EFFICACY AND SAFETY OF BORTEZOMIB BASED REGIMEN IN MULTIPLE MYELOMA WITH CAST NEPHROPATHY

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ABSTRACT

AIM

To assess the efficacy and safety of bortezomib based regimen and plasma exchange in patients with cast nephropathy, the clinical profile of patients with Multiple Myeloma and renal involvement, to assess the factors affecting the renal outcome.

MATERIALS AND METHODS

This prospective observational study done in Department of Nephrology, Medical College, Kozhikode enrolled patients who satisfied Inclusion criteria from October 2013 to September 2015. Clinical, demographic and biochemical profile was studied. Serum free light chain levels were estimated. Renal biopsy and bone marrow biopsy were done. Study patients were managed with plasmapheresis and bortezomib based induction for a period of 16 weeks. Renal and haematologic response was noted.

RESULTS

18 patients satisfied the inclusion criteria and included for analysis. Mean Hb was 7.31 ± 1.25 g/dL. Mean eGFR at presentation was 6.19±2.61 mL/min/1.73 m2. 6 patients kappa myeloma, 12 had lambda (66.67%). Renal biopsy showed cast nephropathy in all patients (100%) with varying degrees of tubular atrophy. 15 patients had dialysis requiring renal failure (83.33%). Following treatment, 8 patients had complete renal response (44.44%), 7 patients had partial renal response (38.88%). All patients achieved haematologic remission. Mean eGFR at end of therapy was 56.79 mL/min/1.73 m2, which was statistically significant. The FLC reduction at the end of 16 weeks was statistically significant. ($p < 0.01$). 5 patients developed peripheral neuropathy, 2 patients had cytopenia, 5 patients had non-life threatening infection episodes.

DISCUSSION

Bortezomib based regimen combined with plasma exchange sessions upfront demonstrated a high haematologic response and renal response in the study population. Our study group had a predominant lambda subtype myeloma in contrast to other studies. There is emerging data regarding the use of renal biopsy as a prognostic tool in cast nephropathy. In our study group, tubular atrophy predicted renal response.

CONCLUSION

Bortezomib based regimens with plasma exchange is effective in inducing haematologic and renal response in Cast nephropathy by a prompt reduction in the free light chain load with occurrence of peripheral neuropathy as a common side effect with no life threatening infective episodes.

KEYWORDS

Bortezomib, Plasma Exchange, Cast Nephropathy.

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INTRODUCTION: Multiple Myeloma is a plasma cell dyscrasia that accounts for almost 10% of haematological malignancies.[1,2] The annual incidence of Multiple Myeloma is 4.3 per 100,000 people.[3,4] The incidence ranges from 1 per 100,000 for people who are aged 40 to 49 years of age to 49 per 100,000 population in those who are above 80 years of age.

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Renal disease in myeloma often presents as renal insufficiency and proteinuria. Occasionally, myeloma patients can present with renal tubular dysfunction including defects in concentration and acidification or rarely as Fanconi syndrome.[5] Renal insufficiency (S. Creatinine > 1.5 mg/dL) is found at presentation in almost 50% of patients with myeloma.

The spectrum of renal lesions seen in myeloma includes myeloma kidney or cast nephropathy, light chain amyloidosis, monoclonal immunoglobulin deposition disease; less frequently cryoglobulinaemic glomerulonephritis and proliferative glomerulonephritis.[6]

The autopsy studies in patients with multiple myeloma found cast nephropathy in 30–50 % patients, light chain

deposition disease in 2-3%, amyloidosis in 4-5% cases. In one study, acute tubular necrosis was seen in 34% of cases.[7] In native kidney biopsy studies of patients with myeloma and renal disease, 40-63% had cast nephropathy, 19-26% had light chain deposition disease, 7-30% had amyloidosis and <1% had cryoglobulinaemic renal disease.[8]

The presence of monoclonal immunoglobulin light chains is essential for the pathogenesis of myeloma kidney. In order to be pathogenic, the light chains must be free from intact immunoglobulin to enable filtration at the glomerulus. When the FLCs enter proximal tubules in high concentrations, the absorptive capacity of the multi ligand endocytic receptor complex is overwhelmed and the FLCs pass through the tubules into the urine. Two sites of injury predominate in myeloma kidney. First, excessive endocytosis of FLCs in the proximal tubule creates a cascade of inflammatory pathways which result in apoptotic and profibrotic transition. Second, the distal tubules are the sites where FLCs encounter and bind to Tamm-Horsfall protein with differing degrees of affinity resulting in precipitation. The waxy casts are formed which obstruct tubular flow, which results in interstitial leak of fluid and subsequent inflammatory reaction.

