RESEARCH

RENAL FAILURE IN MULTIPLE MYELOMA: THE ROLE OF PLASMAPHERESIS AND CHEMOTHERAPY ON REVERSIBILITY AND PROGNOSIS - A SINGLE CENTER EXPERIENCE FROM INDIA

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Abstract

Background: Renal failure in multiple myeloma is a frequent complication and has a significant impact on overall survival. Severe degree of renal failure and dialysis dependency are associated with poor outcomes despite adequate chemotherapy. The role of plasmapheresis and use of newer chemotherapeutic agents are lacking from India and hence this study was undertaken. **Materials and Methods:** Retrospective study of 125 patients from 2011-2015 with diagnosis of multiple myeloma and renal failure admitted in nephrology unit. **Result:** Out of 125 patients 76.8% (96) had severe degree of renal failure & 51.2% (64) were dialysis dependent. Commonest precipitating factor was hypercalcemia- 35%. Renal histology was available in 40 patients and cast nephropathy was seen in 60% of them. 11.2% (14) could not be given any form of treatment. 26% (11) in G-1 & 35% (6) in G-2 respectively became dialysis independent at time of discharge. At 3months 59% (25/42) in G-1 & 41% (7/17) were still dialysis dependent & non-significant (p-NS). At the end of study period 34% in G-1 and 47% in G-2 respectively were dialysis dependent (p-NS). Mortality was 56.6% (51) & 76.1% (16) in G-1 & G-2 respectively at the end of follow up. Median survival time in G-1 is 24 months & in G-2 it was 14 months & was not significant. 49% in Td group & 61% in VDT group respectively were dialysis dependent. Renal response was better in patients with VDT than Td group. At the end of study period dialysis dependency rates were comparable (42% in either group were dialysis dependent). Overall, 1 year survival rate of patients with multiple myeloma and renal failure was 59.2% and actuarial 3-year survival rate was- 45.6% & 5 year- 39.2%. **Conclusion:** Renal failure in multiple myeloma is associated with increased morbidity & mortality. Plasmapheresis can be used in selected cases to decrease the free light chain load early in the course of disease. Bortezomib based regimens had better survival rates than dexamethasone and thalidomide.

INTRODUCTION

Multiple myeloma is a malignancy characterized by neoplastic proliferation of a single clone of plasma cells derived from B cells. It accounts for about 1% of all types of malignancy and slightly more than 10% of hematologic malignancies.[1,2] The reasons for renal failure are multifactorial and early accurate diagnosis of the renal alterations may significantly impact morbidity and survival. The reported incidence varies from 18-56% depending on definition.[3,4,5] Severe renal failure requiring dialysis is reported in 10-20%.[6] Renal failure is associated with increased morbidity and mortality.[7] Treatment options include novel chemotherapeutic agents, plasmapheresis and the use of recently proposed HCO-HD.[8] Studies from India addressing the utility of Bortezomib based regimens and utility of plasmapheresis in patients with multiple myeloma and renal failure are lacking.[6,9] Hence this retrospective study was undertaken to report the presenting features, the response to therapy, the impact of plasmapheresis and chemotherapy and factors associated with the reversibility of renal insufficiency and survival.

MATERIALS AND METHODS

This retrospective observational study was undertaken at a state government run tertiary care

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referral institute of North India. A total of 125 patients were identified after screening the medical records of patients admitted with a diagnosis of multiple myeloma under Nephrology Unit & Kidney biopsy registry with a diagnosis of cast nephropathy. The diagnosis of myeloma was reconfirmed based on International Myeloma Working Group Diagnostic Criteria for Multiple Myeloma.[10]

- Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extra medullary plasmacytoma

Any one or more of the following myeloma defining events (MDE's):

Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: (CRAB criteria)

1. Hypercalcemia: serum calcium >1 mg/dl higher than the upper limit of normal or > 11mg/dl
2. Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >2 mg/dl
3. Anaemia: haemoglobin value of >2 g/dl below the lower limit of normal, or a haemoglobin value <10 g/dl
4. Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT)

- Clonal bone marrow plasma cell percentage ≥60%
- Involved: uninvolved serum free light chain (FLC) ratio ≥100 (involved free light chain level must be ≥100 mg/L)
- >1 focal lesions on magnetic resonance imaging (MRI) studies (at least 5 mm in size)

Renal failure was defined by a serum creatinine persistently >1.5 mg/dl after correction of volume deficit or urinary tract obstruction. Three subgroups were defined as follows: (1) mild renal impairment: plasma creatinine1.5-2mg/dl; (2) moderate renal impairment plasma creatinine 2-4mg/dl; (3) severe renal impairment: plasma creatinine >4mg/dl. Oliguria was defined by documentation of urine output < 400 mL/day for 2 consecutive days despite correction of dehydration. Diagnosis of acute kidney injury (AKI), chronic kidney disease (CKD), rapidly progressive renal failure (RPRF) or nephrotic syndrome was made using standard criteria.[8]

Details of history and physical examination were recorded. Laboratory tests included urinalysis, 24 hours urinary protein and radiological survey for lytic bone lesions, a complete hemogram and serum biochemistry. Bone marrow examination, serum electrophoresis, the type of monoclonal (M) protein was identified by immunofixation, type of light chain was all recorded. Creatinine clearance was calculated based on MDRD formula.

