dL or an increase ≥ 0.5 mg/dL or an increase ≥ 0.5 mg/dL or an increase ≥ 0.5 mg/dL</td>
<td>III</td>
</tr>
<tr>
<td>L</td>
<td>Complete loss of kidney function (need for RRT) &gt; 4 weeks</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>End stage kidney disease (need for RRT) &gt; 3 months</td>
<td></td>
</tr>
<tr>
<td>AKI</td>
<td>Abrupt (1-7 days) and sustained (&gt; 24 hours) reduction in kidney function*</td>
<td>Abrupt (within 48 hours) reduction in kidney function defined by stage Ia</td>
</tr>
</tbody>
</table>

NOTE. The AKIN modifications of RIFE criteria can be summarized as follows: broadening of the risk category of RIFE to include increase in Scr of at least 0.3 mg/dL even if this does not reach the 50% threshold; setting a 48-hour window on the first documentation of any criteria; categorizing patients as failure if they are treated with RRT regardless of what their Scr or urine output is at the point of initiation; AKIN also proposed that stages 1, 2 and 3 be used instead of R, I, and F. Abbreviations: RIFE, risk, injury, failure, loss and end-stage kidney disease; AKIN, Acute Renal Injury Network; GFR, glomerular filtration rate; Scr, serum creatinine; pCr, plasma creatine; RRT, renal replacement therapy.

* A baseline Scr is required. If a measured Scr is unavailable, the Acute Dialysis Quality Initiative recommend back-calculating the Scr using the Modification of Diet in Renal Disease equation with an estimated GFR of 75 to 100 mL/min.
of RI is defined as a decrease in the serum creatinine level to lower than 1.5 mg/dL, the frequency of reversal of RI ranges from 20% in the past to 73% in most recent series.6,10 Blade et al reported three parameters associated with recovery of renal function: serum creatinine lower than 4 mg/dL, 24-hour urine protein excretion lower than 1 g, and serum calcium higher than 11.5 mg/dL.10 With the CKD classification, new criteria for the improvement of renal function in MM have been recently proposed.44,45 Renal complete response (CRrenal) was defined as sustained (ie, lasting at least 2 months) improvement of CrCl from lower than 50 mL/min at baseline to >60 mL/min. Renal partial response (PRrenal) was defined as sustained improvement of CrCl from lower than 15 at baseline to 30 to 59 mL/min. Renal minor response (MRrenal) was defined as sustained improvement of baseline CrCl of lower than 15 mL/min to 15 to 29 mL/min or if baseline CrCl was 15 to 29 mL/min improvement to 30 to 59 mL/min. Based on these criteria, Dimopoulos et al44 recently described a series in which 30% of 46 patients treated with these therapies, respectively.46 In that series, bortezomib-based regimens and CrCl higher than 30 mL/min were the only factors independently associated with a higher probability of achieving renal response (PR + CRrenal).

We recommend the use of the novel proposed criteria for the definition of renal reversibility in both clinical trials and every day clinical practice as they better reflect the depth of renal response to therapy based on serum creatinine measurements only. The MDRD equation is recommended for the estimation of GFR as presented in Table 4.

### MANAGEMENT OF PATIENTS WITH MYELOMA WITH RI

#### Supportive Care

Adequate hydration, urine alkalinization, and management of hypercalcemia are important measures for the management of patients with myeloma with acute renal failure and can improve renal function in a subset of patients.2,47 Although bisphosphonates are effective for control of malignancy-related hypercalcemia, they can further impair renal function and cause symptomatic hypocalcemia in patients with acute renal failure and their use is discouraged in such patients.48 The use of loop diuretics for the management of hypercalcemia is also discouraged due to the enhancement of the cast formation in the renal tubules. Drugs that may contribute to renal damage, such as nonsteroid anti-inflammatory drugs, intravenous contrast dyes, aminoglycosides or other antibiotics that cause renal adverse events, should be avoided.2,47 Contrast media can be efficiently removed from blood by hemodialysis. In general, dialysis immediately after radiographic contrast studies has been suggested for two groups of patients—those on chronic hemodialysis and those at very high risk for contrast nephropathy, such as patients with MM and RI.49