If it remains untreated, it can cause rapid progression of interstitial injury leading to fibrosis and irreversible renal failure.

A potential treatment strategy to enable early renal recovery alone can improve the patient survival. Essential for such a renal recovery is a rapid reduction in serum immunoglobulin free light chain concentration.

In 2008, a study of bortezomib based regimens in patients with multiple myeloma and renal failure showed that a majority (87.5%) who recovered renal function had at least a partial response.[9] In a retrospective study of plasma exchange as a method to reduce rapidly FLCs, a reduction in FLCs >50% was associated with renal recovery in patients with biopsy proven cast nephropathy.[10]

Patients who achieved a sustained reduction of FLCs within 21 days were significantly more likely to recover their renal function than those who did not achieve a reduction.[11] International Myeloma Working Group (IMWG) has published a consensus statement on management of myeloma patients with renal impairment.[12] The working group recommends that bortezomib based regimen should be used as first option in patients with renal impairment related to myeloma. The combination of bortezomib with thalidomide and dexamethasone is also offered as an option.

AIMS AND OBJECTIVES:

1. To assess the efficacy and safety of Bortezomib Based Regimens and Plasma exchange in patients with Multiple Myeloma and Cast Nephropathy.
2. To study the clinical and demographic profile of patients presenting with renal involvement and Multiple Myeloma.
3. To assess the factors that influence the renal outcome of these patients.

MATERIALS AND METHODS: This prospective observational study was conducted in Department of Nephrology during the study period from October 2013 to September 2015.

Study Population: Patients who were admitted in Nephrology ward/ICU with renal failure who were diagnosed with Multiple Myeloma satisfying the inclusion criteria during the study period were enrolled into the study.

Inclusion Criteria:

1. Patients diagnosed with Multiple Myeloma presenting with renal failure, not improving with routine conservative measures.
2. Patients with Multiple Myeloma who develop relapse with renal involvement, not improving with routine conservative measures.

Exclusion Criteria:

1. Patients who are diagnosed de novo with Multiple Myeloma or Patients already diagnosed with Multiple Myeloma who develop a relapse with renal involvement, whose renal impairment improves with conservative measures.
2. Patients who are diagnosed with Multiple Myeloma who develop renal involvement secondary to underlying unrelated causes will be excluded from the study.

Sample Size: 25 patients.

METHODOLOGY: Patients who were admitted in Nephrology ward/ICU who satisfied the inclusion criteria were enrolled in the study. The clinical, biochemical and demographic profile of these patients were noted. The duration of the symptomatology was also noted down. Patients who had persistent renal derangement in spite the initial stabilisation and correction of reversible causes like dehydration, hypercalcaemia, and treatment of any underlying infection were further evaluated.

Baseline bone marrow evaluation, skeletal survey, serum immunofixation electrophoresis were done. The baseline β2 microglobulin estimation was done. The functional capacity of the patient was also noted down using the Karnofsky score/ECOG Grade. The free light chain estimation and the typing of light chain were also done. These patients underwent renal biopsy to ascertain the nature of renal involvement.

The diagnosis of Multiple Myeloma was done using the following IMWG (International Myeloma Working Group) Guidelines.