40 patients had undergone kidney biopsy & their reports were recorded. Details of treatment received; chemotherapy, hemodialysis, plasmapheresis sessions were noted. Serum creatinine was recorded at regular intervals. Treatment response, renal response, treatment failure was assessed using standard criteria's. Disease relapse, time to relapse was also noted. All patients were followed-up till the outcomes were met or till last follow up which was Dec-2016.

Primary Outcome

- Death due to any cause

Secondary Outcome

- Renal outcome at 3 months

Response Criteria

Objective response was defined as

- A reduction of 50% or more in the M-component size in both serum and urine,
- A decrease of 50% or less in the size of plasmacytomas, and
- Recovery of renal function, improvement in the symptoms of bone pain and anemia and performance status, with no increase of lytic bone lesions and correction of hypercalcemia if initially present. Patients who did not fulfill the criteria for objective or partial response were considered treatment failures.

Renal response was defined according to IMWG consensus 2010.[8]

- Renal complete response (CRrenal) was defined as sustained (ie, lasting at least 2 months) improvement of CrCl from lower than 50 mL/min at baseline to_60 mL/min.
- Renal partial response (PRrenal) was defined as sustained improvement of CrCl from lower than 15 at baseline to 30 to 59 mL/min.
- Renal minor response (MRrenal) was defined as sustained improvement of baseline CrCl of lower than 15mL/min to 15 to 29mL/minor if baseline CrCl was15 to 29 mL/min improvement to 30 to 59 mL/min.

Analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, non-parametric setting for Qualitative data analysis. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Kaplan- Meier survival analysis used for calculating the median survival. Log rank test was used for the significance between different groups. SPSS version 15.0 software was used for the above analysis.

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RESULTS

The patients' characteristics are listed in [Table 1]. A total of 125 patients were analyzed Mean age was 57.5 years (35-80). Males constituted 70.4% (88) & females 29.6% (37). 90.4% (113) patients were admitted for the evaluation of renal failure & were diagnosed as multiple myeloma after admission to nephrology unit, whereas 6.4% (8) & 3.2% (4) patients respectively were diagnosed as multiple myeloma following evaluation of chronic anemia & unexplained fractures respectively elsewhere. AKI with 80% (100) was the commonest renal syndrome & rest are given in [Table 1]. Uremic symptoms (fatigue, anorexia, nausea) 71.2% (89) was the most frequent presenting complaint. Others were bony pains- 13.6% (17), oliguria & edema- 28% (35), fractures- 3.2% (4). Hypercalcemia- 35.2% (44) was the most common precipitating factor followed by NSAIDs intake- 16.8% (21), infections & multifactorial causes- 16% (20) each, volume depletion-12% (15) & nephrotoxic drugs- 4% (5). 43.2% (54) patients did not have any co-morbid conditions, while 37.6% (47) were hypertensive, 15.2% (19) diabetics. One patient had pre-existing cancer. 67.2% (84) had lytic lesions.

Out of 125 patients, 76.8% (96) had severe degree of renal insufficiency (RI), 16.8% (21) had moderate degree of RI, 4.8% (6) had mild degree of RI & 1.6% (2) had normal renal functions.

51.2% (64) were dialysis dependent & 48.8% (61) were dialysis independent at time of admission [Table 3]. Mean values of hemoglobin & all biochemistry values are given in [Table 2].

27.2% (34) patients had nephrotic range proteinuria. Serum electrophoresis was done in all patients. 91.2% (114) were positive for M-band & 8.8% (11) were negative for M-band. However all patients had serum free light chain positivity, kappa light chain-52% (65), lambda light chain-48% (60). Median kappa SFLC load was 4898.26mg/L (8.9-69000mg/L) & Lambda SFLC load was 2375.76mg/L (2.9-24200mg/L). Immune-fixation typing was available in 87cases. 38.4% (48) were positive for IgG, 24% (30) were positive only for light chains, 6.4% (8) with IgA & one patient had IgM. Renal histology was available in 40 patients & cast nephropathy was the commonest finding.

Mean duration of hospital stay was 14.68 ± 7.54 days. Out of 125 patients, 11.2% (14) patients could not be given any form of treatment- 8 refused treatment & were discharged against medical advice & 6 patients died during their hospitalization. 16.8% (21) patients were treated with plasmapheresis+ chemotherapy and the remaining 72% (90) were treated with only chemotherapy. Patients either received Dexamethasone + Thalidomide (C-1) - 58.4% (73) or Dexamethasone + Thalidomide + Bortezomib (C-2) - 30.4% (38). 27.2% (34) patients developed complications during hospital stay & infection related complication was the commonest 24.8% (31).

