Short Term Renal Outcome of Bortezomib Based Therapy in Patients with Multiple Myeloma Requiring Dialysis

Sir,

Renal failure is a common and severe complication of multiple myeloma (MM). Renal failure requiring dialysis is associated with significant mortality and morbidity. Treatment is challenging and includes supportive care and rapid institution of systemic antimyeloma therapy. Recent guidelines recommend Bortezomib-based regimens as the cornerstone of the management of myeloma-related renal impairment.[1] However, there is a scarcity of data regarding the outcome of these regimes in MM patients with severe renal impairment requiring dialysis.

This prospective observational study included 32 newly diagnosed patients of MM presenting with renal failure requiring dialysis between July 2015 and June 2017. In addition to supportive treatment, all patients received four cycles of bortezomib 1.3 mg/m^2 and dexamethasone 40 mg intravenously given weekly (each cycle consists of 4 weeks). Patients were evaluated to rule out side-effects or contraindication of bortezomib therapy, which included grade 2 or greater peripheral neuropathy, platelets count <50 000/μL, absolute neutrophil count <1000/μL, transaminases elevated two or more times, and presence of active infections. Hemodialysis was provided by regular dialyzer. Renal response was categorized according to the International Myeloma Working Group (IMWG) renal response criteria.[2] Estimated Glomerular Filtration Rate (eGFR) was calculated by Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula.

Characteristics of the study population are presented in Table 1. Two patients (6.2%) died, one due to cerebrovascular accident and the other due to acute myocardial infarction. Twenty-five (78.1%) patients had renal response, eight (25.0%) had complete renal response (CR), 13 (40.6%) had partial renal response (PR), four (12.5%) had minor renal response (MR), and five (15.6%) had no renal response. All five patients who had no renal response remained dialysis dependent even after four cycles (16 doses of bortezomib) of induction therapy. All five patients had myeloma cast nephropathy. The mean eGFR (ml/min/1.73m^2) of those who achieved CR was 67.1 ± 7.3 while those with PR and MR were 36.5 ± 7.6 and 21.7 ± 6.7, respectively. The median time to dialysis independence was 37 (IQR: 22.7–74.5) days. Patients with light chain deposition disease (LCDD) required significantly lesser time for dialysis independence compared to those with myeloma cast nephropathy (MCN) [15.5 (IQR: 9.7–31.0) vs. 40 (IQR: 23.2–98.5) days $P = 0.005$)] [Figure 1].

Most common side-effects observed were nausea (53.1%), fatigue (37.5%), thrombocytopenia (28.1%), and peripheral neuropathy (12.5%). None had platelets counts <50000/μL requiring discontinuation of therapy. One patient who had grade II neuropathy required dose reduction of bortezomib. Herpes zoster (12.5%), diarrhoea (12.5%), and pneumonia (9.4%) were common infectious complications related to the therapy.

Our outcomes are comparable to those by Dimopoulos *et al*. who reported at least MR in 65% of the patients. Forty-eight percent of their patients who required dialysis became dialysis-independent.[3] Patients

Table 1: Demographic and clinical characteristics of the study population

Characteristics	*N*=32
Age (years)	59.0±9.7
Male:female	21:11
Serumcreatinine (mg/dl)	11.1±4.7
Estimated glomerular filtration rate (ml/min/1.73 m^2)	5.2±2.7
Serum M band (gm/dl)	3.9±1.9
Involved light chain (mg/l)	3761.2±2369.3
Hemoglobin (g/dl)	7.3±1.4
Platelet count (10^6 per ml)	1.7±0.7
Percentage of plasma cells in bone marrow	22.8±17.2
S. Protein (g/dl)	9.4±2.6
S. Albumin (g/dl)	3.1±0.6
24-h urinary protein (g)	1.1±0.7
Serum calcium (mg/dl)	8.9±2.0
Serum uric acid (mg/dl)	9.9±3.7
Renal histology	
Myeloma cast nephropathy	25 (78.1%)
Light chain deposition disease	6 (18.7%)
Myeloma cast nephropathy + glomerular amyloid deposition	1 (3.1%)
Interstitial fibrosis and tubular atrophy	24.3±11.8

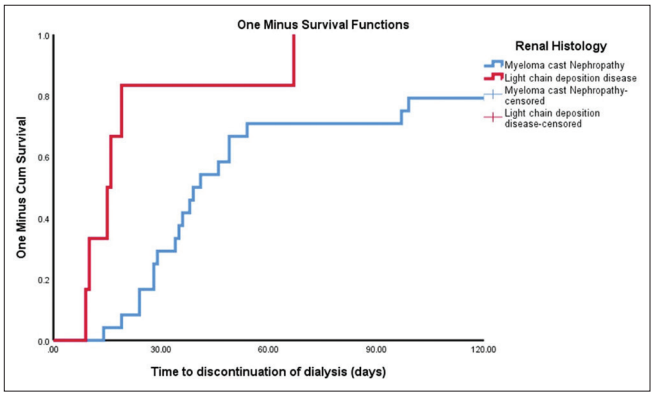

Figure 1: Time to dialysis discontinuation in patients with Myeloma cast nephropathy and light chain deposition diseases

with LCDD have rapid renal recovery and became dialysis-independent early as compared with those with MCN. This might be due to low tumor burden in LCDD compared to MCN, as well as less tubule-interstitial damage than in MCN.

Two-drug regimen used in our study had fewer side-effects compared with that of the three-drug regimen, particularly in the setting of renal failure.[4,5] Further, a weekly regimen of bortezomib instead of the twice weekly regimen, (on days 1, 4, 8, and 11 of a 21-day cycle) might have further reduced the incidence of adverse effects in our study. The biweekly regimen has been associated with a high risk of grade 3 or higher peripheral neuropathy requiring discontinuation of therapy.[5] Most of the side-effects in our patients were manageable and did not require discontinuation of therapy. Two deaths in our study seem to be due to an unrelated cause.

Our study intends to describe the short-term outcome of MM patients with severe renal impairment. Long-term follow-up might present a different picture with regard to dialysis requirement. We did not evaluate myeloma response, which was one of the other major limitations of the study. Although the regimen used had shown a good response with few adverse effects, the long-term outcome with this regimen is not known. Current IMWG guidelines recommend a biweekly dose of bortezomib and favor the addition of a third drug to the regimen.[1] Further studies will be needed to compare the adverse effects of the different regimens.

To conclude, bortezomib plus dexamethasone regimen has a good renal response with manageable adverse effects. Patients with LCDD show rapid renal recovery compared to those with MCN.

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Conflicts of interest

There are no conflicts of interest.

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