Diagnosis	Criteria
Symptomatic Myeloma (All 3 required)	✓ Monoclonal plasma cells in bone marrow >10% and/or presence of biopsy proven plasmacytoma

	✓ Monoclonal protein present in serum and/or urine ✓ Myeloma related organ dysfunction (≥1) (C) Hypercalcaemia (>10.5 mg/dL); (R) Renal insufficiency; (A) Anaemia; (B) Lytic bone lesions/osteoporosis
Smoldering/ Indolent Myeloma	✓ Monoclonal protein present in serum or urine (>3 g/dL or higher) ✓ Monoclonal plasma cells >10 % present in marrow ✓ No evidence of end organ damage attributable to the clonal plasma cell disorder

ECOG performance status is graded as below:

Grade	ECOG
0	Fully active
1	Ambulatory and able to carry out work of a sedentary nature.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about >50% waking hours
3	Capable of only limited self-care. Confined to bed or chair more than 50% waking hours.
4	Completely disabled. Cannot carry on self-care. Confined to bed or wheelchair.
5	Dead

Once the diagnosis of Multiple Myeloma is confirmed, if active myeloma with presence of end organ damage due to the malignant clone, IMWG recommends bortezomib based regimen as the first line treatment more so if there is renal involvement. IMWG does not recommend treatment for a smoldering myeloma, but considers these patients at high risk for progression to symptomatic disease.

Based on the IMWG consensus statement, study patients were started on bortezomib based regimen which included: (1) Inj. Bortezomib 1.3 mg/m2 i.v./s.c. weekly dose, (2) Tab. Thalidomide 100 mg HS (3) Tab. Dexamethasone 40 mg p.o. weekly once., after consultation with Haematologist. Depending on the renal indication, these patients were supported with sessions of Haemodialysis as and when need arose.

If free light chain levels > 500 mg/L, our patients were subjected to 5-7 sessions of plasma exchange. These patients were kept under out-patient based follow-up after the initial sessions of Haemodialysis and plasma exchange during which the patients were hospitalised.

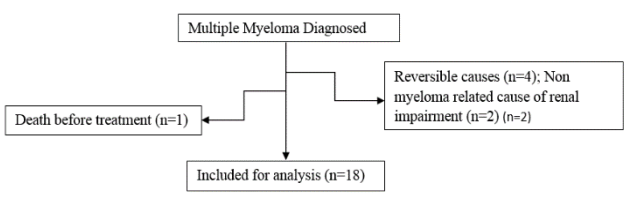
The induction regimen was continued for 16 weeks with a break of 1 week after every four weekly bortezomib doses. The haematological and renal parameters were monitored every 2 weeks during the induction regimen. The occurrence of any side effect was also noted down. After the induction regimen is completed, these patients were subjected to repeat Bone marrow aspiration and biopsy to assess the haematological response. The eGFR at the end of induction was also calculated. A repeat renal biopsy was done in all patients who consented to the procedure. The renal response was categorised as per IMWG criteria.

Renal Response	Baseline eGFR	Best eGFR
Complete	< 50 mL/min/1.73 m2	>60 mL/min/1.73 m2
Partial	<15 mL/min/1.73 m2	30-59 mL/min/1.73 m2
Minimal	<15 mL/min/1.73 m2	15-29 mL/min/1.73 m2

Based on the haematological response, these patients were put on maintenance treatment with Tab. Thalidomide 100 mg HS if they were in remission as per the advice of Haematologist. In case of refractory disease, 2nd line regimens were initiated.

Ethical Clearance: All the patients were informed of the study purpose and were given the right to quit at any time without having to give reasons. All the patients' information was dealt with confidentiality. The study protocol was submitted to Institute Research Committee and after approval was cleared by Institute Ethics Committee.

RESULTS: 25 patients were admitted in Nephrology with Multiple Myeloma and renal impairment during the study period. Of these patients, 4 patients had Acute Interstitial Nephritis secondary to NSAID intake, which responded to conservative measures including stopping the drug and hydration. 2 patients had longstanding hypertension with renal biopsy suggestive of hypertensive nephrosclerosis. 1 patient expired before the induction regimen was initiated. Excluding these patients, 18 patients satisfying the inclusion criteria were analysed.



Baseline Characteristics:

Demographic Characteristics: The study population included 5 males (27.8%) and 13 females (72.2%) (Table 1). The mean age was 57.89±6.26 years. Out of 18 patients, 15 patients were diagnosed with Multiple Myeloma de novo (83%) and 3 patients who were on maintenance regimen had relapsed with renal impairment (17%) (Figure 1).

