Acute Renal Failure Associated with Lenalidomide Treatment in Multiple Myeloma: A Rare Occurrence?

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Abstract. *Renal failure is a frequent complication of multiple myeloma (MM). Recently, the combination of lenalidomide-dexamethasone has become one of the cornerstone regimens for the treatment of MM. Impairment of renal function exacerbation is a rare, but potential, complication of lenalidomide therapy in plasma cell dyscrasias. We present two patients who developed exacerbation of renal function during their first cycle of therapy with lenalidomide. In the first case, we present a 76-year-old-male with MM and impaired renal function, who declined two weeks after initiation of second-line therapy with lenalidomide. His renal functions improved after discontinuation of lenalidomide and with supportive care. In the second case, we describe a 61-year-old woman who was started on lenalidomide for relapsed MM and admitted to intensive care unit three weeks later due to severe renal failure. Despite intensive supportive care, her renal function deteriorated even more and she died. We conclude that renal failure is an uncommon, but serious, potential complication of lenalidomide therapy in plasma cell dyscrasias, particularly MM. Close monitoring of renal function is clearly recommended during this treatment.*

Kidney injury in patients with multiple myeloma (MM) and other plasma cell dyscrasias is not a rare complication; however, its pathogenesis varies (1). One of the most frequent causes of renal failure relates to the development of high levels of free light chains (FLC) that bind with Tamm-Horsfall proteins (THP) and generate casts that obstruct the renal-tubular flow. Other mechanisms, like increased levels of immunoglobulins, can also induce kidney damage and are associated with proximal tubular toxicity or tubulointerstital nephritis (2, 3).

The lenalidomide-dexamethasone (RD) combination has become one of the cornerstone regimens for MM both for therapy-naïve patients and at relapse (4, 5). Dose adaptation of lenalidomide is required depending on the individual patient's renal function; however, kidney failure is not a contraindication for its use in MM. Several studies have shown that rapid and significant myeloma and renal responses can be achieved using this combination even in patients with pre-existing renal impairment (6-9).

Herein, we report two patients with MM who developed acute kidney injury, probably related to lenalidomide therapy, and highlight this rare adverse effect of the drug.

Case 1

A 76-year-old male was diagnosed with smoldering multiple myeloma (SMM) in July 2013. He had no past medical history and was not taking any medications or supplements prior to diagnosis of SMM. At presentation, he had FLC: Kappa: 19,100 mg/l, Lambda: 12.1 mg/l, ratio: 1,578; creatinine: 1.23 mg/dl, hemoglobin: 14 g/dl and a normal calcium level. Bone marrow biopsy showed 15% plasma cells and there was no evidence of lytic lesions on positron emission tomography–computed tomography (PET-CT). During 5 months of follow-up, his serum creatinine progressively increased reaching 1.9 mg/dl. Treatment with velcade, cyclophosphamide and dexamethazone (VCD) was then initiated. He received 4 cycles of VCD, without any substantial impact on FLC or creatinine levels (Kappa: 14,100, Lambda: 11.2, ratio: 1,250; creatinine: 1.7 mg/dl). Due to the very high FLC level and the possible danger of aggravation of the renal injury, a nephrologist, who did not favor

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performing high cut-off dialysis at that time, was consulted. Second-line therapy with lenalidomide 10 mg/day and dexamethasone 20 mg/once weekly (RD) and aspirin 100 mg/day was then begun. Two weeks after starting this regimen, there was deterioration in his general condition accompanied by severe nausea and weakness. Renal function declined with creatinine increasing to 3.5 gr/dl with development of anemia and hemoglobin decreasing to11.2 g/dl. RD was discontinued and intensive intravenous fluids were given. There was satisfactory improvement in renal function associated with decrease in creatinine, which returned to the previous level of 1.65 mg/dl, while hemoglobin raised slowly to 14.7 g/dl. The patient is now being followed as an outpatient without any further therapy with stable FLC levels (Kappa: 13,500 mg/l) and renal function (creatinine: 1.7 mg/dl) (Figure 1a).

Case 2

A 61-year-old woman had a prior history of breast cancer treated and was cured in 2005, also presenting diabetes mellitus, hypertension, hyperlipidemia, hypothyroidism, congestive heart failure and obesity.