At the time of discharge 38.4% (48) were still dialysis dependent as against 51.2% (64) who were dialysis dependent at the time of admission.

At the end of 3 months of follow up 25.6% (32) were dialysis dependent, 37.6% (47) progressed to different stages of CKD, 15.2% (19) had normal renal functions, 13.6% (17) died & 8% (10) were lost to follow-up.

Treatment outcomes [Table 4]

In our study there were 111 patients who received treatment & we stratified them into 2 groups. Chemotherapy alone group (G-1) & Chemotherapy + Plasmapheresis group (G-2). On an average 4-5 session of plasmapheresis & a targeted volume of 40-50ml/kg/session was the standard prescription in most of our patients. In G-1 we had 90 patients & in G-2 there were 21 patients. Characteristics of the two groups are given in [Table 4].

72.2% (65) in G-1 & 100% (21) in G-2 had severe degree of renal failure. 46.6% (42) in G-1 & 80.9% (17) in G-2 were dialysis dependent at the time of admission & was statistically significant $p<0.0.5$. Mean serum creatinine at the time of admission was significant between the groups $p<0.05$. Renal histology was significant in both the groups $p<0.05$. Both the groups had 12 patients who had cast nephropathy. Groups did not differ between the type of free light chain, immune fixation studies, mean kappa SLFC load, lambda SFLC load. There was also significant association between groups in terms of treatment received $p<0.05$. In patients who were undergoing plasmapheresis the serum free light chain load before initiation & after the last session of plasmapheresis was assessed. Median pre-PP load was 4800 ± 5366 mg/L & post-PP load was 157 ± 2270 mg/L. Complications during hospitalization was more in G-2 than G-1 (57.1% vs. 18.8%) & was significant $p<0.05$. There was non-significant decrease in dialysis dependency at the time of discharge with 34.4% (31) in G-1 & 52.3% (11) respectively. There was no significant difference between the two groups in terms of renal response criteria based on IMWG. At three months of follow up 27.7% (25) & 33.3% (7) were still dialysis dependent in G-1 & G-2 respectively. Also there were 7.7% (7) & 4.7% (1) deaths in G-1 & G-2 respectively. However outcomes at three months were not significant. Mean duration of follow up was 17.84 ± 14.87 months & 22.04 ± 17.35 months in G-1 & G-2 respectively & was non-significant. At the end of study period in G-1 34.4% (31) are dialysis dependent, 36.6% (33) are CKD & 14.4% (13) had normal renal functions. In G-2 47.6% (10) were dialysis dependent, 33.3% (7) were CKD & 19% (4) had normal renal functions. Overall 14.4% (13) in G-1 & 23.8% (5) in G-2 respectively had disease relapse. Mean time for relapse of the disease was 15.15 ± 7.19 months & 22 ± 10.9 months in G-1 & G-2 respectively & was non-significant. Among those who had relapsed, 3 patients in G-1 & none in G-2 was dialysis dependent. Also in G-1 group 9/13

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were on C-1 & 4/13 were on C-2. All patients who had relapse in G-2 were on C-2.
Overall mortality was 56.6% (51) & 76.1% (16) in G-1 & G-2 respectively. Kaplan-Meier survival analysis Median survival time in G-1 is 24 months & in G-2 it was 14 months & was not significant [Figure 2].

Table 1: General characteristic of study population

Patient Characteristics		**Percentage (n)**
Mean Age		57.5 ± 10.5 yrs
Sex	Male	70% (88)
	Female	30% (37)
Diagnosis of Multiple myeloma	After Hospitalisation	90% (113)
	Pre-Hospitalisation	10% (12)
Renal Syndrome	AKI	80% (100)
	RPRF	15% (18)
	Pre-existing CKD	4% (5)
	Nephrotic Syndrome	1% (2)
Co morbid conditions	Hypertension	37.6% (47)
	Diabetes	15.2% (19)
	CAD	2.4% (3)
	Cancer	2% (2)
	None	42.4% (53)
Presenting Complaints	Uraemic Symptoms	71.2% (89)
	Bony pains	13.6% (17)
	Oliguria & edema	28% (35)
	Fractures	3.2% (4)
Precipitating Factors	Hypercalcemia	35.2% (44)
	NSAID Intake	16.8% (21)
	Infection	16% (20)
	Multifactorial causes	16% (20)
	Volume Depletion	12% (15)
	Nephrotoxic drugs	4% (5)

