Novel Therapeutic Agents for the Management of Patients with Multiple Myeloma and Renal Impairment

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Abstract

Renal impairment is a major complication of multiple myeloma. Patients presenting with severe renal impairment represent a greater therapeutic challenge and generally have poorer outcome. However, once patients with renal impairment achieve remission, their outcomes are comparable with those of patients without renal impairment. Therapies that offer substantial activity in this setting are needed. Bortezomib, thalidomide, and lenalidomide have substantially improved the survival of patients with multiple myeloma. Here we review the pharmacokinetics, activity, and safety of these agents in patients with renal impairment. Bortezomib can be administered at the full approved dose and schedule in renally impaired patients; similarly, no dose reductions are required with thalidomide. The pharmacokinetics of lenalidomide is affected by its renal route of excretion, and dose adjustments are recommended for moderate/severe impairment. Substantial evidence has emerged showing that these novel agents improve outcomes of patients with renal impairment, including impairment reversal. Bortezomib, thalidomide, and lenalidomide (at the recommended doses) are active options for patients with mild to moderate impairment, although limited data are available for thalidomide. Information on lenalidomide-based combinations is still emerging, but the available data indicate considerable activity. Substantial evidence indicates that bortezomib–high-dose dexamethasone with or without a third drug (e.g., cyclophosphamide, thalidomide, or doxorubicin) is an appropriate option for patients with any degree of renal impairment.

Introduction

Impairment of renal function can affect drug pharmacology because many drugs are partially or fully cleared via the kidneys (1). Net renal excretion is the result of 3 distinct processes: glomerular filtration, tubular secretion, and tubular reabsorption (2). Impaired renal excretion of a specific drug can result from a global decrease in all kidney functions, or from specific impairment of active renal transport/secretion, which can occur through drug–drug interactions (3). Renal impairment can thus affect a drug’s pharmacokinetic profile, and starting dose adjustments may be recommended to compensate for these effects (1). The main parameters used to assess renal function are serum creatinine (SCr) concentrations, calculated or measured creatinine clearance (CrCl) rates, and glomerular filtration rate (GFR). GFR is the most accurate assessment parameter and provides a true reflection of renal function (4, 5). SCr is easier to assess, but it is not directly related to renal function and depends on factors such as age, sex, and body size/muscle mass (5). Therefore, in elderly patients and patients with low muscle mass, such as cancer patients, the degree and incidence of renal impairment may be underestimated in assessments using SCr (4–9). GFR may be estimated from the CrCl rate, which is calculated with the Cockcroft–Gault formula (10) based on a patient’s SCr, age, weight, and sex. This formula may overestimate GFR in heavy people. Other equations have been developed, such as the modification of diet in renal disease (MDRD) equation (4), which overestimates GFR in underweight people. Because the majority of patients with multiple myeloma are of normal or low weight, the Cockcroft–Gault formula is preferentially used by several centers; however, others prefer the MDRD formula.

Renal Impairment in Patients with Multiple Myeloma

Renal impairment is one of the major complications in patients with multiple myeloma (6, 11). Approximately
Renal impairment is a major complication of multiple myeloma. Therapies that offer substantial activity in this setting are needed. Bortezomib, thalidomide, and lenalidomide have substantially improved the survival of patients with multiple myeloma. Here we review the pharmacokinetics, activity, and safety of these agents in patients with renal impairment, with the aim of providing recommendations for treatment in this setting. We conclude that bortezomib, thalidomide, and lenalidomide (at the recommended adjusted doses) are active options for patients with mild to moderate impairment, and that substantial evidence indicates that bortezomib–high-dose dexamethasone with or without a third drug (e.g., cyclophosphamide, thalidomide, or doxorubicin) is an appropriate option for patients with any degree of renal impairment. It is hoped that this comprehensive review of the available data will help improve the management of patients with multiple myeloma and renal impairment.

30% of patients present with SCr ≥ 1.5 mg/dL (6, 7, 12), 20% present with SCr ≥ 2.0 mg/dL (13–16), and 1% to 13% of patients with multiple myeloma have sufficiently severe renal failure to require dialysis support (7, 14, 15, 17, 18). Renal impairment remains a problem or evolves over time in a substantial proportion of patients, with an estimated 50% being affected during the course of their disease (6, 19, 20).

Renal impairment in patients with multiple myeloma is mainly caused by light-chain tubular cast nephropathy, known as "myeloma kidney" (refs. 11, 14, 21–23; Fig. 1), and may also arise as a result of amyloidosis and light-chain deposition disease (11, 22). Myeloma kidney is associated with high levels of light-chain protein excretion in the urine leading to cast formation, tubular obstruction, and distal tubular dysfunction (11, 23). The specific physicochemical characteristics of individual light chains determine their nephrotoxic potential, i.e., whether they are toxic, amyloidogenic, or result in light-chain deposition disease, Fanconi syndrome, or cast nephropathy (11). Cast nephropathy is caused by light chains that are able to bind to Tamm-Horsfall protein (11). Hypercalcemia, a serious complication of multiple myeloma, is often associated with renal failure. The kidneys increase calcium excretion and this results in dehydration and reduction of renal blood flow and GFR, often aggravating myeloma kidney (19, 24).

It is important to note that in many studies of patients with multiple myeloma and renal impairment, the cause of the impairment was not thoroughly elucidated and renal biopsies were not usually done. Common alternative causes of renal impairment include infections, use of nephrotoxic drugs, hypovolemia (often associated with hypercalcemia), use of contrast media, and renal amyloidosis. Therefore, a thorough diagnosis of the primary underlying cause of renal impairment is important for distinguishing light-chain–related impairment from non–multiple-myeloma–related causes that may be readily addressed through supportive measures. However, such a differentiation may be clinically difficult as patients may be suffering from one or both of these pathologies. Thus, it should be stressed that prompt initiation of therapeutic measures related to both pathologies, including rigorous hydration, treatment of infections and hypercalcemia, and discontinuation of nephrotoxic drugs, as well as anti–multiple-myeloma therapy including high-dose dexamethasone, is important.

Impact of Renal Impairment on Outcome in Patients with Multiple Myeloma

The presence of renal impairment in patients with multiple myeloma is associated with poorer survival (7, 14–17, 25–30). Patients requiring dialysis have been shown to have particularly poor prognosis (7). The poorer outcomes in populations of patients with renal impairment may be associated with the increased risk of early death (7, 12, 14). In addition, renal impairment is associated with advanced disease and higher tumor burden (6, 16).

Depending on the definition used, renal impairment may be reversed with antimyeloma treatment in up to 73% of patients with multiple myeloma (7, 14, 16, 24, 31, 32), although a very poor GFR is prognostically unfavorable in terms of correction of renal function. In some studies, this reversibility was associated with improved survival compared with patients with irreversible renal failure (7, 14, 16, 30). For example, in a study of 775 patients with multiple myeloma in Nordic countries, 58% of the patients experienced reversal of their renal impairment within 12 months of diagnosis, and in patients who were alive at 12 months, reversibility of renal impairment was a significant prognostic factor for survival (7). It is important to stress that in some studies and patients, the renal impairment may have been due to non–multiple-myeloma–related causes, such as hypercalcemia, which is more rapidly reversible than myeloma-kidney–related renal injury. For this reason, reports of a short median time to renal recovery in patients with multiple myeloma may reflect a rapid recovery from non–multiple-myeloma–related impairment in a proportion of patients, and should thus be interpreted with caution. For improvement of myeloma-induced renal impairment, an excellent response of the disease to treatment is required.