Most of the patients (n=15) had body aches (83%). 2 patients had presented with gastrointestinal symptoms, one patient with persistent dyspepsia, which entailed a detailed gastroenterology evaluation. One patient had severe

constipation, possible secondary to severe hypercalcaemia. The symptom duration was less than 3 months in 8 patients (44.6%), and lasting for more than 6 months in 5 patients (27.7%) (Table 2). Of the 18 patients, 4 patients were also detected to have other comorbidities, 3 of them had hypertension and one was diabetic.

Biochemical and Haematologic Characteristics: All the patients in the study group had significant anaemia. The mean Hb level was 7.31±1.25 g/dL. The other cell lines were not affected except in 1 patient who had significant thrombocytopenia at presentation. The mean ESR was 121.17±22.62 mm/hr. The peripheral smear study was normal except in one patient who had plasma cell leukaemia (5.55%).

All the patients in study group had presented with AKI stage III (AKIN). The mean eGFR at presentation was 6.19±2.61 mL/min/1.73 m2. The mean Serum Creatinine was 7.95±2.07 mg/dL. 4 patients had hyperkalaemia (>5.5 mEq/L) at presentation (22.2%). 14 patients had significant hypercalcaemia (77.78%). 3 patients had severe hypercalcaemia (16.67%). The mean serum calcium was 12.25±1.6 mg/dL. The mean uric acid level was 10.67±1.57 mg/dL.

All the patients had A:G reversal. All patients showed multiple lytic lesions on skeletal survey. The bone marrow biopsy of the study population showed > 50% plasmacytosis in 6 patients (33.3%). 4 patients had bone marrow plasmacytosis between 10-20%; 8 patients had bone marrow plasmacytosis from 20-50% (Table 4).

The mean serum albumin was 3.28±0.35 g/dL. The mean β2 microglobulin level was 19990.59±10878 µg/L. All our study patients were staged as stage III myeloma as per International Staging System. The baseline performance status of the study population was graded as per ECOG grading system. 9 patients (50%) had a good functional index (grade 0-1); 2 patients were grouped in grade 4. (Table 5).

Light Chain Characteristics: Out of the total of 18 patients in the study population, 6 patients had elevated light chain of κ subtype (33.33%); remaining 12 patients had elevated λ subtype (66.67%). Serum immune fixation electrophoresis was uniformly positive in all patients. (Table 6)

Renal Biopsy Characteristics: All the 18 patients in the study group underwent renal biopsy to ascertain the pathological diagnosis. All the patients tolerated the procedure well with no post biopsy complications.

All the patients had evidence of cast nephropathy in renal biopsy (100%): There was evidence of fractured casts in many tubules with surrounding dense inflammatory infiltrate. There was varying amount of tubular atrophy and interstitial fibrosis in the study population, severe (>50% involvement) in 4 patients (22.22%), moderate (25-50% involvement) in 2 patients (11.11%) and mild in 12 patients (66.67%).

Response to Bortezomib Based Regimen: 15 patients in the study population presented with Dialysis-requiring severe renal failure (83.3%). All the patients were weaned off Haemodialysis after 3 sessions (n=8) or 4 sessions (n=5) with 2 patients requiring a maximum of 5 sessions. The patients underwent a minimum of 5 to a maximum of 7 plasma exchange sessions.

8 patients attained complete renal response as defined by IMWG criteria (44.44%), followed by 7 patients who had a partial renal response (38.89%). 3 patients had minimal renal response (16.67%) (Table 7). All the patients had achieved complete haematologic remission (100%). The free light chain load assessed at the end of 16 weeks regimen also showed a statistically significant reduction ($p<0.01$) (Table 8).

The mean serum creatinine and mean eGFR during follow-up are tabulated in table below and plotted in graph. It showed a steady improving trend and when analysed by repeated ANOVA, the trend was statistically significant ($p<0.001$) (Table 9).

