EVALUATION OF IMPROVEMENT IN RENAL FUNCTION AFTER FIRST-LINE CHEMOTHERAPY IN MULTIPLE MYELOMA PATIENTS PRESENTING WITH RENAL IMPAIRMENT

Syed Abdul Mannan Hamdani, Abdul Wahab, Musa Azhar, Faiza Iftikhar, Bushra Ahsan, Usman Ahmad

Shaukat Khanum Memorial Cancer Hospital, Lahore Pakistan

ABSTRACT

Objective: To evaluate the effect of response to first-line chemotherapy on renal functions in multiple myeloma (MM) patients.

Study Design: Cross-sectional study.

Place and Duration of Study: Shaukat Khanum Memorial Cancer Hospital, Lahore, from Jan 2013 to Dec 2017.

Methodology: Multiple myeloma patients with renal impairment (RI) at baseline were included. Data was collected from the hospital registry. The variables assessed pre and post first-line chemotherapy were age, gender, initial estimated glomerular filteration rate and serum creatinine levels. Progression-free survival and overall survival (OS) was calculated for both groups of patients i.e those who had improvement in renal funtions and those who did not show improvement. Kaplan-Meier curves were drawn, and SPSS-20 was used for data analysis.

Results: Mean age was 48 ± 7 years. Out of 139 myeloma patients, 35 (25.1%) had RI at baseline. Males were 23 (65.7%), while females were 12 (34.3%). Cyclophosphamide, thalidomide and deamethsone (CTD) were used in the majority 30 (85.7%) followed by boretzomib, thalidomide and dexamethasone (VTD) in 2 (5.7%) patients. Boretezomib and dexamethasone (BorDex), lenalidomide and dexamethasone (Len Dex), lenalidomde, cyclophosphamide and dexamethasone (LCD) were given to 1 (2.8%) patient each. Serum creatinine levels normalized in 19 (54.3%). Dialysis was required in 11 (31.4%) patients out of which 3 (8.6%) got dialysis-independent while 8 (22.9%) patients remained dialysis-dependent. The median overall survival in whom creatinine levels normalized was 35 months while it was 15 months in those in whom it did not normalize.

Conclusion: Prompt administration of chemotherapy regimens can lead to an improvement in renal functions and ultimately have a substantial effect on survival outcomes.

Keywords: Boretzomib and dexamethasone, Boretezomib, Cyclophosphamde, Cyclophosphamide and dexamethasone, Estimated glomerular filtration rate, Lenalidomide, Multiple myeloma, Renal impairment, Thalidomide and dexamethasone, Thalidomide and dexamethasone.

INTRODUCTION

Multiple myeloma (MM) is aplasma cell neoplasmusually associated with presence of amonoclonal paraprotein (M protein). The most frequent clinical features includeanaemia, bone pains, fractures, cord compression, hypercalcemia, infections, and renal impairment[1]. It is a relatively uncommon malignancy accounting for 1-2% of all the cancers and 10-15% of all haematological cancers[2]. About 20-40% of patients of MM have renal impairment atpresentation, 10% of which require dialysis[3,4]. The kidney involvement at presentation mostly occurs in patients who have a high tumour burden, and it can lead to acute or chronic kidney disorder[3]. A variety of factors leadtorenal impairment (RI) in MM including light chain cast nephropathy (most common), hypercalcemia, light chain (AL) amyloidosis, light chain deposition disease, drug-induced renal damage, hyperviscosity and severe hyperuricemia[4-6]. The RI on presentation is associated with poor overall survival (OS), especially if there is a need for dialysis; however, reversal of renal functions back to normalcan lead to improvedsurvivals[5,7].

Risk factors for developing RI include hypovolemia, diuretics use, hypercalcemia with or without nephrocalcinosis, repeated use of contrast agents, and drugs. Hypercalcemia can also lead to diabetes insipidus (DI) secondary to vasopressin resistance which in turn can lead to diuresis and hypovolemia and further aggravation of RI[8].

The myeloma-related RI is a medical emergency which requires prompt initiation of treatment with adequate fluid replacement, discontinuation of nephrotoxic medication, correction of electrolytes and hemodialysis in selected patients[5,9,10]. Moreover, the early initiation of anti-myeloma therapy is the cornerstone of MM management. The neweragents thalidomide, lenalidomide, and bortezomib have become the standard of care in the last 10-15 years. Bortezomib based treatment has shown significant improvements in OS[4].