Management of Patients with Renal Impairment

Renal impairment results in a population of patients who are more difficult to treat compared with patients with normal renal function. Rapidly evolving renal impairment is an emergency that requires rapid diagnosis and treatment initiation. Aggressive therapy is generally recommended to rapidly reduce the tumor burden, in addition to correction of hypercalcemia, hyperuricemia, and dehydration (33, 34). High-dose dexamethasone-based regimens are important treatment options for patients with multiple myeloma.
with renal impairment because they result in rapid responses (32). Vincristine, doxorubicin, and dexamethasone (VAD) and single-agent dexamethasone have been among the preferred first-line treatment options for patients with renal impairment (35, 36). However, these therapies have been shown to be inferior to novel-agent-based therapies (37–44), although dexamethasone in combination with novel agents may represent a feasible, highly active treatment approach for obtaining very rapid responses (32).

Other conventional treatments have limitations in patients with multiple myeloma and renal impairment, due to an increased likelihood of toxicities or a need for dose reductions. In newly diagnosed patients with multiple
myeloma and renal impairment, renal dysfunction was shown to correlate with increased hematologic and infectious toxicity with melphalan plus prednisone (45); therefore, melphalan dose reduction should be considered in such patients (35, 36, 45). Patients with renal impairment were also likely to receive a reduced dose of melphalan as conditioning prior to stem cell transplantation, due to toxicity (13, 46). Autologous stem cell transplantation has been shown to be feasible in patients with renal impairment (13, 31, 47, 48), including those requiring dialysis (13, 31, 47). However, limited outcome data (some of which are suggestive of poorer outcomes for patients with substantial renal impairment at the time of transplantation), coupled with toxicity concerns in these patients, emphasize the importance of better induction therapies to reduce disease burden and reverse renal dysfunction prior to high-dose melphalan therapy.

Management of patients with multiple myeloma has evolved substantially over the past decade with the introduction of the proteasome inhibitor bortezomib (Velcade; Millennium Pharmaceuticals, Inc., and Johnson and Johnson Pharmaceutical Research and Development, LLC) and the immunomodulatory drugs (IMiD) thalidomide (Thalomid; Celgene Corporation) and lenalidomide (Revlimid; Celgene Corporation). Bortezomib and the IMiDs are approved for the treatment of multiple myeloma in various settings and regimens, and these novel agents have shown substantial activity in first-line treatment (49, 50) and relapsed multiple myeloma (50, 51), contributing to significantly improved outcomes in multiple myeloma, especially in younger patients (52–54).

Below, we discuss the pharmacokinetics, safety, and activity of novel-agent–based treatment regimens in patients with multiple myeloma and renal impairment. It should be noted that the number of patients included in prospective studies of novel-agent–based therapies who had severe renal impairment was generally small, due to study exclusion criteria; for example, SCr > 2 mg/dL in the phase III VISTA study of bortezomib plus melphalan–prednisone (VMP) versus MP (55), CrCl < 20 mL/min in the phase III APEX study of bortezomib versus dexamethasone (56), and SCr > 2.5 mg/dL in the MM-009 and MM-010 phase III studies of lenalidomide–dexamethasone versus dexamethasone (37, 41).

Pharmacokinetics and Dosing of Novel Agents in Patients with Renal Impairment

Bortezomib can be administered at the full approved dose and schedule in patients with impaired renal function. The pharmacokinetics of bortezomib is not affected by the degree of renal impairment, and therefore dosing adjustments are not necessary for patients with renal insufficiency, including patients requiring dialysis (57). This is because the primary metabolic pathway of bortezomib, as shown in in vitro studies, is oxidative deboronation by hepatic cytochrome P450 enzymes (57–59), mainly CYP3A4, CYP2C19, and CYP1A2 (57, 59, 60). U.S. Food and Drug Administration (FDA) approval of the labeling regarding the use of bortezomib in patients with renal impairment was based on the findings of a U.S. National Cancer Institute–sponsored dose-escalating and pharmacologic study (61). In this prospective phase I study, 59 patients with various degrees of renal function impairment, including 14 patients with multiple myeloma, were enrolled to receive bortezomib at escalating doses of 0.7, 1.0, and 1.3 mg/m². Dose escalation to the standard dose of 1.3 mg/m² was well tolerated in all groups of patients with renal impairment, including those requiring dialysis. Toxicities were reported to be generally mild, with a similar safety profile among all groups of patients with renal impairment. Furthermore, pharmacokinetic analyses showed that there were no significant differences in bortezomib clearance between patients regardless of CrCl (61).

Similarly, no dose reductions seem to be required when administering thalidomide to patients with renal impairment, although data are limited (62, 63). A study of patients with multiple myeloma and impaired renal function showed that thalidomide pharmacokinetics did not seem to be affected by renal impairment, with no significant correlation between thalidomide clearance and CrCl (62). In dialysis-dependent patients, clearance was doubled during dialysis, but the authors suggested that no dose reduction was required and no supplementary dose was needed due to hemodialysis (62).

The pharmacokinetics of lenalidomide is affected by renal impairment, and lenalidomide dose adjustments are recommended for patients with moderate or severe impairment (64, 65). This is because lenalidomide is substantially excreted by the kidneys (65), likely through both glomerular filtration and active tubular secretion (64). In a study of the pharmacokinetics of lenalidomide following a single 25 mg dose, among 30 patients with normal renal function (CrCl > 80 mL/min); mild, moderate, or severe renal impairment (CrCl 50–80, 30–49, or <30 mL/min, respectively); or end-stage renal disease (requiring dialysis), mean urinary recovery of unchanged lenalidomide declined from 84% in patients with normal renal function to 38% and 43% in patients with moderate and severe impairment, respectively. Total and renal clearance of lenalidomide decreased with diminishing renal function, whereas total exposure and mean terminal half-life increased. For patients with moderate and severe impairment, the mean area under the curve increased by ~185% to 420%, and terminal half-life was prolonged by 6 to 12 hours (64).

Based on the findings of this single-dose study (64), the authors recommended dose adjustments for patients with multiple myeloma and moderate or severe renal impairment, or end-stage renal disease. They suggested a standard starting dose and schedule of 25 mg once daily for patients with mild impairment, 10 mg once daily for those with moderate impairment, 15 mg every other day for severe impairment, and 15 mg three times a week following each dialysis for patients with end-stage renal disease. The latter recommendation has since been revised to 5 mg once daily,
with postdialysis dosing on days of dialysis (65, 66). It is important to note that these recommendations were based on pharmacokinetic data; studies testing efficacy, safety, and pharmacokinetics at these adjusted doses in patients with multiple myeloma have been undertaken (67–69), as discussed in the next section.

Activity and Safety of Novel Agents in Patients with Renal Impairment

**Bortezomib**

A substantial and growing body of evidence shows that bortezomib is active and well tolerated in patients with renal impairment, including those who require dialysis (Tables 1 and 2). In the phase III VISTA study of VMP versus MP alone in previously untreated patients with multiple myeloma who were ineligible for high-dose therapy (55), VMP did not seem to be affected by renal impairment, with no differences seen in complete response (CR) rate (31% vs. 30%) or time to progression (TTP) between patients with baseline GFR \(\leq 50\) versus \(> 50\) mL/min. Overall survival (OS) seemed somewhat longer in patients with GFR \(> 50\) mL/min. Reversal of renal impairment (GFR \(< 50\) mL/min at baseline to \(> 60\) mL/min) was seen in 44% of patients, in a median of 2.1 months. The safety profile was similar between patients with GFR \(\leq 50\) versus \(> 50\) mL/min in terms of rates of grade 3 adverse events (AE) and discontinuations and bortezomib dose reductions due to AEs, although rates of grade 4 and 5 AEs and serious AEs (SAE) seemed somewhat higher in those with GFR \(\leq 50\) mL/min (55). In the small group of patients with GFR \(\leq 30\) mL/min, hematologic toxicities were more common, and rates of SAEs and grade 4 AEs were somewhat higher, possibly associated with melphalan use (55). Thus, VMP is an active and relatively well-tolerated regimen in myeloma patients with mild or moderate renal impairment.

