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Outcome profile in multiple myeloma patients with renal dysfunction: A tertiary care hospital experience

[1]Mir Sadaqat Hassan Zafar, Consultant Department of Medicine and Clinical Hematology Government Medical College and associated Superspeciality Hospital, Srinagar, India

[2] Raiesa, Postgraduate Government Medical College, Srinagar, India

[3]Sajad Ahmad Geelani, Additional Professor Department of Clinical Hematology Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India

Corresponding Author: Mir Sadaqat Hassan Zafar, Consultant Department of Medicine and Clinical Hematology Government Medical College and associated Superspeciality Hospital, Srinagar, India

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Introduction

Multiple myeloma (MM) is characterized by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin. The plasma cells proliferate in the bone marrow and often results in extensive skeletal destruction with osteolytic lesions, osteopenia, anemia, renal failure and/or pathologic fractures. The diagnosis of MM is often suspected because of one (or more) of the following clinical presentations: bone pain with lytic lesions discovered on routine skeletal films or other imaging modalities, increased total serum protein concentration and/or the presence of a monoclonal protein in the urine or serum, systemic signs or symptoms suggestive of malignancy, such as unexplained anemia, hypercalcemia, which is either symptomatic or discovered incidentally, acute renal failure with a bland urinalysis or rarely the nephrotic syndrome due to concurrent immunoglobulin light chain (AL) amyloidosis.MM is a disease of older adults. The median age at diagnosis is 66 years; only 10 and 2 percent of patients are younger than 50 and 40 years, respectively. [1]

The serum creatinine concentration is increased in almost one-half of patients at diagnosis; renal failure may be the presenting manifestation of MM. Two major causes of renal insufficiency in patients with MM are light chain cast nephropathy (also called myeloma kidney) and hypercalcemia. Patients who do not secrete light chains are not at risk for myeloma kidney. In the absence of other causes of renal failure, a presumptive diagnosis of light chain cast nephropathy can be made in the setting of high involved free light chain (FLC) levels (typically >1500 mg/L). In contrast, renal biopsy should be performed to document typical histologic changes in patients with suspected cast nephropathy. [2]

Other causes of renal failure in a patient with MM include concurrent light chain (AL) amyloidosis, light chain deposition disease, and drug-induced renal damage. The survival ranges from few months to more than 10 years. Availability of novel agents such as

Thalidomide, Lenalidomide and Bortezomib over recent years, substantially improved the outcome of MM patients. Largely focus has been put on improving complete response (CR) rates by including these agents in induction regimens. [3-4] Importantly, a number of studies have found bortezomib to be a useful agent in the setting of renal impairment. It has rapid onset of action and its elimination is independent of renal clearance, indicating that dose adjustments are not necessary in renal impairment, including those requiring dialysis. [5]

Materials and Methods

This study was conducted in the Departments of Clinical Hematology of a tertiary care hospital from north India. The main aim of this study was to assess the presenting features and outcome in patients of multiple myeloma with renal failure. It was an open lable single arm prospective observational study. A total of 36 newly diagnosed patients of multiple myeloma were enrolled after taking an informed consent. The primary end point of our study was the response after four cycles of induction therapy. The study was started after the clearance from ethical committee which is an independently functioning body of the hospital. Newly diagnosed patients whose age was >18 years with symptomatic disease were included in the study. Patients with relapse or refractory disease or associated with another cancer were excluded.

Before the start of study, demographic data, detailed medical history and examination and all the baseline investigations (complete blood count, ESR, kidney function tests, liver function tests, serum and urine protein electrophoresis, serum and urine immunofixation electrophoresis, free light chain ratio, bone marrow examination, cytogenetics, serum β_2 microglobulin, serum lactate dehydrogenase, serum uric acid, random blood glucose and serum calcium) were documented for each patient. The International Myeloma Working Group (IMWG) criteria were used for diagnosis and International Staging System (ISS) for disease staging. Patients were started on weekly injection of bortezomib 1.3 mg/m^2, cyclophosphamide 300 mg/m^2 and dexamethasone 40mg. A total of four such cycles were given to each patient and monitered for respone. The patients who had a dose modification were included in the study. Response was monitored as per International Myeloma Working Group uniform response criteria for multiple myeloma.