#### Mechanical Approaches

Mechanical means include long-term dialysis, plasmapheresis, and novel dialysis filters for the removal of free light chains. Long-term dialysis is a worthwhile procedure for patients with MM and ESRD. If we exclude patients with dialysis-dependent RI who die within the first 2 months of therapy (approximately 30% of the total), then long-term dialysis in combination with conventional antineyeloma therapy can lead to a median survival of approximately 2 years.2,47 Plasma exchange has been used as a temporary method of reducing serum free light chain levels in the first 1 or 2 weeks after diagnosis until a response to chemotherapy can occur. So far, two small prospective studies have shown no clear benefit of plasma exchange.50,51 In the largest study to date, 97 patients with acute renal failure at the onset of myeloma were randomly assigned to conventional chemotherapy (melphalan and prednisone [MP] or vincristine, Adriamycin, and dexamethasone [VAD]) plus 5 to 7 plasmaphereses with albumin replacement or to conventional chemotherapy alone. The authors found no significant differences in the probability of death, dialysis dependence, or GFR lower than 30 mL/min/1.73 m² at 6 months.51 This result is in accordance with smaller studies in the field.52 However, due to the small sample size and the wide 95% CI (~8.3% to 29.1%), one cannot rule out the possibility of benefit in subsets of patients.53 There were also other limitations of these studies including the fact that renal pathology was confirmed in only a small percentage of patients and MRrenal was not included as a response. This may explain other reports suggesting that myeloma patients who were treated with chemotherapy and plasma exchange recovered renal function more frequently than those treated only with chemotherapy.53

Based on the available data we do not recommend plasma exchange as a standard procedure for the management of renal failure in patients with myeloma. However, in selected patients with acute renal failure that is proven or strongly suspected to be related to light chain cast nephropathy, some of the physicians perform plasma exchange daily for the first few days. Further studies are needed to reveal possible subsets of patients who may be benefited from this procedure.

The removal of free light chains with dialysis is another alternative approach and a new hemodialysis membrane that removes efficiently the circulating light chains has been recently developed. In a small study of 19 patients with cast nephropathy and dialysis-dependent acute renal failure, Hutchison et al54 evaluated the role of extended hemodialysis using a high-cutoff dialyzer that removes large dyes, aminoglycosides or other antibiotics that cause renal damage, such as nonsteroid anti-inflammatory drugs, intravenous contrast dyes, aminoglycosides or other antibiotics that cause renal adverse events, should be avoided.2,47 Contrast media can be efficiently removed from blood by hemodialysis. In general, dialysis immediately after radiographic contrast studies has been suggested for two groups of patients—those on chronic hemodialysis and those at very high risk for contrast nephropathy, such as patients with MM and RI.49

**Table 4. Criteria for the Definition of Renal Response to Antimyeloma Therapy**

<table>
<thead>
<tr>
<th>Response</th>
<th>Baseline eGFR* (mL/min/1.73 m²)</th>
<th>Best CrCl Response (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRrenal</td>
<td>&lt; 50</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>PRrenal</td>
<td>&lt; 15</td>
<td>30-59</td>
</tr>
<tr>
<td>MRrenal</td>
<td>&lt; 15</td>
<td>15-29</td>
</tr>
<tr>
<td></td>
<td>15-29</td>
<td>30-59</td>
</tr>
</tbody>
</table>

Abbreviations: eGFR, estimated glomerular filtration rate; CrCl, clearance of creatinine; CRrenal, sustained (ie, lasting at least 2 months) improvement of CrCl from lower than 50 mL/min at baseline to >60 mL/min; PRrenal, sustained improvement of CrCl from lower than 15 at baseline to 30 to 59 mL/min; MRrenal, sustained improvement of baseline CrCl of lower than 15 mL/min to 15 to 29 mL/min or if baseline CrCl was 15 to 29 mL/min improvement to 30 to 59 mL/min.

*eGFR based on Modification of Diet in Renal Disease equation.
whom became dialysis independent by 27 days. These patients had better survival than the six patients who did not achieve dialysis independence. Standard dialysis membrane does not achieve this effect. However, although promising, these results need further evaluation in well-designed clinical trials.