In a recent analysis of the HOVON-65/GMMG-HD4 phase III trial comparing bortezomib, doxorubicin, and dexamethasone (PAD) with VAD as induction therapy in previously untreated patients with multiple myeloma proceeding to transplant (70), response rates, 2-year progression-free survival (PFS), and 2-year OS were similar following PAD induction in patients with SCr \(< 2\) or \(\geq 2–5\) mg/dL, whereas following VAD induction, efficacy was markedly inferior in the latter group with renal impairment. The authors concluded that the use of bortezomib-based therapy in this trial was able to overcome the negative prognostic impact of impaired renal function (70).

In an exploratory subgroup analysis of the phase III APEX trial of bortezomib versus high-dose dexamethasone in patients with relapsed multiple myeloma following 1–3 prior lines of therapy (56), the response rate to bortezomib was similar (37%–47%) between patients with severe (CrCl \(< 30\) mL/min), moderate (30–50 mL/min), mild (51–80 mL/min), and no (>80 mL/min) renal impairment, and the median time to first response was 0.7–1.6 months, indicating rapid responses to treatment regardless of renal impairment. Median TTP and OS also seemed similar across renal subgroups, with no significant difference seen in median TTP between patients with severe-to-moderate or mild/no renal impairment (4.9 vs. 6.2 months, \(P = 0.62\)). There was a trend toward shorter OS in patients with severe-to-moderate renal impairment (22.8 vs. 30.0 months, \(P = 0.07\) (56]). The safety profile of bortezomib seemed similar across renal subgroups. Bortezomib retained the overall superiority seen versus dexamethasone in terms of response rate, TTP, and OS (40, 71) across the 4 renal subgroups (56). Median TTP was significantly longer with bortezomib versus dexamethasone in patients with severe-to-moderate (4.9 vs. 2.8 months, \(P = 0.02\)) and mild/no renal impairment (6.2 vs. 3.5 months, \(P < 0.0001\)), and there was a trend toward prolonged median OS with bortezomib in both of these broader subgroups (22.8 vs. 12.6 months, \(P = 0.09\); and 30.0 vs. 25.3 months, \(P = 0.09\), respectively). Overall, these findings suggest that bortezomib may potentially overcome the poor prognosis associated with renal impairment (56).

In an analysis of 256 relapsed and/or refractory patients with multiple myeloma treated with bortezomib with or without dexamethasone in the phase II SUMMIT and CREST studies, renal impairment did not seem to substantially affect the response rate, incidence of grade \(\geq 3\) toxicities, or discontinuation rate (72). Of note, among 10 patients with severe renal impairment (CrCl \(< 30\) mL/min), treatment resulted in a decrease in mean Scr, from \(\sim 3.1\) to \(2.1\) mg/dL during the first 3 cycles of therapy, followed by stabilization above the upper level of normal (72). In a single-center study of 66 consecutive patients with multiple myeloma treated with various bortezomib-based regimens (73), 33 previously untreated and 33 relapsed/refractory patients were stratified by renal function into 5 stages, per the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative [GFR \(> 90\), 60–89, 30–59, 15–29, and \(< 15\) mL/min (requiring dialysis)]. The overall response rate was 50%, including 12% CR, and no significant association was seen between renal function and response \((P = 0.53)\) (73).

Reversibility of renal impairment has been seen in a number of studies, including a retrospective multicenter analysis of bortezomib-based treatment in 24 patients with multiple myeloma and advanced renal failure requiring dialysis (74). Three patients became dialysis-independent after achieving a CR or a minimal response (MR), and another patient was spared imminent dialysis after a rapid response to bortezomib-based therapy. Overall, in the group of response-evaluable patients, the rate of CR plus partial response (PR) was 75%, which included 30% with CR or near-CR (74). Substantial reversal of renal impairment, including reversal of dialysis-dependence, was also reported in an Italian retrospective multicenter analysis (75) and in a study of 4 newly diagnosed and 16 relapsed/refractory patients with multiple myeloma with SCR \(\geq 2\) mg/dL (76). Furthermore, in a phase II study of bortezomib, doxorubicin, and dexamethasone in patients with multiple myeloma and acute renal failure, 62% of patients achieved a renal response and 31% achieved a complete renal response.
Table 1. Activity and safety of bortezomib alone or in combination in patients with multiple myeloma and renal failure