After the start of treatment, patients were monitored every two cycles for the response of ongoing regimen i;e serum and/ or urine electrophoresis, serum and/ or urine immunofixation electrophoresis, free light chain ratio, serum β_2 microglobulin and bone marrow examination. Complete blood count (CBC), kidney function tests (KFTs), serum calcium, random blood glucose, serum lactate dehydrogenase (LDH) and serum uric acid were done before the start of each cycle. Patients were monitored closely for any adverse effects of the drug combination. A detailed medical history and physical examination was noted at each follow up visit.

After the completion of four cycles, eligible patients were treated with peripheral blood autologous stem cell transplant followed by maintenance while as non-eligible patients were treated with two more cycles of induction chemotherapy followed by maintenance.

Statistical Analysis

The data in each case was collected based on the proforma attached. Descriptive statistics was used for data analysis. Continuous variables are presented as mean ± SD or median (range). Categorical variables are expressed as frequencies and percentages. SPSS 17 for

Windows statistics package (Microsoft Corp., Richmond, VA) was used for the analysis.

Observations and results

In present study, out of 36 patients, 16 (44.44%) had renal failure at presentation. There were 12 (75%) males and 4 (25%) females with overall age distribution of 51-78 years. Anemia was seen in 13 patients (81.25%), bone pains in 8 patients (50%) hypercalcemia in seven patients (43.75%), and pathological fracture in 2 patients (12.5%).

Out of 16 renal failure patients, 12 patients (75%) attained very good partial respnse (VGPR), 3 patients (18.75%) attained the partial remission (PR) and 1 patient (6.25%) attained minimal response after 2 cycles of treatment. After the completion of 4 cycles of treatment, 10 patients were in VGPR (62.5%), 4 patients in complete remission CR (25%), 1 patient in PR (6.25%) and 1 patient showed no response (6.25). ORR was 93.75%. Three patients (18.75) had ISS-I disease, 7 patients (43.75) had ISS-II and 6 patients (37.5%) had ISS-III disease. After the completion of 4 cycles of treatment, 3 out of 3 patients with stage I disease were in CR. Out of stage II patients 4 were in CR, 2 in VGPR and 1 in PR. Out of stage III disease patients, 4 were in VGPR and 2 showed no response. Mean Hemoglobin at the start of therapy was 7.92 gm/dl and mean hemoglobin at the end of induction was 10.1 gm/dl in renal failure patients.[Figure 1] Mean ± SD of serum creatinine at the start of treatment was 5.65 ± 3.62 (mg/dl) and mean ± SD of serum creatinine after the completion of treatment was 1.34 ± 0.62 (mg/dl). Twelve (75%) out of 16 patients showed normalization of serum creatinine after 2 cycles of treatment and maintained the response at the end of treatment. Remaining 4 patients (25%) showed more than 50% reduction in serum creatinnine at the end of treatment. Thus 75% of patients showed complete reversal of renal failure and 25% of patients showed partial reversal of renal failure [Table 1].

Discussion

The main target for the frontline treatment of multiple myeloma (MM) is achievement of complete response (CR) or at least very good partial response (VGPR); treatment of choice remains high-dose melphalan with peripheral blood autologous stem cell transplant (PBASCT) after induction therapy. The introduction of thalidomide, lenalidomide, or bortezomib into induction regimens has increased the rates of response. [6]

According to recent reports, approximately 30% of patients with diagnosed MM present with baseline renal dysfunction. Renal dysfunction has been associated with shorter survival or early death. [7]