Table 2: Clinical parameters

Laboratory values		**Values**
Haemogram	Haemoglobin (gm/dl)	7.9 ± 1.7
	TLC (x 10^3/dl)	9.0 ± 4.0
	Platelet (x 10^3/dl)	140 ± 62
Chemistry	Serum creatinine (mg/dl)	6.2 ± 3.2
	Sodium (mEq/L)	137 ± 5.4
	Pottassium (mEq/L)	4.6 ± 0.5
	Calcium (mg/dl)	9.7 ± 1.5
	Phosphorus (mg/dl)	5.8 ± 1.8
	Uric acid (mg/dl)	8.12 ± 2.6
	Total protein (g/dl)	7.7 ± 1.9
	Serum Albumin (g/dl)	3.2 ± 0.5
Percentage of Plasma cells in BM		50% ± 23
M Band	Positive	91.2% (114)
	Negative	8.8 % (11)
Light chain type	Kappa	52% (65)
	Lambda	48% (60)
Immunofixation studies	IgG + κ	20% (25)
	IgG + λ	18.4% (23)
	IgA + κ	3% (4)
	IgG + λ	3% (4)
	IgM + λ	0.8% (1)
	Kappa light chain only	28% (35)
	Lambda light chain only	23% (32)
Serum Kappa FLC		4898.2 mg/L
Serum Lambda FLC		2375.7 mg/L
Nephrotic Range proteinuria		27.2% (34)

Table 3: Degree of renal failure and Dialysis dependency at admission

	Percentage (number)
1. Degree of renal failure	
Normal renal function	1.6% (2)
Mild renal failure	4.8% (6)
Moderate renal failure	16.8% (21)
Severe renal failure	76.8% (96)
2. Dialysis dependent at presentation	51.2% (64)
Dialysis Independent at presentation	48.8% (61)

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Table 4: Comparison between Chemotherapy alone and Plasmapheresis + Chemotherapy

	Chemotherapy only	Chemotherapy + Plasmapheresis	P value
Age	58.06 ± 10	51.76 ± 9.48	0.010
Sex	M- 68%(61) vs F- 32% (29)	67% (14) vs 33% (7)	0.887
Creatinine at admission	5.9 ± 2.8	8.0 ± 3.6	0.004
Degree of renal failure			
Normal renal function	3.3 % (3)	-	0.042
Mild renal failure	3.3% (3)	-	
Moderate renal failure	21% (19)	-	
Severe renal failure	72% (65)	100 % (21)	
Renal morphology			
Cast Nephropathy	13.3% (12)	27% (12)	0.001
ATN	6.6% (6)		
TIN	1.1% (1)		
Cast Nephropathy + TIN	1.1% (1)	19%(4)	
Amyloidosis	2.2% (2)		
ATN + TIN	2.2% (2)		
Kappa value (median)	4688.82 ± 1064.2	5856 ± 6165	0.631
Lambda value (median)	2651.31 ± 5283	1552 ± 2972	0.362
Treatment given			
Thalidomaide + Dexa	77% (69)	19% (4)	0.001
Thalidomaide + Dexa + Bortezomib	23% (21)	81% (17)	

	Chemotherapy only	Chemotherapy + Plasmapheresis	P value
Duration of hospital stay at first admission in days	13.09 ± 5.2	21 ± 10.1	0.001
Inhospital complications during stay	19% (17)	57% (12)	0.001
Dialysis dependency at discharge	34% (31)	52% (11)	0.127
Creatinine at 3 months	4.021 ± 2.36 (n = 77)	4.60 ± 2.1% (n = 19)	0.334
IMWG – eGFR response			
Complete	14% (11)	11% (2)	0.864
Partial	18% (14)	16% (3)	
Minor	68% (77)	73% (14)	
Dialysis dependency at 3 months	34% (31)	38% (8)	1.00
Creatinine at 6 months	3.5 ±2.19 (n = 63)	3.819 ± 22 (n = 16)	0.616
Creatinine at 1 year	3.072 ± 2.18 (n = 47)	3.58 ± 2.2 (n = 12)	0.542
Creatinine at 2 years	3.04 ± 2.4 (n=28)	3.0 ± 2.2 (n = 10)	0.979
Creatinine at 3 years	3.06 ± 1.7 (n = 14)	2.75 ± 2.2 (n= 8)	0.719
Creatinine at 4 years	4.07 ± 2.3 (n = 7)	2.4 ± 1.83 (n = 2)	0.392
Time to attain ESRD in months	8.32 ±14.15 (n = 31)	7.3 ± 10.46 (n=10)	0.835
Total duration of follow up in months	17.84 ± 14.8	22 ± 17	0.265
Degree of renal failure at the end of follow up			
Normal renal function	14% (13)	20% (4)	0.593
Mild renal failure	16% (14)	14% (3)	
Moderate renal failure	19% (17)	14% (3)	
Severe renal failure	7% (6)	5% (1)	
ESRD	39% (35)	48% (10)	
Dialysis dependency at the end of follow up	41% (35)	48% (10)	0.593