<table>
<thead>
<tr>
<th>Study, N</th>
<th>Regimen</th>
<th>Baseline renal impairment</th>
<th>Response/CR + PR rate</th>
<th>Time to event</th>
<th>Safety</th>
<th>Changes in renal impairment</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GFR ≤30 mL/min 6%</td>
<td>74% (37% CR)</td>
<td>TTP similar</td>
<td>Grade 3/4/5 AEs 42/42/</td>
<td>44% renal impairment reversal (baseline CrCl &lt;50 to &gt;60 mL/min)</td>
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<tr>
<td></td>
<td>VISTA phase III study (55), 344</td>
<td>GFR 31–50 mL/min 27%</td>
<td>67% (29% CR)</td>
<td>OS somewhat</td>
<td>Grade 3/4/5 AEs 41/36/</td>
<td></td>
</tr>
<tr>
<td></td>
<td>previously untreated MM</td>
<td>GFR &gt;50 mL/min 67%</td>
<td>72% (30% CR)</td>
<td>GFR &gt;50 mL/min</td>
<td>12%; SAEs 50%</td>
<td></td>
</tr>
<tr>
<td>APEX phase III study (56), 313 relapsed MM</td>
<td>Single-agent bortezomib</td>
<td>CrCl &lt;30 mL/min 5%</td>
<td>47%</td>
<td>TTP: 4.2 mo; OS: 22 mo</td>
<td>Safety profile comparable in patients with CrCl ≤50 and &gt;50 mL/min</td>
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<tr>
<td></td>
<td></td>
<td>CrCl 30–50 mL/min 14%</td>
<td>37%</td>
<td>TTP: 5.6 mo; OS: 22.8 mo</td>
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<tr>
<td></td>
<td></td>
<td>CrCl 51–80 mL/min 44%</td>
<td>40%</td>
<td>TTP: 6.2 mo; OS: 30 mo</td>
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<tr>
<td></td>
<td></td>
<td>CrCl &gt;80 mL/min 36%</td>
<td>36%</td>
<td>TTP: 6.3 mo; OS: NE</td>
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<td></td>
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<td>CrCl &lt;60 (≥30) mL/min 29%</td>
<td>49% (27% ≥VGPR)</td>
<td>TTP: 10.9 mo</td>
<td>CrCl &lt;60 vs. ≥60 mL/min:  Improvement from baseline similar toxicity profile; drug-related SAEs 28% vs. 19%; grade ≥3 anemia 13% vs. 8%; grade ≥3 diarrhea 18% vs. 7%</td>
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<tr>
<td></td>
<td></td>
<td>CrCl ≥60 mL/min 71%</td>
<td>47% (29% ≥VGPR)</td>
<td>TTP: 8.9 mo</td>
<td>CrCl &lt;60 vs. ≥60 mL/min:  Improvement from baseline similar toxicity profile; drug-related SAEs 28% vs. 19%; grade ≥3 anemia 13% vs. 8%; grade ≥3 diarrhea 18% vs. 7%</td>
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<tr>
<td></td>
<td></td>
<td>CrCl &lt;60 (≥30) mL/min 30%</td>
<td>42% (22% ≥VGPR)</td>
<td>TTP: 6.5 mo</td>
<td>CrCl &lt;60 vs. ≥60 mL/min:  Improvement from baseline similar toxicity profile; drug-related SAEs 28% vs. 19%; grade ≥3 anemia 13% vs. 8%; grade ≥3 diarrhea 18% vs. 7%</td>
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<tr>
<td></td>
<td></td>
<td>CrCl ≥60 mL/min 70%</td>
<td>44% (18% ≥VGPR)</td>
<td>TTP: 6.3 mo</td>
<td>CrCl &lt;60 vs. ≥60 mL/min:  Improvement from baseline similar toxicity profile; drug-related SAEs 28% vs. 19%; grade ≥3 anemia 13% vs. 8%; grade ≥3 diarrhea 18% vs. 7%</td>
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<td></td>
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<td>SCr &gt;5 mg/dL</td>
<td>60% (20% ≥VGPR); post-transplant: 60% (≥40% VGPR)</td>
<td>1-/2-/3-yr PFS: 60/40/40%; 1-/2-/3-yr OS: 60/60/60%</td>
<td>NR</td>
<td>NR</td>
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<td></td>
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<td>SCr 2–5 mg/dL</td>
<td>58% (28% ≥VGPR); post-transplant: 84% (16% CR, 42% ≥VGPR)</td>
<td>1-/2-/3-yr PFS: 89/78/56%; 1-/2-/3-yr OS: 89/89/83%</td>
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<td>NR</td>
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<tr>
<td></td>
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<td>SCr &lt;2 mg/dL</td>
<td>79% (7% CR, 43% ≥VGPR); post-transplant: 89% (22% CR, 62% ≥VGPR)</td>
<td>1-/2-/3-yr PFS: 88/67/48%; 1-/2-/3-yr OS: 93/86/78%</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
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<td>Bortezomib ± dexamethasone</td>
<td>CrCl &lt;30 mL/min 4%</td>
<td>30%</td>
<td>Similar toxicity profiles and rates of discontinuations, Mean SCr, then stable above normal range</td>
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<tr>
<td></td>
<td></td>
<td>CrCl 30–50 mL/min 16%</td>
<td>24%</td>
<td>NR</td>
<td>Similar toxicity profiles and rates of discontinuations, Mean SCr, then stable above normal range</td>
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<td></td>
<td></td>
<td>CrCl 51–80 mL/min 39%</td>
<td>33%</td>
<td>NR</td>
<td>Similar toxicity profiles and rates of discontinuations, Mean SCr, then stable above normal range</td>
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<td>CrCl &gt;80 mL/min 41%</td>
<td>45%</td>
<td>NR</td>
<td>Similar toxicity profiles and rates of discontinuations, Mean SCr, then stable above normal range</td>
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Table 1. Activity and safety of bortezomib alone or in combination in patients with multiple myeloma and renal failure (Cont’d)

<table>
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<tr>
<th>Study, N</th>
<th>Regimen</th>
<th>Baseline renal impairment</th>
<th>Response</th>
<th>CR</th>
<th>Time to event</th>
<th>Safety</th>
</tr>
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<tbody>
<tr>
<td>Phase II study (77), 68 MM patients with ARF [58 response-evaluable (46 first-line, 12 relapsed)]</td>
<td>PAD</td>
<td>GFR &lt; 50 mL/min (first-line); GFR &gt; 25% to &lt; 60 mL/min (relapsed)</td>
<td>78% (43% CR; 62% C21 VGPR)</td>
<td>2.9 mo</td>
<td>TTBR: 2.9 mo; PFS: 13.7 mo; 2-yr OS: 70% (n = 58), 60% (n = 68)</td>
<td>Grade 3/4 AEs: anemia 48%, neutropenia 17%, thrombocytopenia 14%, leukopenia 12%, fatigue 7%, infection 7%, depression/anxiety, GI, neurologic, all 5%</td>
</tr>
<tr>
<td>Single-center consecutive patient study (116), 46 MM patients with renal impairment (10 first-line, 36 relapsed/refractory)</td>
<td>BD (n = 17); VTD (n = 5); VDD (n = 1); VMTD (n = 14); BRD (n = 4)</td>
<td>eGFR &lt; 50 mL/min (83%) with higher rate of renal response and CR (P = 0.004)</td>
<td>63% (response associated with better OS (1-yr rate: 82% vs. 54%; P = 0.025))</td>
<td>NR</td>
<td>Toxicities similar to those seen in MM patients without renal failure treated with bortezomib-based regimens</td>
<td></td>
</tr>
<tr>
<td>Single-center consecutive patient study (73), 66 relapsed/refractory (33) or first-line (33) MM patients</td>
<td>Various bortezomib-based regimens</td>
<td>GFR &gt; 90 mL/min, 14%</td>
<td>50% (12% CR)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Non-interventional study (117)</td>
<td>Bortezomib/C6 dexamethasone or prednisone</td>
<td>SCr reduction in 6 patients with SCr &gt; 2 mg/dL associated with lower CR renal rate (15% vs. 67%, P = 0.046)</td>
<td>61% (7% CR)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dose-escalating and pharmacologic study (61), 59 advanced cancer patients (14 MM)</td>
<td>Single-agent bortezomib</td>
<td>Dialysis-dependent; CrCl &lt; 20. 20–39, 40–59, or &gt; 60 mL/min</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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</table>

(Continued on following page)
### Table 1. Activity and safety of bortezomib alone or in combination in patients with multiple myeloma and renal failure (Cont’d)