**Systemic Treatment With Conventional and High-Dose Therapy**

The response rate to alkylator-based conventional chemotherapy is lower in patients with MM with RI than in those with normal renal function (40% vs 60%). In the study by Alexanian et al, the administration of chemotherapy with alkylating agents, doxorubicin and steroids produced recovery of renal function (defined as a sustained decrease of creatinine to < 1.4 mg/dL) in 51% of patients within a median of 1.2 months. Light-chain myeloma and creatinine higher than 3.1 mg/dL were associated with a lower probability of recovery. The combinations of VAD, or cyclophosphamide and dexamethasone, or even dexamethasone alone are superior to melphalan-containing regimens because of their lower dependency on renal clearance and more rapid antmyeloma effect. In a series of 41 patients with MM with RI treated with high-dose dexamethasone-containing regimens, renal failure reversed in 73%.

High-dose chemotherapy (HCT) with autologous stem-cell transplantation (ASCT) may be another option. In a series of 81 patients with MM with renal failure from Arkansas group, including 38 patients on dialysis, the transplant-related mortality (TRM) was reported to be 6% and 13% after a single or tandem ASCT, respectively. Renal failure did not affect the quality of stem cell collections or engraftment, while melphalan 140 mg/m² appeared as effective as melphalan 200 mg/m² as a preparative regimen with less toxicity. In an update of this series, the 5-year event-free survival and OS of 59 patients on dialysis at the time of ASCT were 24% and 36%. Moreover, 13 (24%) of 54 patients evaluable for renal function improvement became dialysis independent at a median of 4 months after ASCT. In a series from the Spanish Programa para el Estudio de la Terapéutica Hemopatía Maligna (PETHEMA) group that included 14 patients on dialysis at the time of ASCT, the transplant-related mortality was 29% and the en hemodialysis. Regarding cyclophosphamide and its metabolites, their clearance and more rapid antimyeloma effect. In a series of 41 patients with MM with RI treated with high-dose dexamethasone-containing regimens, renal failure reversed in 73%.

Melphalan clearance is renal function dependent as it is both secreted and reabsorbed by the renal tubules. Previous pharmacokinetic studies have demonstrated large interindividual variations in the pharmacokinetic parameters. The administration of standard-dose melphalan in patients with RI is accompanied by higher hematologic toxicity. Based on available data, we recommend a reduction of oral melphalan standard dosage (0.15 to 0.25 mg/kg/d for 4 to 7 days) by 25% when the CrCl is between 15 and 60 mL/min (0.11 to 0.19 mg/kg/d for 4 to 7 days) and by 50% when the CrCl is lower than 15 mL/min or the patient is on hemodialysis (0.0175 to 0.125 mg/kg/d for 4 to 7 days). For high-dose melphalan, 140 mg/m² should be used when CrCl is lower than 60 mL/min or the patient is on hemodialysis. Regarding cyclophosphamide and its metabolites, their excretion in the urine is similar in patients with and without renal failure. Therefore, the amount of cyclophosphamide and metabolite that are measured in the urine do not warrant dose adjustment solely on the basis of decreased baseline renal function. Similarly, VAD can be used without dose adjustments, as vincristine and doxorubicin dosage does not need reduction in renal impairment.

**Systemic Therapy With Bortezomib-Based Regimens**

Bortezomib is the first-in-class proteasome inhibitor with proven efficacy in both newly diagnosed and relapsed/refractory MM. Bortezomib can be administered at the full approved dose and schedule in patients with impaired renal function. The pharmacokinetics of bortezomib are not affected by the degree of renal impairment, as the primary metabolic pathway of bortezomib is the oxidative deboronation by hepatic cytochrome P450 enzymes.

Studies indicate that bortezomib is effective and safe in patients with RI and additionally, that it can produce improvements in renal function. In a subanalysis of the Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy (SUMMIT) and Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma (CREST) phase II studies, three (30%) of 10 patients with CrCl ≤ 30 mL/min demonstrated responses to treatment, compared with a 45% overall response rate in patients with baseline CrCl higher than 80 mL/min. Discontinuation rates and adverse-event profiles were similar between patients with CrCl higher than 80 mL/min or ≤ 50 mL/min (Table 5). In a report of the phase III Assessment of Proteasome Inhibition for Extending Remissions (APEX) study of bortezomib versus high-dose dexamethasone, the efficacy and safety was assessed in patients with relapsed MM with varying degrees of renal impairment. Time to progression (TTP), OS, and safety were comparable between subgroups with CrCl ≤ 50 mL/min and CrCl higher than 50 mL/min, although there was a trend toward shorter TTP and OS in patients with CrCl ≤ 50 mL/min. Response rates with bortezomib were similar and time to response was very rapid (0.7 to 1.6 months) across the different subgroups. Toxicity after bortezomib treatment was similar in all subgroups but the incidence of adverse events and discontinuations was higher in patients with moderate-to-severe versus mild/no renal impairment. Concerning patients with ESRD, Chanan-Kahn et al, in a retrospective series of 24 patients with relapsed/refractory MM and dialysis-dependent renal failure, reported an overall response rate of 75% with 30% CR/nearCR. Three patients became dialysis independent after bortezomib therapy. Importantly, the toxicity profile was similar to that reported in patients with normal renal function treated with bortezomib.