Two years earlier, in December 2013, she was diagnosed with symptomatic IgA Kappa multiple myeloma, International Staging System (ISS)-Stage III, with normal cytogenetic studies. At diagnosis, CT scan revealed signs of osteoporosis and a pathological fracture of L5 lumbar vertebra. Levels of Kappa FLC were mildly elevated (53.2 mg/l) and urinary electrophoresis was also positive for Kappa FLC; bone marrow biopsy revealed extensive involvement by monoclonal Kappa-positive plasma cells. She was then treated with 8 cycles of VCD and achieved a partial response.

In May 2015, after 12 months follow-up, she relapsed with gradual increase in FLC levels and monoclonal protein, leading to combined therapy with lenalidomide, 25 mg per day, and dexamethasone, 20 mg weekly, as well as anti-thrombotic prophylaxis with aspirin, 100 mg once daily. Before starting lenalidomide, her creatinine level was mildly elevated (1.5 mg/dl) and the calculated creatinine clearance test (CCT), using the Cockcroft-Gault Equation was 62.2 ml/min. Three weeks later, she was admitted to hospital with extreme weakness, confusion and anuria and her medication list then included lenalidomide, dexamethasone, aspirin, metformin, calcium, iron and folic acid supplements, as well as duloxetine. Her laboratory tests revealed low hemoglobin of 6.9 g/dl, mild thrombocytopenia (110×10^9/l), mild leucopenia (3.7×10^9/l) and severe renal failure with creatinine of 10.1 mg/dl, urea of 212 mg/dl, hypocalcemia of 6.6 mg/dl, mild hypoalbuminemia of 3.31 g/dl, hyperkalemia of 6.2 meq/l and high anion gap metabolic acidosis. Electrocardiography revealed picked T waves and QT prolongation. She was then admitted to the intensive care unit and started on dialysis, together with intravenous antibiotic coverage with ceftriaxone, although there were no signs of infection and both blood and urinary cultures were negative. Lenalidomide was stopped but, despite intensive supportive therapy, she developed severe hospital-acquired *E. coli* sepsis, nosocomial pneumonia and pulmonary edema; she died after twelve days of hospitalization (Figure 1).

Discussion

Lenalidomide is a second-generation immunomodulatory drug (IMiD) currently used for the treatment of both relapsed and refractory myeloma and newly-diagnosed multiple myeloma (NDMM) patients (10). Despite primary excretion by the kidney, dose adjusted lenalidomide-based treatment is a highly effective therapeutic option for patients with MM with impaired renal function (11). Dimopoulos *et al*. assessed the impact of renal impairment on outcomes after lenalidomide and dexamethasone treatment in patients with NDMM who had renal impairment and were ineligible for stem cell transplant (SCT). They showed progression-free survival (PFS) benefit for continuous lenalidomide and dexamethasone compared to melphalan, prednisone and thalidomide (MPT) in all patient subgroups, except for those with severe renal insufficiency. Overall survival (OS) improvements were seen in patients who either had no renal impairment or only mild kidney failure (7).

In 2010, Ludwig and Zojer reported the case study of a patient with bortezomib-resistant MM who had renal function recovery after lenalidomide (6). Furthermore, Oehrlin collected data on 26 patients treated at four different German centers and demonstrated improved renal function in a substantial proportion of cases with relapsed and/or refractory MM with impaired renal function, after treatment with lenalidomide/dexamethasone-based regimens (11). Similar observations were also reported by Tosi *et al*. who showed complete and partial renal responses in 4 and 3 patients, respectively, in a cohort of 20 consecutive patients with relapsed or refractory MM with moderate to severe renal failure who received lenalidomide-based regimens (12). However, this does not appear to be the general experience when treating patients with Amyloid Light-chain (AL) amyloidosis and, although IMiDs represent one of the backbone therapies for this type of plasma cell dyscrasia, some studies have reported worsening of kidney function during lenalidomide treatment for AL amyloidosis (13).

In contrast to the above experience in amyloidosis, "lenalidomide-induced renal failure" has rarely been reported in MM. After an extensive literature search, we were only able to identify one case report describing this complication in MM: In 2010, Lipson and co-workers reported a single case of acute interstitial nephritis that seemed to be related to