<table>
<thead>
<tr>
<th>Study, N</th>
<th>Regimen</th>
<th>Baseline renal impairment</th>
<th>Response/CR + PR rate</th>
<th>Time to event</th>
<th>Safety</th>
<th>Changes in renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-center retrospective patient series (118), 21 first-line MM</td>
<td>Bortezomib + dexamethasone</td>
<td>16 patients had renal failure</td>
<td>71% (24% CR, 48% ≥ VGPR)</td>
<td>NR</td>
<td>19% mild/moderate PN, 19% severe pain PN, 24% thrombocytopenia requiring bortezomib dose reduction; 19% herpes zoster</td>
<td>Improvement or independence from dialysis in 12/16 patients</td>
</tr>
<tr>
<td>Single-center prospective study (78), 18 first-line MM</td>
<td>BD</td>
<td>Median SCr 5.3 mg/dL (range 2.1–10.5) Median Cr Cl 11.9 mL/min (range 4.7–28.4)</td>
<td>83% (33% CR)</td>
<td>TTR: 1.4 mo; PFS 12.6 mo</td>
<td>Grade 3/4 AEs: infection 17%, PN 17%, recurrent ileus 6%</td>
<td>39% reversal of renal impairment; time to reversal: 0.5 mo; 33% had 50% ↓ in SCr; 1/5 became dialysis-independent</td>
</tr>
<tr>
<td>Single-center retrospective analysis (79), 8 relapsed MM</td>
<td>BD ± doxorubicin or melphalan</td>
<td>ARF</td>
<td>75%</td>
<td>NR</td>
<td>Toxicities similar to those in patients without renal failure</td>
<td></td>
</tr>
<tr>
<td>Case studies (20), 7 first-line, 1 relapsed MM</td>
<td>Single-agent bortezomib; BD; PAD</td>
<td>GFR &lt; 20 mL/min</td>
<td>3 CR/nCR, 1 VGPR, 1 PR, 1 transient PR, 1 MR, 1 PD</td>
<td>TTR 1.4 months</td>
<td>NR</td>
<td>Five patients with reversal of renal failure (median SCr 9.05 → 2.1 mg/dL)</td>
</tr>
<tr>
<td>Case studies (80), 3 first-line, 3 relapsed/refractory advanced MM</td>
<td>Single-agent bortezomib</td>
<td>Mean CrCl 15.6 mL/min (all &lt;30 mL/min)</td>
<td>2 CR, 3 PR</td>
<td>NR</td>
<td>Nausea (n = 3), PN (n = 3, 2 grade 3), fatigue, limb aches, insomnia (all n = 2)</td>
<td>Reversal of renal failure in all patients (CrCl 49–68 mL/min)</td>
</tr>
<tr>
<td>Case review (81), 6 advanced MM</td>
<td>BD</td>
<td>SCr 3.0, 2.5, 2.6, 2.6, 10, 6.8 mg/dL, respectively</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Scr: 2.7 at 2 mo; 2.3 at 1 mo; 1.5 at 2 mo; 1.2 at 12 mo; 3.7 at 16 days; 4.0 mg/dL at 1 mo, respectively</td>
</tr>
<tr>
<td>Cohort report (119), 5 first-line MM</td>
<td>BD</td>
<td>Dialysis-dependent</td>
<td>2 CR, 3 PR</td>
<td>NR</td>
<td>No grade 3/4 AEs reported</td>
<td>NR</td>
</tr>
<tr>
<td>Acute renal failure case studies (82), 3 first-line MM 1 relapsed MM</td>
<td>BD</td>
<td>SCr 6.4, 6.2, 3.1 mg/dL, respectively</td>
<td>2 nCR, 1 PR</td>
<td>NR</td>
<td>Scr 2.1, 1.2, 1.3 mg/dL, respectively</td>
<td>Scr 1.6 mg/dL</td>
</tr>
<tr>
<td>Single-agent bortezomib</td>
<td>SCr 3.7 mg/dL</td>
<td>nCR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued on following page)
Table 1. Activity and safety of bortezomib alone or in combination in patients with multiple myeloma and renal failure (Cont’d)

<table>
<thead>
<tr>
<th>Study, N</th>
<th>Regimen</th>
<th>Baseline renal impairment</th>
<th>Response/CR + PR rate</th>
<th>Time to event</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>(218, 2 refractory MM)</td>
<td>Cast nephropathy case studies</td>
<td>Dialysis-dependent</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>(243)</td>
<td>PAD and extended hemodialysis</td>
<td>Progressive renal failure</td>
<td>SCr 2.9 mg/dL, CrCl 30 mL/min</td>
<td>Patient responded</td>
<td>NR</td>
</tr>
<tr>
<td>(258)</td>
<td>Single-agent bortezomib, then BD</td>
<td>Progressive renal failure</td>
<td>SCr 2.9 mg/dL, CrCl 30 mL/min</td>
<td>Patient responded</td>
<td>NR</td>
</tr>
<tr>
<td>(282)</td>
<td>Prospective analysis of Cys-C (88), 28 relapsed MM</td>
<td>Progressive renal failure</td>
<td>SCr &gt; ULN 21%</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: ARF, acute renal failure; BD, bortezomib, dexamethasone; BRD, bortezomib, lenalidomide, dexamethasone; CrCl, creatinine clearance; CR, complete response; CR renal: CrCl/GFR < 50 to > 60 mL/min; Cys-C, cystatin-C; eGFR, estimated GFR; FLC, free light chain; GFR, glomerular filtration rate; MM, multiple myeloma; mo, months; MR, minimal response; MR renal: CrCl/GFR < 15–29 or 15–29–30–59 mL/min; NR, not reported; OS, overall survival; nCR, near CR; PAD, bortezomib, doxorubicin, dexamethasone; PFS, progression-free survival; PN, peripheral neuropathy; PR, partial response; PR renal: CrCl/GFR < 15–30–59 mL/min; SAE, serious adverse event; SCr, serum creatinine; sCR, stringent CR; TTBR, time to best response; TTP, time to progression; TTR, time to response; TTRR, time to renal response; VDD, bortezomib, liposomal doxorubicin, dexamethasone; VDT, bortezomib, thalidomide, dexamethasone; VMTD, bortezomib, melphalan, thalidomide, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone.
Table 2. Activity and safety of bortezomib and thalidomide-based regimens in patients with multiple myeloma and renal failure

<table>
<thead>
<tr>
<th>Study, N</th>
<th>Regimen</th>
<th>Baseline renal impairment</th>
<th>Response/CR - PR rate</th>
<th>Time to event</th>
<th>Safety</th>
<th>Changes in renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter retrospective analysis (74), 24 relapsed (23) or first-line (1) MM</td>
<td>Single-agent bortezomib, BD, VTD, VDT, other combinations</td>
<td>All patients requiring dialysis; median SCr 6.8 mg/dL</td>
<td>75% (30% CR/nCR)</td>
<td>DOR 12.5 ± months</td>
<td>Toxicities similar to those in overall populations in phase II and III studies</td>
<td>Four improved renal function (1 spared dialysis, 2 CR, and 1 MR became dialysis independent)</td>
</tr>
<tr>
<td>Multicenter retrospective analysis (75), 117 first-line (27), relapsed (55), or refractory (35) MM</td>
<td>BD (54); BD + thalidomide/melphalan/cyclophosphamide/liposomal doxorubicin (63)</td>
<td>GFR &gt; 30 mL/min 70% (12% dialysis-dependent)</td>
<td>70% (28% CR/nCR)</td>
<td>2-yr DOR: 70%, 2-yr OS: 51%, OS longer in patients with renal impairment reversal</td>
<td>Discontinuations 11%, dose reductions 16%, WHO grade III-IV AEs: hematologic 66%, nonhematologic 16%</td>
<td>41% reversal of renal impairment, in median of 2.3 months (range, 0.4–7.9), 61% vs. 37% in patients with untreated vs. relapsed refractory MM (P = 0.014), 67%, 78%, 27% in patients with mild, moderate, severe impairment (P &lt; 0.0001) 3/14 patients became dialysis-independent after 1, 1, and 4 mo 66% vs. 29% C21 VGPR in patients with vs. without reversal of renal impairment (P &lt; 0.0001)</td>
</tr>
<tr>
<td>Single-center consecutive patient series (32), 41 first-line MM</td>
<td>Thalidomide–dexamethasone, VTD, or BD (n = 15) or high-dose thalidomide-based regimen (r = 26)</td>
<td>Median SCr 3.4 mg/dL; 10 patients required dialysis</td>
<td>53% (64% in patients receiving thalidomide or bortezomib, vs. 46%)</td>
<td>OS: 23 mo</td>
<td>Toxicities similar to those in patients without renal failure</td>
<td>SCr &lt; 1.5 mg/dL in 73–80% patients receiving thalidomide or bortezomib, vs. 69%; 80% dialysis patients became independent</td>
</tr>
<tr>
<td>Single-center consecutive patient series (78), 20 relapsed (16) or first-line (4) MM</td>
<td>BD ± thalidomide, doxorubicin, or melphalan</td>
<td>Median SCr 3.9 mg/dL; median CrCl 14.3 mL/min</td>
<td>65% (5% CR)</td>
<td>PFS: 11.8 mo, PFS (responders): 17.9 mo</td>
<td>Toxicities similar to MM patients without renal failure; grade 3/4 thrombocytopenia in 20%</td>
<td>40% SCr &lt; 1.5 mg/dL, median time to reversal: 17 days; 50% in SCr in 50%, median time to decrease: 35 days; 1/5 dialysis patients became independent</td>
</tr>
<tr>
<td>Single-center retrospective analysis (120), 12 first-line MM</td>
<td>MPT, thalidomide ± dexamethasone, bortezomib ± dexamethasone (n = 8), VAD (n = 4)</td>
<td>Dialysis dependence</td>
<td>67% (25% CR)</td>
<td>OS longer in patients who became dialysis-independent (n = 8; P = 0.021)</td>
<td>Line infections 50%, cytomegalovirus infection 33%, DVT 25%</td>
<td>All responders became dialysis-independent in a median of 2.0 months; 7 (58%) had reversal of renal failure (SCr &gt; 2.0 mg/dL)</td>
</tr>
<tr>
<td>High tumor burden case study (94), 1 first-line MM</td>
<td>VTD</td>
<td>SCr 2.2 mg/dL</td>
<td>CR</td>
<td>NR</td>
<td>NR</td>
<td>SCr 1.4 mg/dL</td>
</tr>
<tr>
<td>Severe renal failure case study (86), first-line MM</td>
<td>VTD</td>
<td>Dialysis-dependent</td>
<td>VGPR (sCR post-transplant)</td>
<td>Remained in sCR 1 yr after initiation of therapy</td>
<td>DVT</td>
<td>Patient became independent of dialysis post-VTD</td>
</tr>
</tbody>
</table>