But a recent subanalyses of patients with impaired renal function from two phase 2 studies showed that renal dysfunction did not appear to have a negative impact on response rates, toxicity, or treatment discontinuation in patients with relapsed and/or refractory multiple myeloma receiving bortezomib therapy. [8] Studies indicate that bortezomib is effective and safe in patients with renal impairment and that it can improve renal function. Chanan-Khan et al, in their retrospective case analysis evaluated the feasibility and activity of bortezomib-based therapy in multiple myeloma patients requiring dialysis support for advanced renal failure, ORR (CR plus PR) was 75%, with 30% CR plus near CR. [9] Ludwig et al, reported the reversal of light-chain-induced acute renal failure with bortezomib based therapy in 5 out of 8 MM patients. [10] Dimopoulos et al, analyzed 46 consecutive multiple myeloma patients who presented with renal impairment and received bortezomib with dexamethasone with or

without other agents. Renal response was documented in 59% of patients (30% achieved CR-renal). [11] Inanother recent retrospective analysis, bortezomib-based regimens were given to 117 multiple myeloma patients with renal impairment, including 14 patients who required dialysis. At least a PR-renal was documented in 83 out of 113 evaluable patients (73%), including 27% of the CR-renal or near CR-renal patients. [29] Li et al in their retrospective study of 18 patients newly diagnosed with multiple myeloma, showed reversal of renal impairment in 38.9% of patients, 33.3% of the patients achieved renal response (a 50% decrease in serum creatinine). The ORR of myeloma was 83.3%, including a 33.3% CR rate, a 16.7% near-CR rate, a 16.7% VGPR rate, and a 16.7% PR rate. [30]

In present study 72.72% of patients showed complete reversal of renal failure and 27.27% of patients showed partial reversal of renal failure as defined by Burnette and colleagues. [31] Mean Hemoglobin at the start of therapy was 7.56 gm/dl and mean hemoglobin at the end of induction was 10.4 gm/dl in renal failure patients. Mean ± SD of serum creatinine at the start of treatment was 5.05 ± 3.64 (mg/dl) and mean ± SD of serum creatinine after the completion of treatment was 1.31 ± 0.73 (mg/dl). In comparison to previous studies, the response as per CR is comparable but with higher ORR. In addition present study showed higher rates of renal response (CRrenal and PRrenal). Thus present study adds to the scarce data available for the role of bortezomib plus dexamethasone in MM with renal failure and supports the use of bortezomib plus dexamethasone in all the grades of renal failure including dialysis patients for the improvement of renal function, MM response and overall survival. Additionally there were no added toxicities as compared to non renal failure patients.

Conclusion

Combination chemotherapy may be an ideal frontline therapy for MM with renal failure including patients on dialysis both with respect to MM response and renal response. Bortezomib plus dexamethasone is well tolerated frontline regimen for MM even in stage III disease or advanced renal failure including patients on dialysis. Our study has limitation of a smaller sample size. Thus higher quality of response (especially in renal failure patients) and less severe adverse effects can be confirmed by a future prospective observational study in a larger sample size.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics 2021. CA Cancer J Clin 2021; 71:7.
2. Winearls CG. Acute myeloma kidney .Kidney Int 1995; 48:1347.
3. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia 2009; 23:3-9.
4. Ludwig H, Beksac M, Blade J, Boccadoro M, Cavenagh J, Cavo M et al. Current myeloma treatment strategies with novel agents:A european perspective. The Oncologist 2010; 15:6-25.
5. San-Miguel JF, Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA et al. Efficacy and safety of bortezomib in patients with renal impairment: results from the APEX phase 3 study. Leukemia 2008; 22:842-9.
6. Joseph RM, Andrew RB, Prince HM, Maria NL, Angelo M, Alessandro C et al. High response rate to bortizomib with or without dexamethasone in patients with relapsed or refractory multiple myeloma: results of a global phase 3b expanded

excess programme. British Journal of Hematology 2009; 144: 169-75.