Table 5: Survival Outcomes

	Chemotherapy only	Chemotherapy + Plasmapheresis	P value
Outcomes at 3 months			
Survivors	77% (69)	81% (17)	0.543
Death	18% (16)	19% (4)	
Lost to follow up	5% (5)	0	
Outcomes at follow up			
Survivors	31% (28)	24% (5)	0.139
Death	57% (51)	76% (16)	
Lost to follow up	12% (11)	0	

Table 6: Chemotherapy outcomes

	Steroids + Thalidomide (Td)	Bortezomib + Dexa + Thalidomide (VDT)	P value
Degree of renal failure at admission			
Mild	1.3 % (1)	5.2% (2)	0.80
Moderate	22% (16)	7.8% (3)	
Severe	72.7% (53)	86% (33)	
Dialysis dependency at admission	49% (36)	70% (23)	0.318
IMWG eGFR response			
Complete	8.2% (6)	18.4% (7)	0.264
Partial	18% (13)	10.5% (4)	

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Minor	54% (39)	71% (27)	
Degree of renal failure at follow up			
Normal renal function	14% (10)	18% (7)	0.512
Mild renal failure	14% (10)	18% (7)	
Moderate renal failure	20% (15)	13% (5)	
Severe renal failure	5% (4)	8% (3)	
Dialysis dependency	40% (29)	42% (16)	
Final outcome			
Survivor	25% (18)	40% (15)	0.210
Death	63% (46)	55% (21)	
Lost follow up	12% (9)	5% (2)	