Abbreviations: DOR, duration of response; DVT, deep-vein thrombosis; MPT, melphalan, prednisone, thalidomide.
Management of Patients with Multiple Myeloma and Renal Impairment

Table 3. Activity and safety of novel agent-based regimens in patients with multiple myeloma and renal failure

<table>
<thead>
<tr>
<th>Study N</th>
<th>Regimen</th>
<th>Baseline renal impairment</th>
<th>Time to event</th>
<th>Changes in renal impairment</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-center retrospective analysis (171, 175 MM)</td>
<td>Any novel agent 86%, including 65% lenalidomide</td>
<td>Median SCR 1.1 mg/dL (0.5–2 mg/dL)</td>
<td>Time to event</td>
<td>No differences in toxicity among patients with or without renal impairment in all treatment groups</td>
<td>P = 0.21</td>
</tr>
<tr>
<td>Multicenter retrospective analysis (66, 2155)</td>
<td>Conventional dexamethasone-based regimen (n = 32)</td>
<td>CCI &lt; 30 mL/min 55%</td>
<td>Time to event</td>
<td>No differences in toxicity vs. other groups: other groups = 47%, MRrenal = 41%, CRrenal = 51%</td>
<td>P = 0.54</td>
</tr>
<tr>
<td>Multicenter retrospective analysis (66, 2155)</td>
<td>Bortezomib-based regimen (n = 47)</td>
<td>CCI &lt; 30 mL/min 41%</td>
<td>Time to event</td>
<td>No differences in toxicity vs. other groups: other groups = 51%, MRrenal = 41%, CRrenal = 51%</td>
<td>P = 0.54</td>
</tr>
<tr>
<td>Multicenter retrospective analysis (66, 2155)</td>
<td>MiDS + dexamethasone-based regimen (n = 17)</td>
<td>CCI &lt; 30 mL/min 41%</td>
<td>Time to event</td>
<td>No differences in toxicity vs. other groups: other groups = 51%, MRrenal = 41%, CRrenal = 51%</td>
<td>P = 0.54</td>
</tr>
</tbody>
</table>

Abbreviations: IMiD, immunomodulatory drug; NKF-KDOQI, National Kidney Foundation-Kidney Disease Outcomes Quality Initiative.

[GFR > 60 mL/min (77)]. Among all treated patients, the response rate was 72%, including 53% CR/very good partial response (VGPR) (77). A multivariate analysis showed that response to multiple-myeloma therapy and baseline GFR were significantly associated with renal response (77). Additional data showing the activity of bortezomib alone and in combination in renally impaired patients, plus reversibility of renal impairment with bortezomib-based treatment, have been provided by numerous case series and case reports (20, 78–88), as summarized in Tables 1–3.

Thalidomide

In addition to some of the studies noted above (Table 2), the activity and tolerability of single-agent thalidomide and thalidomide–dexamethasone in patients with renal impairment have been described (Table 4; refs. 32, 89–94). In a single-center series of 20 patients with relapsed, refractory multiple myeloma and renal impairment (SCR > 2 mg/dL), treatment with thalidomide alone (8 patients) or thalidomide–dexamethasone (12 patients) resulted in a PR rate of 45%, with an additional 6 patients (30%) achieving MR; the median duration of response was 7 months (91). Twelve of the 15 responding patients saw an improvement in their renal function (SCR < 2 mg/dL). Toxicities were reported as comparable to those seen with thalidomide in patients with normal renal function (91). In another study, 41 patients with newly diagnosed multiple myeloma and renal impairment (SCR > 2 mg/dL), including 15 who received thalidomide and/or bortezomib plus dexamethasone (32), were treated with high-dose dexamethasone-based regimens. The overall response rate was 53%, including 64% in patients receiving thalidomide/bortezomib, and the median OS was 23 months. Reversal of renal failure to a sustained SCR level < 1.5 mg/dL was seen in 73% of patients, including 80% of patients receiving thalidomide/bortezomib. The median time to reversal was 1.9 months overall, and was significantly more rapid in patients who received thalidomide/bortezomib (0.8 months) compared with those who did not [2 months (32)]. Again, toxicities were similar to those seen in patients without renal failure. Treatment with thalidomide has been associated with severe and possibly fatal hyperkalemia in occasional patients with renal impairment, particularly those undergoing dialysis (92, 93).

Lenalidomide

Lenalidomide-based therapies have also shown notable activity in patients with multiple myeloma and renal impairment (Table 5). In a combined analysis of the MM-009 and MM-010 phase III studies of lenalidomide–dexamethasone versus dexamethasone alone in patients with relapsed multiple myeloma (66), no significant differences in response rate or quality were observed among patients with mild or no renal impairment (CrCl ≥ 60 mL/min, n = 243), moderate impairment (≥ 30–<60 mL/min, n = 82), and severe impairment (< 30 mL/min, n = 16), with ≥ VGPR rates of 34%, 27%, and 38%, respectively. TTP was similar between the no/mild-impairment and moderate-impairment subgroups (median...
Table 4. Activity and safety of thalidomide-based regimens in patients with multiple myeloma and renal failure

| Study Type | N | Regimen | Baseline renal impairment | Response/CR PR rate | Time to event | Safety
|------------|---|---------|---------------------------|---------------------|-------------|--------|
| Single-center prospective study (122), 31 first-line MM | | Thalidomide – dexamethasone | CrCl/C20 50 mL/min, 7 dialysis-dependent | 74% (74% VGPR 26%) | EFS 30 mo | 17/26 (65%) patients had stem cell yield of >4 x 10^6 CD34+ cells/kg; 82% vs. 37% renal function improvement in patients achieving ≥ PR vs. < PR (p = 0.04)
| Single-center consecutive patient series (90), 29 first-line MM | | Thalidomide – dexamethasone / cyclophosphamide | SCr/C21 > 2 mg/dL | 66% | NR | Toxicities comparable with those in patients with normal renal function
| Single-center consecutive patient series (91), 20 relapsed/refractory MM | | Single-agent thalidomide or thalidomide – dexamethasone | SCr > 2 mg/dL | 45%/75% | DOR 7 mo, OS 7 mo | 55% reversal of renal failure in a median of 0.8 mo; 45% had a 50% SCr in a median of 1.2 mo
| Hyperkalemia case studies (92), 8 relapsed or refractory MM | | Thalidomide; thalidomide plus dexamethasone; TVAD; CTAD | Significant renal failure; 6 dialysis-dependent | 2 remission, 2 plateau | NR | Hyperkalemia in 6 patients, including 4 deaths
| Case studies (93), 7 relapsed or refractory MM | | Thalidomide alone or with steroids | CrCl 14 – 47 mL/min; 1 dialysis-dependent | 3 CR, 1 PR, 3 MR | DOR 2–12 mo | Severe hyperkalemia in 1 patient, PR in 2 patients
| Chronic dialysis case study (94), relapsed MM | | Thalidomide | SCr 6.1 mg/dL | NR | PN, constipation | NR