Ludwig et al reported the reversal of light chain-induced acute renal failure (LC-ARF) with bortezomib-based therapy in five of eight patients with MM. The same group reported the effect of bortezomib, doxorubicin, and dexamethasone regimen on the reversal of LC-ARF. They found that 42 (72%) of 58 patients achieved a renal response (36% CRrenal, 9% PRrenal, and 27% MRrenal), and three of nine dialysis-dependent patients became dialysis independent after bortezomib therapy. Importantly, the toxicity profile was similar to that reported in patients with normal renal function treated with bortezomib. Ludwig et al reported the reversal of light chain-induced acute renal failure (LC-ARF) with bortezomib-based therapy in five of eight patients with MM. The same group reported the effect of bortezomib, doxorubicin, and dexamethasone regimen on the reversal of LC-ARF. They found that 42 (72%) of 58 patients achieved a renal response (36% CRrenal, 9% PRrenal, and 27% MRrenal), and three of nine dialysis-dependent patients became dialysis independent after bortezomib therapy. Renal response was observed at a median time of 38 days, while the median time to CRrenal was 111 days.

Blade et al reported that the response rate and median TTP were comparable in patients with RI (n = 193) treated with bortezomib plus pegylated liposomal doxorubicin compared with patients treated with bortezomib alone. There was an improvement of renal function for patients with RI in both treatment arms; however, patients with RI were at an increased risk of a drug-related serious adverse event.
Renal Impairment in Multiple Myeloma

Table 5. Effect of Bortezomib-Based Regimens on Patients With Multiple Myeloma and RI