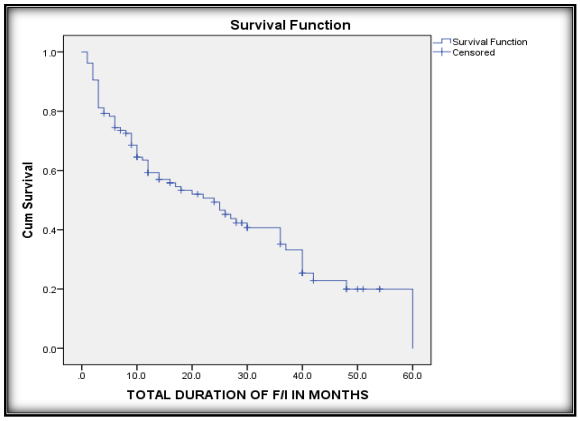

Figure 1: Overall Survival

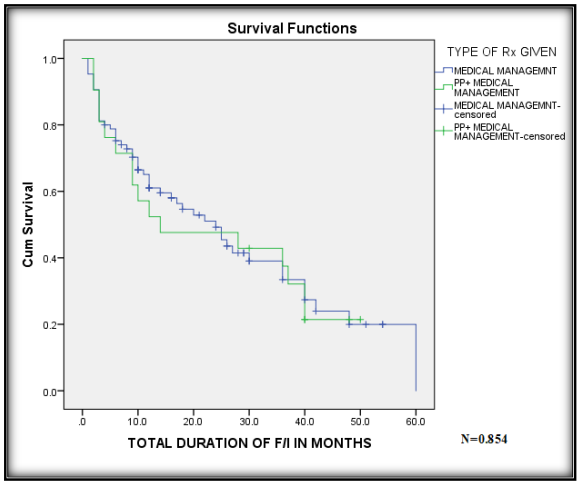

Figure 2: Outcomes of PLEX + Chemotherapy vs. Chemotherapy only

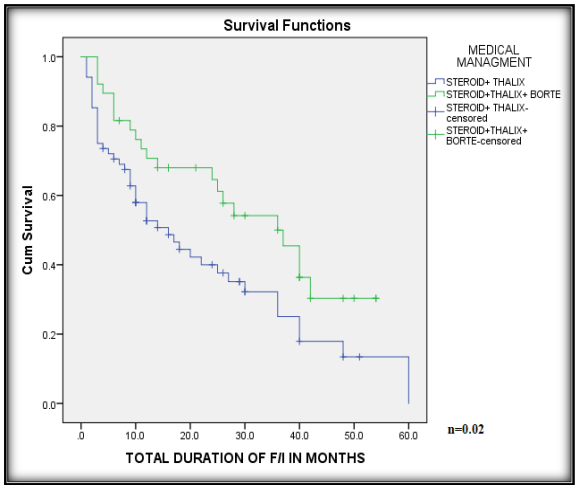

Figure 3: survival outcomes of chemotherapeutic agents

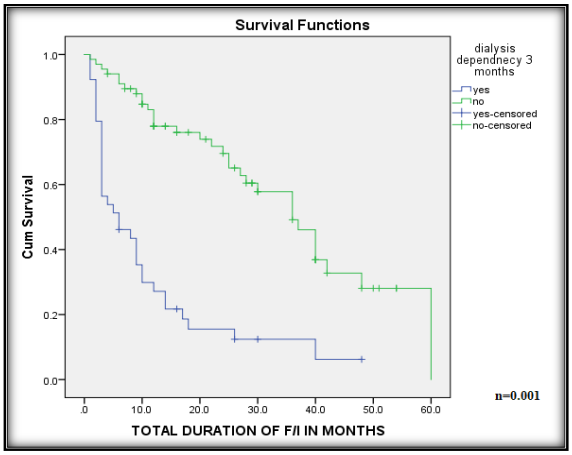

Figure 4: Survival outcomes of dialysis dependency at 3 months

DISCUSSION

The present study focused on the spectrum of renal manifestations in multiple myeloma, importance of renal failure at the time of diagnosis in multiple myeloma, the prognostic significance of reversibility of renal failure and the response to different chemotherapy regimens & the role of plasmapheresis.

Renal insufficiency is the commonest mode of presentation in those with renal involvement.[4,6,7,9] The incidence and the degree of renal failure vary considerably from one series to another because of the differences between the populations included in the studies and the criteria used to define renal failure. Patients with severe renal insufficiency constitute a larger proportion of cases in series reported by most renal units.[11,12] In our study nearly 77% of patients in the present study, had severe RI and 51% required dialysis. The proportion of myeloma patients who require dialysis has been reported to vary from 2 to 66%.[13,14,15,16]

Oliguric RI was 28% in the present study & has varied from 24-50% in previous studies. The diagnosis of multiple myeloma was made after admission to our hospital in over 90% (113) of those with renal involvement indicating that renal involvement antedated or coincided with the diagnosis of myeloma in them. Under-diagnosis of the disease & lower degree of suspicion by the primary care physicians may be the reason for higher number of our patients being diagnosed multiple myeloma after admission. Pozzi et al. diagnosed

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multiple myeloma along with or after the detection of renal failure in 78% cases.[17] In other series, the figures vary from 50-76%.[6,9,12,17] AKI was the most common presenting syndrome in 80% (100). Similar incidences have been observed in other studies.[9,17,18]
The role of precipitating factors in development of renal failure in myeloma has been stressed in many studies.[12,13] In our study the most common was hypercalcemia in 35% (44). The role of hypercalcemia in the development of renal failure in patients with myeloma has been emphasized in a number of studies.[12,13,16,17] The measured serum calcium value may be normal or even low in those with renal insufficiency and/or hypoalbuminemia. Hypercalcemia predisposes to AKI by volume depletion as a result of emesis and by inducing nephrogenic diabetes insipidus. Volume depletion may enhance light chain nephrotoxicity and the aggregation of light chains with Tamm-Horsfall protein in the kidneys.[12,13,19]
Most of our patients had anemia, hypercalcemia, hyperuricemia. Over 27% our patients had nephrotic range proteinuria. Any elderly patient presenting with unexplained renal failure along with a bland urinary sediment, anemia out of proportion to renal failure, hypercalcemia, protein-albumin disassociation and normal sized kidneys should be investigated for multiple myeloma.
The commonest histological finding in patients with renal failure in multiple myeloma is myeloma cast nephropathy, also called `myeloma kidney".[6,9,12,20] In our study there were 40 patients who underwent kidney biopsy & commonest histological lesion was myeloma cast nephropathy present in 60% (24) of biopsy cases. This condition is characterized by the presence of numerous large laminated eosinophilic casts composed of light chains. Tamm-Horsfall protein and fibrin. The casts show fissures and are surrounded by inflammatory reaction including giant cells. Associated tubular atrophy and interstitial fibrosis is seen frequently. This characteristic histological appearance is not seen in renal disease unrelated to plasma cell dyscrasias. Quite often, the diagnosis of multiple myeloma is first suspected on discovery of the classical histological picture of cast nephropathy.
Some workers have shown the severity of cast formation to be directly proportional to the degree of renal insufficiency and its reversibility.[17] In contrast, others have emphasized the importance of tubulointerstitial damage as being predictive of a worse renal outcome.[14,18] In our study, 100% (24) patients with cast nephropathy had severe renal failure, 75% (18) required dialysis at the time of admission and 67% (16) remained dialysis dependent at the end of follow up. Amyloidosis has been observed in 5-11% of cases with multiple myeloma though it is detected more frequently at autopsy than on renal biopsies.[18,21] In our study 5% (2) showed amyloid in renal biopsy.
91.2% (114) were secretory myeloma & 8.8% (11) oligo-secretory myeloma. Recently published studies have also quoted similar incidences of oligo-secretory myelom.[22] Kappa light cahin was positive in 52% (65) & Lambda light chain positive in 48% (60). Serum immune-fixation typing was done. IgG was positive in 38.4% (48), 6.4% (8) for IgA & one patient had IgM. 24% (30) had only light chain positivity. Various studies have reported similar findings.[7,20]
Out of 125 patients who were admitted to the hospital, 6.4% (8) refused any form of further treatment after diagnosis of multiple myeloma. Poor financial status of the family was the major factor for opting out of treatment. 4.8% (6) patients died during first hospitalization. All patients had severe degree of renal failure & advanced stage of disease.