Repeat renal biopsy was performed in 10 patients who had consented for the procedure. Casts were dramatically absent and the inflammation was substantially reduced. Significant tubular atrophy and interstitial fibrosis was present in 3 patients (30%), all of them who had a minimal or partial renal response. Those patients who had a complete renal response (n=6) and one patient with a partial renal response who underwent renal biopsy had minimal to mild tubular atrophy and interstitial fibrosis.

Side Effect Profile: Of the study population, 5 patients developed peripheral neuropathy (27.77%). None of the patients developed severe debilitating form of peripheral neuropathy. Of the 5 patients, 3 of them had mild neuropathy with pins and needle sensation and paraesthesias; but no weakness.

1 patient developed neutropenia during the regimen, which spontaneously improved. The bortezomib dose was temporarily withheld for 2 weeks. 1 patient had thrombocytopenia which improved with the regimen. None of our patients developed thromboembolic manifestations as 2 of them were on low dose antiplatelets.

Infective complications were rare during the induction regimen. 3 patients had oral candidiasis (16.67%) which responded readily to antifungals and did not warrant discontinuation of the induction regimen. 2 patients had developed herpes zoster (11.11%) after completion of induction regimen. No life threatening infections were documented during the induction phase.

1 patient developed an episode of supraventricular tachycardia during the maintenance phase, which responded to beta blockers. No cardiac events were reported during the induction phase.

Mortality Statistics: After the induction phase, repeat bone marrow evaluation was done which showed a complete haematologic response in all the patients. They were put on maintenance regimen with thalidomide 100 mg daily. They

were followed up for next 12 months. 3 patients died during the follow-up; the causes being acute coronary syndrome in a patient, perforation peritonitis and pneumonia sepsis in the other two patients. The 1-year survival was 83.33%.

DISCUSSION: Bortezomib is the first in class proteasome inhibitor that has been approved for treatment of patients with Multiple Myeloma. A boronic acid dipeptide, bortezomib is highly selective reversible inhibitor of the 26S proteasome. Through a number of mechanisms including blocking the activation of nuclear factor κB, bortezomib promotes myeloma cell apoptosis and also sensitises these cells to other chemotherapeutic agents.[13] With a serum half-life that is independent of the renal function, this agent attracted attention for use in patients with renal impairment.[14]

Reversal of renal impairment has been observed in several studies involving patients with renal failure secondary to involvement by multiple myeloma. Some patients became independent of dialysis after treatment with bortezomib.[15]

Data from phase III VISTA study, comparing Melphalan and prednisolone with or without Bortezomib in patients ineligible for haematopoietic stem cell transplantation indicated that the rate of renal recovery was higher when bortezomib (44% of patients with baseline GFR < 50 mL/min improved their GFR to > 60 mL/min) was used than when only Melphalan and Prednisolone were used (34% of patients improved their GFR to > 60 mL/min). This difference was more pronounced in those patients with eGFR < 30 mL/min/1.73 m2.[16]

In our study as well, bortezomib based regimen was effective in producing a complete haematological response in all the patients, irrespective of whether the disease was de novo diagnosed or was a relapsed disease. All the relapsed patients in our study group were previously treated with non bortezomib containing regimens which may be a factor responsible for the prompt response to bortezomib now. Our response rates are in accordance with various trials which report a response rate using bortezomib as upfront therapy as 80-90%.[17]

In accordance with IMWG criteria, 15 patients (83.33%) attained a favourable renal response with the induction regimen either a complete or a partial response. 8 patients (44.44%) achieved a complete renal response which was defined as a baseline GFR < 50 mL/min/1.73 m2 to end of therapy GFR > 60 mL/min/1.73 m2. 3 patients had a minimal renal response, which attains importance in the fact that they had dialysis requiring renal impairment at presentation from which they were weaned off.

The renal response rates which we attained was in line with rates reported by Brian. N. Brunette, Nelson Leung, Vincent Rajkumar et al in their patients in Mayo clinic, where they achieved a renal response of 86% (43% complete renal response; 43% partial renal response).[18] The achievement of renal response correlated with achievement of haematological response in our study population as with other study groups. The mean eGFR at presentation was 6.19±2.61 mL/min/1.73 m2, which improved to 56.79±5.46 mL/min/1.73 m2, which was significant statistically ($p<0.01$).