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Study Drug Dosage</th>
<th>Efficacy Data</th>
<th>Discontinuation Rate</th>
<th>SAE Rate</th>
<th>Renal Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jagannath et al\textsuperscript{a5} SUMMIT and CREST (phase II studies in relapsed/refractory myeloma)</td>
<td>258 B: 1.3 mg/m\textsuperscript{2} on days 1, 4, 8, 11 of 21- to 4-week cycles for at least 6 cycles; dexamethasone: 20 mg on the day of and the day after B administration</td>
<td>Percentage of Patients With CRi, (No. of evaluable patients)</td>
<td>&lt; 30 50 80</td>
<td>30 (n = 10) 23 (n = 42) 33 (n = 9) 45 (n = 115)</td>
<td>38 22 28 60</td>
<td>51 41</td>
</tr>
<tr>
<td>San Miguel et al\textsuperscript{a6} APEX (phase III study in relapsed/refractory myeloma)</td>
<td>669 B: 1.3 mg/m\textsuperscript{2} on days 1, 2, 4, 8, 11, for eight 3-week cycles and then on days 1, 3, 5, 14, 22, 25, 29, 32, cycles 1-4; 17.20 for four 5-week cycles and then on days 1, 4, 14 for five 4-week cycles (n = 336)</td>
<td>Overall Response Rate%</td>
<td>B Arm</td>
<td>47 (n = 19) 37 (n = 43) 40 (n = 137) 36 (n = 118)</td>
<td>38 35 37 49 39 46</td>
<td>Dexamethasone Arm</td>
</tr>
<tr>
<td>Blade et al\textsuperscript{d7} (retrospective analysis of a phase III trial in relapsed/refractory patients with renal impairment, CRi &lt; 60 mL/min)</td>
<td>646 B: 1.3 mg/m\textsuperscript{2} on days 1, 4, 8, 11 of each 3-week cycle (n = 320) or the same B regimen plus IV PLD 30 mg/m\textsuperscript{2} on day 4 (n = 324) of each cycle.</td>
<td>CRI (ml/min, No. of evaluable patients)</td>
<td>≥ 60 (n = 193)</td>
<td>60 (n = 453)</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Moranzo et al\textsuperscript{d6} (retrospective analysis including both newly diagnosed and relapsed/refractory MM)</td>
<td>117 BD standard dosage in 54% or BD in combination with other agents (n = 63)</td>
<td>Percentage of Patients With CRi, (No. of evaluable patients)</td>
<td>&lt; 30 30-50 51-80</td>
<td>30 (n = 82) (n = 23) 51-80 (n = 12)</td>
<td>11 5 0</td>
<td>65 52</td>
</tr>
<tr>
<td>Dimopoulos et al\textsuperscript{d8} VISTA trial (phase III study in newly diagnosed patients)</td>
<td>682 VMP: B 1.3 mg/m\textsuperscript{2}, days 1,4,8,11,22,25,29,32, cycles 1-4 &amp; days 1,2,22,29, cycles 5-8, plus melphalan 9 mg/m\textsuperscript{2} and prednisone 60 mg/m\textsuperscript{2}, days 1-4, cycles 1-9 (n = 344) or MP (n = 338)</td>
<td>Percentage of Patients With CRi, (No. of evaluable patients)</td>
<td>&lt; 30 31-50</td>
<td>&gt; 50</td>
<td>30-50</td>
<td>&gt; 50</td>
</tr>
</tbody>
</table>
| Abbreviations: RI, renal impairment; SAE, serious adverse event; SUMMIT, Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy; CREST, Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma; B, bortezomib; CRi, creatinine clearance; PLD, pegylated liposomal doxorubicin; GFR, glomerular filtration rate; APEX, Assessment of Proteasome Inhibition for Extending Remissions; NE, not evaluated; TTP, time to progression; OS, overall survival; CR, complete response; PR, partial response; MR, minimal response; VMP, bortezomib, melphalan, prednisone; MP, melphalan and prednisone. *Patients who received at least six cycles were allowed to switch to less intensive schedules of bortezomib—either twice weekly for 2 weeks with a 17-day rest period or once weekly for 4 weeks with a 13 to 20-day rest period. Includes CR + PR + MR. #Includes CR + PR. 

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Other retrospective studies confirmed the beneficial effect of bortezomib on RI in the relapsed/refractory setting.44,68 In newly diagnosed patients who are not eligible for an autologous transplantation, Dimopoulos et al has recently reported the results of the subgroup analysis of the Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment With Melphalan and Prednisone (VISTA) phase III trial, regarding the effect of the VMP (bortezomib, melphalan, prednisone) combination on RI. Response rates were higher and TTP and OS were longer with VMP versus MP across renal cohorts. RI reversal, defined as a baseline eGFR lower than 50 improving to higher than 60 mL/min, was seen in 49 (44%) of 111 patients receiving VMP versus 40 (34%) of 116 of those receiving MP. Younger age (<75 years) and eGFR ≥ 30 mL/min were independently associated with higher reversal rates. In both arms, rates of grade 4 and 5 adverse events appeared higher in patients with RI; with VMP, rates of discontinuation or bortezomib dose reduction due to AEs did not appear to be affected (Table 5). 69 Bortezomib was also shown to reduce cystatin-C levels, a marker of GFR and thereby an early marker for RI, in patients with relapsed MM.14

**Systemic Therapy With Immunomodulatory Drugs-Based Regimens**

Thalidomide is the first immunomodulatory drug with proven activity in MM. Thalidomide pharmacokinetics are not affected by RI, and thus, no dose reduction is required in patients with MM with RI.73 There are limited data for the efficacy of thalidomide-based regimens in such patients with MM. In 20 patients with relapsed/refractory MM and RI (defined as serum creatinine > 2 mg/dL), treatment with thalidomide alone (n = 8) or thalidomide plus dexamethasone (n = 12) resulted in 45% PR and 30% MR. The median duration of response was 7 months, while 12 of 15 responding patients had improved renal function defined as serum creatinine lower than 2 mg/dL, while two additional patients on chronic hemodialysis showed a reduction of serum creatinine. Toxicities were similar to those reported with thalidomide in patients with normal renal function.74 Kastritis et al also observed reversal of renal failure with thalidomide, in combination with high-dose dexamethasone, with or without bortezomib, in 80% of previously untreated patients.12 Treatment with thalidomide has been associated with severe hyperkalemia in occasional patients with RI, particularly those undergoing dialysis.75,76 Based on this data and in the absence of randomized results showing that thalidomide adds a benefit in patients with myeloma with renal impairment, its use should be discouraged outside of the context of a carefully designed clinical trial with intensive electrolyte monitoring to maximize patient safety.