Abbreviations: CTAD, cyclophosphamide, thalidomide, doxorubicin, dexamethasone; TVAD, thalidomide, vincristine, doxorubicin, dexanmethasone.
<table>
<thead>
<tr>
<th>Study, N</th>
<th>Regimen</th>
<th>Baseline renal impairment</th>
<th>Response/CR + PR rate</th>
<th>Time to event</th>
<th>Safety</th>
<th>Changes in renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM-009/MM-010 phase III studies (66), 341 relapsed or refractory MM</td>
<td>Lenalidomide + dexamethasone</td>
<td>CrCl &lt; 30 mL/min (severe) 5%</td>
<td>50% (6% CR, 38% ≥ VGPR)</td>
<td>TTP: 7.8 mo; PFS: 7.8 mo; OS: 18.4 mo</td>
<td>Grade 3/4 AEs: neutropenia 36%, thrombocytopenia 38%, anemia 44%, thrombotic 6%, pneumonia 25%</td>
<td>72% with moderate/severe impairment had CrCl improvement by ≥ 1 level</td>
</tr>
<tr>
<td>CrCl ≥30–&lt;60 mL/min (moderate) 24%</td>
<td>56% (16% CR, 27% ≥ VGPR)</td>
<td>TTP: 11.1 mo; PFS: 9.5 mo; OS: 29.0 mo</td>
<td>Grade 3/4 AEs: neutropenia 48%, thrombocytopenia 22%, anemia 21%, thrombotic 15%, pneumonia 9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl ≥60 mL/min (mild or no impairment) 71%</td>
<td>64% (16% CR, 34% ≥ VGPR)</td>
<td>TTP: 12.0 mo; PFS: 11.1 mo; OS: 38.9 mo</td>
<td>Grade 3/4 AEs: neutropenia 32%, thrombocytopenia 9%, anemia 5%, thrombotic 13%, pneumonia 7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-center retrospective study (95), 167 relapsed or refractory MM</td>
<td>Lenalidomide + dexamethasone</td>
<td>CrCl &lt; 50 mL/min 20% (n = 33)</td>
<td>49% (31% CR, 12% ≥ VGPR)</td>
<td>TTP: 6.0 mo; OS: trend to shorter OS vs. no impairment</td>
<td>Grade 3/4 AEs: neutropenia 39%, thrombocytopenia 17%, anemia 33%, infections 39%, DVT/PE 0%</td>
<td></td>
</tr>
<tr>
<td>CrCl ≥50–&lt;80 mL/min 24% (n = 40)</td>
<td>60% (10% CR, 30% ≥ VGPR)</td>
<td>TTP: 7.7 mo</td>
<td>Grade 3/4 AEs: neutropenia 39%, thrombocytopenia 16%, anemia 16%, infections 42%, DVT/PE 3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl ≥80 mL/min 56% (n = 94)</td>
<td>67% (15% CR, 28% ≥ VGPR)</td>
<td>TTP: 13.0 mo</td>
<td>Grade 3/4 AEs: neutropenia 20%, thrombocytopenia 14%, anemia 10%, infections 20%, DVT/PE 9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multicenter phase II study (69), 75 relapsed/ refractory MM</td>
<td>Lenalidomide + dexamethasone</td>
<td>CrCl ≤60 mL/min (n = 28)</td>
<td>69% (73% in patients with renal impairment)</td>
<td>TTP: 13 mo</td>
<td>Grade 3/4 AEs (patients with renal impairment): infections 8%, VTE 4.8%</td>
<td></td>
</tr>
<tr>
<td>Single-center analysis, phase II study (98), 72 first-line MM</td>
<td>Lenalidomide + corticosteroids</td>
<td>CrCl ≤40 mL/min 19% (n = 14)</td>
<td>NR</td>
<td>NR</td>
<td>Grade ≤3 neutropenia 43%; febrile neutropenia 19%; DVT/PE 19%</td>
<td></td>
</tr>
<tr>
<td>NR</td>
<td>NR</td>
<td>3/14 had ≥1 CrCl improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued on following page)
Table 5. Activity and safety of lenalidomide-based regimens in patients with multiple myeloma and renal failure (Cont’d)

<table>
<thead>
<tr>
<th>Study, N</th>
<th>Regimen</th>
<th>Baseline renal impairment</th>
<th>Response/CR: PR rate</th>
<th>Time to event</th>
<th>Safety</th>
<th>Changes in renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expanded access program analysis (99), 69 relapsed MM</td>
<td>Elevated SCr (&gt; 1.0 mg/dL in females; &gt; 1.5 mg/dL in males), 33%</td>
<td>Normal SCr, 67% 54%</td>
<td>PFS: 50%, OS: 76%</td>
<td>infection 17%; G-CSF use 66%; grade ≥3 thrombocytopenia and platelet transfusion 52%</td>
<td>Grade ≥3 neutropenia 48%; febrile neutropenia 9%; infection 20%; G-CSF use 57%; grade ≥3 thrombocytopenia and platelet transfusion 17%</td>
<td></td>
</tr>
<tr>
<td>Multicenter retrospective analysis (96), 15 relapsed MM</td>
<td>Lenalidomide + dexamethasone</td>
<td>Dialysis-dependent 60% (29% CR)</td>
<td>PFS: 15 mo; OS: 20 mo</td>
<td>Grade 3/4 neutropenia 40%, infection 40%, thrombocytopenia 7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consecutive patient series (67), 50 relapsed/refractory MM</td>
<td>Lenalidomide + dexamethasone</td>
<td>CrCl &lt; 50 mL/min 24% (n = 12)</td>
<td>60.5% (8% CR, 33% ≥ VGPR)</td>
<td>PFS: 9.0 mo; OS: 16 mo</td>
<td>Grade 3/4 neutropenia 16.7%, thrombocytopenia 8.3%, fatigue 25%, diarrhea 8.3%, infection 16.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl &gt; 50 mL/min 76% (n = 38)</td>
<td>58% (15% CR, 25% ≥ VGPR)</td>
<td></td>
<td>Grade 3/4 neutropenia 31.6%, NA thrombocytopenia 10.5%, fatigue 13.2%, infection 15.8%, DVT 2.6%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PE, pulmonary embolism; VTE, veno-thromboembolism.
12.0 and 11.1 months, respectively), but shorter in the severe-impairment subgroup (median 7.8 months, \( P = 0.006 \)) and severe-impairment (median 29.0 months, \( P = 0.006 \)) subgroups (66). Among 94 evaluable patients with moderate-to-severe renal impairment, 68 (72%) showed an improvement in renal function following lenalidomide–dexamethasone treatment (66). Additionally, a single-center retrospective analysis of relapsed or refractory patients with multiple myeloma treated with lenalidomide–dexamethasone showed response rates of 67%, 60%, and 49%, and median TTP of 13.0, 7.7, and 6.0 months in patients with CrCl \( \geq 80 \), \( \geq 50\text{–}<80 \), and \( < 50 \text{ mL/min} \), respectively (95). A univariate analysis revealed a trend to shorter OS among patients with CrCl \( < 50 \text{ mL/min} \) compared with patients with CrCl \( \geq 80 \text{ mL/min} \); however, in a multivariate analysis this correlation was overcome by other factors, and there were no significant differences in OS between groups (95). Enhanced renal function was also reported in a Spanish retrospective analysis of 15 dialysis-dependent patients with multiple myeloma treated with lenalidomide–dexamethasone, in which 60% achieved a response and one patient became independent of dialysis (96). Further, Ludwig and Zojer (97) reported renal recovery with lenalidomide therapy in a patient who failed to respond to bortezomib, dexamethasone, and doxorubicin, and developed severe renal failure. After 12 months of lenalidomide-based therapy, the patient underwent transplantation, and remained in partial remission with stable renal function and excellent performance status at 2 years from initiation of lenalidomide.