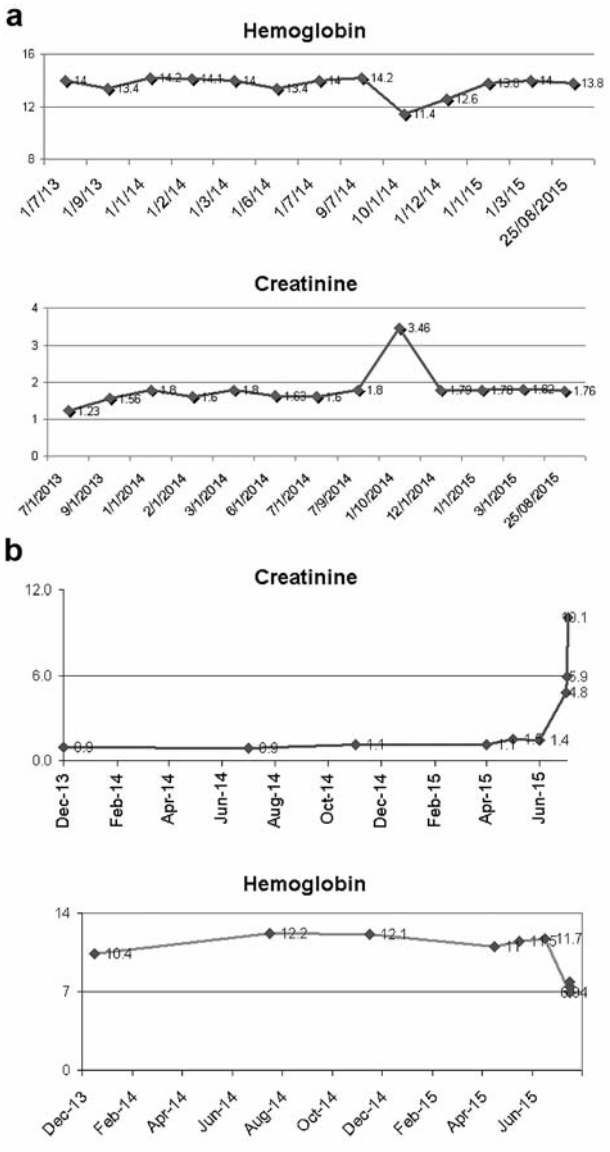

Figure 1. *Presentation of creatinine and hemoglobin values with respect to time and treatment given with lenalidomide in case 1(1a) and 2(1b). Arrow indicates the beginning of treatment with lenalidomide.*

lenalidomide (14). The authors suggested that a combination of factors may have to be present before renal toxicity develops, including predisposition to interstitial nephritis, underlying kidney damage due to myeloma proteins, concomitant use of bisphosphonates, as well as some non-steroidal anti-inflammatory drug use (14).

Both patients described herein were on aspirin for thromboprophylaxis, while receiving lenalidomide. In this respect, it is of interest to note that a recent prospective randomized study showed a benefit for low-molecular-weight heparin (LMWH) in reducing lenalidomide-associated thromboembolic complications, but still continued to support the use of aspirin as an effective and less-expensive alternative in patients with low thromboembolic risk (15-16). Acute renal failure can indeed be a rare adverse side-effect of high doses of aspirin; however low dose aspirin thromboprophylaxis is not generally associated with acute renal failure. In fact, we only found a single study by Segal *et al*. who concluded that short-term low-dose aspirin therapy may have a significant adverse effect on renal function in elderly patients (17). In this regard, we cannot exclude with complete certainty that aspirin can be an aggravating factor in the decrease in kidney function in our cases.

Another important point to highlight here is the importance of performing kidney biopsy in patients with MM who also have renal failure. In the second case, we describe a patient who also had other co-morbidities, including diabetes mellitus and hypertension, both potential causes of chronic renal failure on their own. However, because of her severe multi-organ deterioration, we did not perform a renal biopsy. In this respect, it should be noted that most patients with MM are elderly and many may have age-related co-morbidities, such as hypertension and diabetes, which may contribute to declining kidney function (18). In these particular patients, renal biopsy may indeed be crucial in better understanding the etiology of the kidney disease (19).

In the Mayo clinic experience, which summarized results of 190 kidney biopsies performed in patients with MM, Nasr and colleagues demonstrated a wider spectrum of renal lesions than was previously appreciated and stressed the important additional information that could be obtained from performing this procedure (19). On the other hand, it should always be appreciated that renal biopsy is an invasive procedure with some, occasionally, well-recognized serious complications, especially in patients with plasma cell dyscrasias (20). Accordingly, the decision to perform a biopsy or not in MM should always be very cautiously considered and based on the individual case.

In conclusion, renal failure is an uncommon, but serious, potential complication of lenalidomide therapy in plasma cell dyscrasias in general, particularly in MM. In both cases reported here, renal function was aggravated during the first cycle of therapy with the drug employed. Accordingly, close monitoring of kidney function is clearly recommended during this period of treatment.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

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