7. Augustson BM, Begum G, Dunn JA, Barth NJ, Davies F, Morgan G et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002- Medical Research Council Adult Leukaemia Working Party. J Clin Oncol 2005; 23:9219-26.
8. Jagannath S, Barlogie B, Berenson JR, Singhal S, Alexanian R, Srkalovic G et al. Bortezomib in recurrent and/or refractory multiple myeloma. Initial clinical experience in patients with impared renal function. Cancer 2005; 103:1195-200.
9. Chanan-Khan AA, Kaufman JL, Mehta J, Richardson PG, Miller KC, Lonial S et al. Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: a multicenter retrospective study. Blood 2007; 109:2604-6.
10. Ludwig H, Drach J, Graf H, Lang A, Meran JG. Reversal of acute renal failure by bortezomib based chemotherapy in patients with multiple myeloma. Haematologica 2007; 92:1411-4.
11. Dimopoulos MA, Roussou M, Gavriatopoulou M, Zagouri F, Migkou M, Matsouka C et al. Reversibility of renal impairment in patients with multiple myeloma treated with bortezomib-based regimens: identification of predictive factors. Clin Lymphoma Myeloma 2009; 9:302-6.

Legend Table and Figure

Table 1: Respone in MM patients with renal dysfunction (N=16).

Response	Response after C 2		Response after C 4	
	Frequency	%	Frequency	%
No response	0	0%	1	6.25
Minimal response	1	6.25	0	0%
PR	3	18.75	1	6.25
VGPR	12	75	10	62.5
CR	0	0%	4	25

C2: cycle 2 C4: cycle 4

PR: partial response

VGPR: very good partial response

CR: complete response

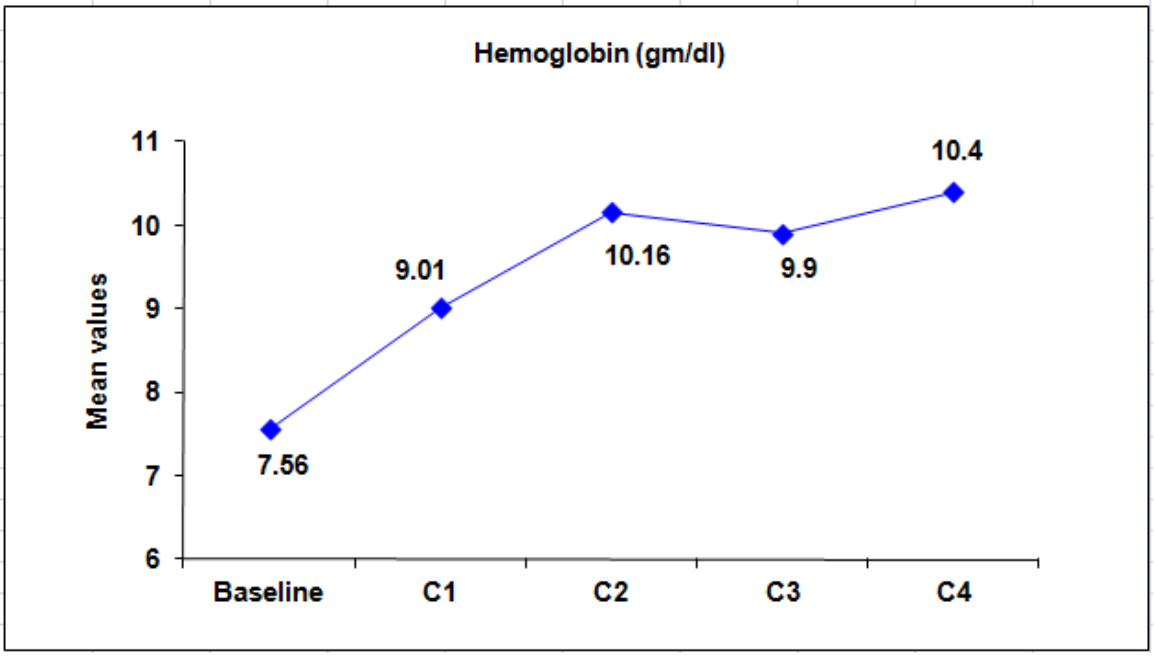

Figure 1: Line diagram showing rise in mean Hb (gm/dl) in 16 renal failure patients.