The light chain more frequently implicated in pathogenesis of cast nephropathy was κ light chain. In contrast, our study had more of λ subtype (66.67%). The light chain subtyping also is proposed to play a role in prognostication of the tumour and survival. λ light chain secreting myeloma was noted to have worse survival as compared with κ secreting myeloma.[19]

The Free light chain response in our study population was also statistically significant ($p<0.01$). In a study[20] the achieved FLC reduction significantly predicted the renal recovery. A persistent reduction in FLCs by 60% by day 21 was associated with renal recovery in 80% of the population. Patient survival strongly associated with renal recovery. The median survival was 42.7 months among those who recovered function compared with 7.8 months among those who did not.

Our study design did not include an assessment of FLC after initiation of bortezomib based regimen and at the end of plasma exchange sessions, which would have given an estimate of the promptness of response induced by this regimen. Our study population had a FLC response assessment done at the end of 16 weeks, which showed a statistically significant reduction ($p<0.01$).

There are conflicting reports regarding the role of plasmapheresis in management of cast nephropathy. A retrospective study [21] suggested that plasma exchange may offer some benefit in preventing initiation of dialysis, as well as preventing acute renal failure progressing to Chronic Kidney Disease. However, its efficacy has been established only in patients with hyperviscosity syndrome. Two small, prospective studies demonstrated improvement in renal function and patient survival after plasmapheresis,[22,23] however findings from a recent large prospective controlled trial failed to show any benefit.[24]

In the absence of any conclusive evidence, our study population underwent sessions of plasma exchange, the number of sessions varying from four to seven with a median of 6 plasma exchanges over the period of initial 2 weeks. Our study was not designed to assess the benefit of plasma exchange in isolation.

The role of renal biopsy in prognostication of cast nephropathy is unclear. Recent studies have analysed this objective and have come up with positive results. In a study by Ecotiere L et al [25] the prognostic value of kidney biopsy in myeloma cast nephropathy was studied. The presence of numerous casts and diffuse tubular atrophy was associated with poor renal outcome. The factors which were significantly associated with an inferior renal outcome in that study were (1) Baseline median eGFR, (2) AKIN stage 3, (3) Haematologic response rate, (4) FLC reduction at day 21, (5) median number of casts and the extent of tubular atrophy.

In our study, all 18 patients had a baseline renal biopsy which confirmed cast nephropathy in all our patients. In those patients who had a complete renal response, 7/8 (87.5%) had mild tubular atrophy (< 25% involvement), in

contrast to patients who had a partial and minimal renal response in which, 4/7 (57.14%) patients and 1/3 (33%) patients had severe tubular atrophy (>50% involvement) respectively.

10 patients consented to a repeat renal biopsy which revealed disappearance of casts and dramatically reduced inflammation. Mild tubular atrophy (<25% involvement) was found in all patients who had a complete renal response, whereas moderate tubular atrophy (25-50% involvement) was present in 50% and 100% of those with partial and minimal renal response. (Table 11).

LIMITATIONS: The main limitation of our study was limited sample size.

Though the reversible causes like dehydration, hypercalcaemia were excluded and renal diagnosis confirmed by means of renal biopsy, the renal response observed in this study population wholly attributable to plasma exchange and bortezomib based regimens is to be ascertained, which would require a larger cohort of patients.

All the patients in study population went into complete haematologic remission, hence better the renal outcome. The efficacy of this regimen in recalcitrant cases needs further investigation.

CONCLUSION: Bortezomib based regimen and plasma exchange upfront was effective in producing a complete haematologic response and favourable renal response in majority of patients. The most common side effect was non-debilitating peripheral neuropathy followed by non-life threatening infections. Renal biopsy may have a prognostic role in patients with cast nephropathy apart from helping in confirmation of pathological diagnosis.