Early studies using full-dose lenalidomide showed that patients with more severe renal impairment experienced higher rates of hematologic toxicities, particularly thrombocytopenia (66, 98, 99), and more frequently required lenalidomide dose reductions compared with patients with mild or no renal impairment. However, following the dose recommendations based upon pharmacokinetic studies, recent analyses have indicated that the use of dose-adjusted lenalidomide in patients with renal impairment is effective and well tolerated (67–69). One retrospective analysis of patients with relapsed/refractory multiple myeloma treated with lenalidomide–dexamethasone suggested that the treatment could overcome the adverse prognosis associated with renal impairment (68). Another analysis showed that dose adjustment of lenalidomide may overcome the elevated safety profile reported in earlier studies (67). In a single-center series of 50 consecutive patients with relapsed/refractory multiple myeloma who received lenalidomide–dexamethasone, 12 had renal impairment (CrCl \( < 50 \text{ mL/min} \)) at baseline (range 13–49 mL/min) and received lenalidomide dosing per the recommendations of Chen and colleagues (64). No statistically significant differences were seen in the rates of neutropenia, thrombocytopenia, infection, or other toxicities between patients with or without renal impairment (67). Response rates, PFS, and OS were also similar between groups, and 5/12 (42%) patients with renal impairment achieved a complete \((n = 3)\) or minimal \((n = 2)\) renal response (67).

Discussion

The available data on novel therapies in patients with multiple myeloma and renal impairment show substantial activity in this difficult-to-treat patient population, with the broadest evidence showing the safety and efficacy of bortezomib-based therapies in this setting. All 3 drugs (bortezomib, thalidomide, and lenalidomide), when used at the recommended reduced doses, represent feasible, effective treatment options for patients with mild- to-moderate renal impairment, although thalidomide should be used with caution due to the lack of evidence from phase III studies. Bortezomib plus high-dose dexamethasone and bortezomib–high-dose dexamethasone-based combinations are appropriate treatment options for patients with multiple myeloma and severe renal impairment. Additional agents independent of renal function that could be considered for such triplet therapy include cyclophosphamide, thalidomide, and doxorubicin. Responses to novel-agent–based therapy have been shown to be rapid, which is an important consideration of therapy for patients with multiple-myeloma–associated renal impairment, and associated rapid reversal of renal impairment, including a decreased need for dialysis, has been reported. Of importance, bortezomib- and IMiD-based treatments have shown superior activity to VAD and dexamethasone (37–44), the previously preferred treatment options for patients with renal impairment, and although no comparative studies have been done specifically in patients with renal impairment, subgroup analyses from phase III studies in this setting support these findings of superior activity (55, 56, 70). Additionally, findings suggest that plasmapheresis for proven cast nephropathy and high cutoff hemodialysis, offering improved light-chain removal, may warrant (re-) consideration as supportive therapy in the context of these improved treatment options for patients with multiple myeloma and renal disease (22, 100–103).

The safety profile of bortezomib seems to be similar regardless of renal impairment. It is generally well tolerated, and no dose reductions are required in the setting of renal impairment, including dialysis dependence. Thalidomide also seems to be generally well tolerated in patients with renal impairment, and limited data suggest that no dose reductions are required, although it has been associated with severe hyperkalemia. Early evidence from studies using dose-adjusted lenalidomide in the setting of renal impairment, based on the dose adjustments recommended according to GFR and dialysis dependence (64, 65), indicated the utility of this approach, and similar safety and efficacy were reported for patients with multiple myeloma and renal impairment compared with standard dosing in
patients with no renal impairment (67). Prospective trials with dose-adjusted lenalidomide are currently ongoing.

Reversal of renal impairment with bortezomib- and IMiD-based treatment in patients with multiple myeloma may occur as a result of these agents’ anti-inflammatory properties, in addition to their antimiyceloma activity (104, 105). For example, the prosurvival NF-κB pathway has been shown to be active in inflammatory pathways in renal disease (106). NF-κB has also been shown to be highly activated in renal tubules in patients with proteinuria (107).

In an in vivo study of glomerulonephritis (108), inhibition of NF-κB with the anti-inflammatory agents gilotoxin and parthenolide was shown to prevent proteinuria and renal lesions, and was suggested as a novel therapeutic approach for immune and inflammatory renal diseases. Therefore, inhibition of NF-κB by bortezomib (104) may be one of the mechanisms associated with improvements in renal function, via reduced inflammation (20). The feasibility and efficacy of bortezomib, a dipeptide boronic acid analog, in this subset of patients with multiple myeloma may thus be an important class effect. However, recently reported data suggest that the newer proteasome inhibitors carfilzomib, a peptide epoxyketone (109), and NPI-0052, a β-lactone compound (110), may be associated with renal effects that are usually seen in the form of transient, manageable creatinine elevation but may occasionally be severe (109–112). These effects are not seen with bortezomib, and this difference may be due to differential nonproteasomal effects of the agents. Emerging preclinical data suggest that bortezomib may have inhibitory effects on serine pro teaseas, including cathepsins A and G, which are not seen with carfilzomib (113), and this may help explain why renal dysfunction is sometimes seen with the peptide epoxyketone and β-lactone proteasome inhibitors. For example, in a pooled safety analysis of results from phase I and II studies, carfilzomib was associated with rates of increased blood creatinine of 8% to 28% (109). Nevertheless, the use of carfilzomib is being studied in an ongoing phase II study in patients with relapsed/refractory multiple myeloma and normal renal function (n = 10); mild (n = 9), moderate (n = 9), or severe (n = 9) impairment; or on hemodialysis (n = 2). Preliminary findings suggest no impact of renal impairment on safety profile or pharmacokinetics, with generally mild and manageable toxicity and encouraging activity [37% ≥ MR (114)]. The final results from this trial will be important to further define the importance of incorporating a proteasome inhibitor early in the treatment of patients with multiple myeloma and renal dysfunction.

Disclosure of Potential Conflicts of Interest

Asher A. Chanana Khan is a consultant to and serves on the advisory boards of Millennium Pharmaceuticals and Celgene Corporation. Jesus San Miguel is a consultant to and serves on the advisory boards of Celgene, Janssen Pharmaceuticals, and Millennium. Sundar Jagannath is a consultant to and serves on the advisory boards of Celgene and Millennium Takeda. Athanasios M. Dimopoulos received honoraria from the Speakers Bureau and is a consultant to and serves on the advisory boards of Ortho-Biotech and Celgene. No other potential conflicts of interest were disclosed.

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