Lenalidomide is another effective agent for the management of MM. It is mainly excreted by the kidneys, through both glomerular filtration and active tubular secretion.77 Based on pharmacokinetic studies, the following dose-adjustments have been recommended: reduce the dose to 10 mg/d in patients with CrCl between 30 and 50 mL/min, to 15 mg every other day in patients with CrCl lower than 30 mL/min not on dialysis, and to 5 mg once daily, with postdialysis dosing on days of dialysis, in patients requiring renal replacement.78 The information for the effect of lenalidomide-based regimens on myeloma patients with RI is limited because in the majority of phase II to III studies serum creatinine of higher than 2 mg/dL was an exclusion criterion. In a combined analysis of the MM-009 and MM-010 phase III studies of lenalidomide and dexamethasone (RD) versus dexamethasone alone in patients with relapsed MM, efficacy and safety were assessed in patients with normal renal function and with mild, moderate, and severe RI (assessed as CrCl > 80, 50 to 79, 30 to 49, and < 30 mL/min, respectively). The renal subgroups did not significantly differ regarding overall response rate (50% to 63%) or response quality (≥ very good PR: 30% to 38%). In all renal subgroups, except for patients with severe RI, TTP, PFS, and OS did not differ significantly compared to patients with normal renal function. Patients with severe RI experienced an increased incidence of thrombocytopenia, required more frequent lenalidomide dose reductions or interruptions, and had shorter OS than those without RI. Improvement in CrCl by at least one level was documented in 68% of patients.79 Similarly, in a series of patients with relapsed/refractory MM who received RD, three (25%) of 12 patients with RI (CrCl < 50 mL/min) achieved a CRrenal and two (16%) achieved a MRrenal,80 while in a Spanish retrospective analysis of 15 dialysis-dependent MM patients who received RD, 57% achieved a response and one patient became independent of dialysis.81 RD was shown to be an active rescue treatment in a patient with renal failure due to cast nephropathy failing to bortezomib-based induction treatment.82 In a phase II study of newly diagnosed patients with MM treated with RD, baseline CrCl ≤ 40 mL/min was associated with grade ≥ 3 myelosuppression and an 8.4-fold increased likelihood of lenalidomide dose reduction compared with patients with CrCl higher than 40 mL/min.83

**RECOMMENDATIONS FOR THERAPY**

High-dose dexamethasone-based therapies are highly active in patients with myeloma with renal impairment. Available data support the safety and efficacy of bortezomib-based therapies in this setting and thus bortezomib plus dexamethasone is the recommended treatment for patients with myeloma with RI of any grade. Bortezomib should be started at the standard dose of 1.3 mg/m² on days 1, 4, 8, and 11 of a 3-week cycle and dexamethasone at a dose of 20 mg on the day of and the day after bortezomib administration. In elderly patients who receive first-line therapy and have renal impairment, VMP is another option at the reported dosage (Table 5). Thalidomide maybe used with caution in the absence of results from randomized trials in this setting. A triple combination of bortezomib, thalidomide, and dexamethasone may be considered in the context of a clinical trial. Lenalidomide is a feasible and effective treatment option for patients with mild-to-moderate renal impairment, if it is used at the recommended reduced dose based on renal function. However, we have to mention that these reduced dosages of lenalidomide have been resulted by pharmacokinetic studies and modeling and not from studies of patients with myeloma with renal impairment. Such studies are now underway and their results are highly anticipated. HDT/ASCT can be an option for such patients; high-dose regimen should consist of melphalan 140 mg/m² and the procedure should be restricted to patients younger than 60 years of age with chemotherapy-sensitive disease and good performance status.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject

Dimopoulos et al
Renal Impairment in Multiple Myeloma

AUTHOR CONTRIBUTIONS

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Data analysis and interpretation: Meletios A. Dimopoulos, Evangelos Terpos
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REFERENCES