Treatment outcomes

The remaining 111 patients who received treatment were stratified into two groups. Group stratification was made to compare different modalities for treatment response & outcomes. Two groups were compared; Chemotherapy alone group (G-1) & chemotherapy + plasmapheresis group (G-2). In G-1 we had 72% (90) patients & in G-2 there were 16.8% (21) patients. Chemotherapeutic regimen differed in the groups. Thalidomide along with low-dose dexamethasone (Td) was the standard chemotherapeutic regimen in the earlier years (2011-2013) of the study period in our institute.[8,16,19] Bortezomib based regimens were not commonly used earlier to due to its high cost in our country. Subsequently with cost reduction in cancer therapeutic agents, Bortezomib based regimen became standard of care in all patients from (2014-2015) with renal failure and multiple myeloma as all three drugs- bortezomib, low dose dexamethasone & thalidomide (VDT) are safe in patients with renal failure & doesn't require any dose modification.[8]
All patients who received plasmapheresis had very high serum free light chain load. On average 4-5 sessions of plasmapheresis with a targeted volume of 40-50ml/kg/session was the standard prescription. In G-1 patients on Td therapy were 77% (69) & VDT therapy 23% (21) respectively. In G-2 patients on Td therapy were 19% (4) & on VDT therapy 81% (17). Both the groups had statistical significance $p<0.05$.
Mean age, sex distribution were comparable between groups. In our study patients were younger than compared to elder patients in other studies.[23,24,25]

Plasmapheresis & Renal recovery [Table 4 & 5]

In our study G-1 had 72.2% (65) & G-2 had 100% (21) severe degree of renal failure at presentation. Also need for dialysis was higher in our study, 46.6% (42) in G-1 & 80.9% (17) in G-2 respectively required dialysis. In comparison with other studies, our study had higher number of patients requiring dialysis.[20,24,25] Mean duration of stay in hospital stay in G-1 was 14 days compared to 23.5 days in G-2. The longer duration in G-2 was because of the need of plasmapheresis. At the time of discharge in G-1 26% (11/42) & in G-2 35% (6/17) became dialysis

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independent. Patients treated with plasmapheresis plus chemotherapy had a slightly higher proportion of renal recovery than chemotherapy alone suggesting that early removal or decreasing of free light chain load from the kidney would improve in the renal status. This is in contrast with the previously done RCT's wherein there were a significant proportion of patients recovering with PLEX.[15,23,24,25] The modest improvement seen in the G-2 group was associated with significant morbidity as evidenced by higher rates of non-severe complications during stay (57.1% in G-2 vs. 18.8% in G-2, $p< 0.05$). Infection related complication was the commonest cause of morbidity. In a study done by Leung et.al more than 50% reduction in free light chain load post PLEX was associated with significant renal recovery.[25] However in our study despite more than 50% reduction in free light chain load post PLEX therapy renal recovery was quite low. This may be due to higher rate of light chain production & disease activity which can be effectively targeted with early institution of chemotherapeutic agents. Also in the absence of clear guidelines on the number of sessions of PLEX, it can be possible that patients may be given over or under- treatment sessions with PLEX. Based on the recently proposed renal response criteria for reversibility of renal failure in multiple myeloma there was no significant difference between the groups.[8] 12.2% (11), 15.5% (14) & 57.7% (52) in G-1 group had complete, partial & minor response respectively. In G-2 group 9.5% (2), 14.2% (3) & 66.6% (14) had complete, partial & minor response. At the end of 3 months, 26% (11/42) in G-1 & 53% (9/17) in G-2 respectively were dialysis independent. Renal recovery (serum creatinine <1.5mg/dl) was seen in only 16.6% (15) in G-1 & 19% (4) in G-2 respectively. There was a higher number of renal recovery & dialysis independency at 3 months of therapy in patients with PLEX + chemotherpay. In comparison with the Previous RCT's renal response rates in PLEX patients was comparable.[15,23,24] However in our study response rates in non-PLEX patients was better than earlier studies could be attributed to early institution of chemotherapy, less degree of severity of the disease and also the effect could be confounded to unequal distribution of patients between the groups (G-1 90 vs. G-2 21).[25] The beneficial effect was lost by the end of follow up as both groups were comparable in terms of renal outcomes, reiterating that effects of PLEX is short lived & future course depends on response to chemotherapy. At the end of follow up in G-1 34%, 36% & 14% respectively were dialysis dependent, CKD & complete renal recovery. In comparison in G-2 it was 48%, 33% & 19% respectively were dialysis dependent, CKD & complete renal recovery. In a recently published systematic review by Gupta et.al did not suggest a benefit of PLEX independent of chemotherapy for multiple myeloma patients with acute renal failure in terms of overall survival, recovery from dialysis, or improvement in renal function.[25] On the contrary the recently published update recommends the use of PLEX in conjunction with chemotherapy in acute renal failure due to suspected cast nephropathy.[26] Until further larger trials are conducted on the effect of PLEX on renal recovery, it can be used in a proportion of patients with proven or suspected cast nephropathy to decrease the free light chain load & thereby preventing chronic changes in the kidney affecting the recovery. Also PLEX can provide a bridge until an effective chemotherapy can be delivered or take effect.[20,26]