Sex	Number	Percent
Male	5	27.8%
Female	13	72.2%
Total	**18**	**100%**

Table 1: Sex Distribution of Study Population

Duration	Number	%
< 3 months	8	44.6
3 – 6 months	5	27.7
> 6 months	5	27.7
Total	**18**	**100**

Table 2: Duration of Symptoms in Study Population

Parameters	Mean
Mean Hb level	7.31±1.25 g/dL
Mean Platelet Count at presentation	2.36 lakhs ± 1.1 lakhs/ mm^3
Mean ESR at diagnosis	121±22 mm/hr.
Mean eGFR at presentation	6.19±2.61 mL/min/1.73 m^2
Mean Serum Calcium at presentation	12.25±1.59 mg/dL
Mean Serum Uric Acid at presentation	10.67±1.57 mg/dL
Mean Serum Albumin at presentation	3.28±0.35 g/dL
Mean serum β 2 microglobulin	19990±10878

Table 3: Biochemical Profile of the Study Population

Plasmacytosis	Number	%
< 20% plasmacytosis	4	22.3
20– 50% plasmacytosis	8	44.4
>50% plasmacytosis	6	33.3
Total	**18**	**100**

Table 4: Bone Marrow Study of the Study Population

ECOG grade	Patients	%
0-1	9	50
2	4	22.22
3	3	16.67
4	2	11.11
Total	**18**	**100**

Table 5: ECOG Grading of Performance Status of Study Population

Type of light chain	Number	%
Kappa light chain myeloma	6	33.33
Lambda light chain myeloma	12	66.67
Total	**18**	**100**

Table 6: Light Chain Typing of Study Population

Renal response	Patients	%
Complete	8	44.44
Partial	7	38.89
Minimal	3	16.67
Total	**18**	**100**

Table 7: Renal Response in the Study Population

Free light chain	Time	Mean	P value
Kappa	Baseline	5307.70	0.01
	16 Weeks	11.17	
Lambda	Baseline	4084.27	0.006
	16 Weeks	16.75	

Table 8: FLC response in the study population

Time	Mean serum creatinine (mg/dL)	Mean eGFR (mL/min/1.73 m2)
Baseline	7.95	6.19
2 weeks	4.08	13.46
4 weeks	3.2	19.76
6 weeks	2.5	32.38
8 weeks	2.21	40.92
10 weeks	1.92	46.54

12 weeks	1.80	50.35
14 weeks	1.71	54.15
16 weeks	1.64	56.79
p Value(by Repeated ANOVA) < 0.001		

Table 9: GFR response in study population

Side effect	Grade/severity	Number	%
Peripheral neuropathy	Mild	3	27.77%
	Moderate	2	
	Severe	nil	
Cytopenias	Neutropenia	1	11.11%
	Thrombocytopenia	1	
Infective complications	Life threatening	Nil	
	Herpes zoster	2	11.11%
	Oral candidiasis	3	16.67%
Cardiac events	SVT	1	5.55%

Table 10: Side-effect profile in study population

Parameters		Complete response (n=8)	Partial response (n=7)	Minimal response (n=3)
Mean Age		60.5 years	54.57 years	58.66 years
Mean Duration of symptoms		3.125 months	3.71 months	5 months
Mean Hb		7.37 g/dL	7.28 g/dL	7.23 g/dL
Baseline serum Creatinine		8.13	7.91	7.53
Baseline eGFR		5.54	6.59	7.04
Baseline FLC level		8917.5	12825	1931.66
Serum Calcium		12.16	13.08	10.53
Serum β 2 microglobulin		17480	26287	14196
Baseline renal biopsy	Mild IFTA	7/8(87.5%)	3/7 (42.85%)	1/3(33.33%)
	Moderate IFTA	1/8(12.5%)	Nil	1/3(33.33%)
	Severe IFTA	Nil	4/7 (57.14%)	1/3(33.33%)
Repeat renal biopsy at 16 weeks	Mild IFTA	6/6(100%)	1/2(50%)	Nil
	Moderate IFTA	Nil	1/2(50%)	2/2(100%)
	Severe IFTA	Nil	Nil	Nil
Repeat FLC level at 16 weeks		11.85	24.38	17.53
% FLC Reduction at 16 weeks		99.87%	99.81%	99.1%

Table 11: Factors affecting the Renal Response in Study Population

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