Chemotherapy & renal recovery [Table 5]

In our study there were 66% (73) on Td and 34% (38) on VDT regimen respectively and there was no significant association between the groups in terms of severity of renal failure & dialysis dependency at the time of admission. In Td group there were 72% (53/73) with severe degree of renal failure & 49% (36/73) were dialysis dependent. In VDT group there were 87% (33/38) with severe degree of renal failure & 61% (23/38) were dialysis dependent. Our study had a higher proportion of patients with severe renal failure & dialysis dependency. Previously published studies had lesser number of patients with severe degree of renal failure & dialysis dependency.[16,19,27] Based on renal response criteria, CRrenal in Td was 10% against 18% in VDT. 53% in Td & 72% in VDT had MRrenal. Renal response rates were better in VDT group.[8,19] Dialysis dependency was similar in both the groups at the end of study period (42.6% in Td group vs. 42% in VDT group), however when compared to previous studies our overall renal response rates were poor in either groups, possibly due to higher proportion of patients with severe degree of renal failure & dialysis dependency.[8,16,19] Reiterating that severity of renal failure & dialysis dependency at the time of presentation has poorer renal outcomes, despite adequate chemotherapy and control of disease activity. In terms of overall disease response, 73.9% (54) in Td group and 76.3% (29) in VDT group was comparable with previous studies.[29] Disease relapse was also more in Td 26% (19) compared to VDT group 23% (9) and was early in patients treated with Td. This was also comparable with previous studies.[26,29] Therefore in patients with severe degree of renal failure & dialysis dependency, Bortezomib based regimen are better in terms of response & extent of tumor reduction than conventional therapies. Several studies have also shown similar satisfactory results with boretzomib.[16,27,28,29,33,34]

Outcome

In our study OS of patients with renal failure and multiple myeloma was comparable with previously published studies [Figure 1].[4,11,30,31,32,33,34,35] Patients presenting with dialysis dependency at presentation lived shorter than those who were dialysis independent. Also seen in our study was despite early institution of chemotherapy, adequate dialytic treatment & regular follow-up mortality was higher

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in patients those who were still dialysis dependent after 3 months of therapy and these patients survived for short time compared to patients who were dialysis independent.[33,35] In our study plasmapheresis did not have any significant bearing on the renal outcomes nor survival. This was in contrast with previously done studies that had better renal response rates & survival benefits with PLEX.[15,23,24] Patients with Bortezomib based regimens had better survival rates & also survived for longer duration when compared to patients treated with only dexamethasone and thalidomide.[33,34] Overall 1 year survival rate of 59% & 3 year survival rate of 45% was comparable to previously done studies.[20,27,31]

Studies in multiple myeloma and severe/advanced renal failure and their outcomes are sparse.[16] Also retrospective studies from Indian sub-continent have looked at epidemiological data & outcomes.[6,9] None of them have discussed the role of PLEX & Bortezomib based regimens. This study not only throws light on the use of PLEX & Bortezomib based regimens also about the utility of the same. The cost involved in the treatment of multiple myeloma alone is expensive upon that cost of dialysis & PLEX is additive, making most patients non-compliant after initial treatment. Also, the relatively poor survival of patients with advanced renal failure and MM has certainly raised questions about the utility of treating such patients and a degree of 'therapeutic nihilism'. However results from our studies are encouraging and treating such patients worthwhile.[20,34,35]

The retrospective design of our study, smaller sample size in PLEX group is the major limitation to draw definitive conclusions on the use of PLEX. Further prospective RCT with larger sample size can throw more light on the role of PLEX for patients with high free light chain load.

Also the use of HCO dialyzer has given promising results albeit in smaller group of patients,[36] very high cost involved in it may preclude the use of it routinely and especially in developing countries.

CONCLUSION

Renal failure in MM has a poor prognosis with high morbidity & mortality. Early diagnosis & institution of Bortezomib based regimens, extended dialytic therapy & decreasing of free light chain load by plasmapheresis or the use of newly developed HCO dialysers can prevent the progression of renal failure, thereby increasing the overall survival of patients. Further larger size and adequately powered trials involving newer chemotherapeutic agents and HCO dialyers especially in patients with severe renal failure are required to address this concern.

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