Correspondence: Dr Syed Abdul Mannan Hamdani, Department of Medical Oncology, SKMCH Lahore Pakistan

The objective of this study was which evaluated the improvement in renal functions in patients of MM who had RI at baseline. Although bortezomib based treat-ment is mostly used for treating patients of MM with RI; ourcentre functions in a resource-constrained environment and Thalidomide based regimens such as CTD (Cyclophos-phamide, thalidomide and dexame-thasone) was mostly used as first-line treatment.

METHODOLOGY

This cross sectional anylysis was conducted at Shaukat Khanum Memorial Cancer Hospital, Lahore, form January 2013 to December 2017. Patient data was extracted from electronic hospital information system after obtaining approval from the institutional review board (EX-24-08-19-01). Informed consent was obtai-ned from the patients in the cohort. The patient's age, laboratory parameters such as initial creatinine and eGFR, chemotherapy used, post-treatment creatinine and eGFR wererecorded in data analysis software. All the patients of MM who had renal impairment at base-line were included. The patients with prior history of chronic renal disease were excluded.

The International Myeloma Working Group (IMWG) criteria was used to describe the improvement in renal functions.Complete renal response was defi-ned as attaining a consistent improvement (≥2 months) in eGFR to >60 ml/min from baseline. Partial response was an uninterrupted increase in eGFR from <15 ml/min to 30-59 ml/min and the minor response was a continual improvement in eGFR from <15 ml/min to 15-29 ml/min or from 15-29 to 30-59 ml/min. Nil res-ponse was defined as a failure to meet the criteria men-tioned above[5]. The response assessment was done after the end of first-line chemotherapy.

The Myeloma response assessment was done acc-ording to IMWG criteria. The stringent complete res-ponse was defined as a normal free light chain (FLC) ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence. Whe-reas, a complete response was defined as negative soft tissue plasmacytomas and <5% plasma cells in the bone marrow. Very good partial response (VGPR) was defined as undetectable serum and urine M proteins by electrophoresis, although they could be detected by immunofixation. The partial response (PR) was defi-ned as >50% reduction of serum M protein and reduc-tion of urinary M protein by 90%. The minimal resp-onse (MR) was ≥25%, but ≤ 49% reduction in serum M protein and 50-89% reduction in urinary M protein, moreover, if plasmacytoma was present at baseline a

≥50% reduction was required in its size. Progressive disease (PD) was defined as an increase of 25% from lowest response value in any one or more of the follo-wing, i.e. serum M component the absolute increase must be >0.5 g/dl or urine M-component the absolute increase must be >200 mg/24 hours. In patients with-out measurable serum and urine M proteins, the diffe-rence between involved and uninvolved FLC levels, the absolute increase must be >10 mg/dl[11].

The OS and progression-free survival (PFS) were calculated for patients in whom creatinine levels nor-malized and in those they did not normalize. They were also assessed for patients who remained dialysis-dependent and got free of dialysis.

SPSS-20 was used for statistical analysis of the data. Mean ± standard deviation was used for contin-uous variables, while frequencies and percentages were reported for categorical variables. OS was defi-ned as the time from date of diagnosis to the time of death of any cause or last follow-up. The Kaplan-Meier method was used to estimate survival as a function of time, and survival differences were analyzed by using the log-rank test. Statistical significance was defined as a two-tailed p-value <0.05.

RESULTS

During the study period 139 patients were diagnosed with MM, 35 of whomhad renal impairment at baseline. The median duration of follow up was 18 months. There were 23 (65.7%) males and 12 (34.3%) females. Pre-treatment and post-treatment lab parame-ters along with responses with regards to IMWG renal response criteria and myeloma response assessment are shown in table-I. Serum creatinine levels normali-zed in 19 patients while in 16it remainedabnormal. The relation between myeloma response and improvement in RI in terms of serum creatinine is shown in fig-1. Among 16 patients who had VGPR, creatinine norma-lized in 12 (75%) patients. Eight patients had PR, and creatinine normalized in 1 (12.5%) patient. Out of 35 patients, 11 (31.5%) required dialysis on the presenta-tion, while 24 (68.6%) did not require dialysis. Among the 11 patient who required dialysis, 3 (27.3%)cameoff dialysis while 8 (72.7%) remained dialysis-dependent. Overall, 16 (45.7%) were alive, and 19 (54.3%) were dead. In 30 (85.7%) patients, CTD regimenwas used as first-line chemotherapy, while in 2 (5.7%) VTD (Borte-zomib, Thalidomide, Dexamethasone) was used. Lena-lidomide/ Cyclophosphamide/Dexamethasone (LCD), Lenalido-mide/Dexamethasone (LenDex) and Borte-zomib/Dexamethasone (BorDex) were used in one

Parameter	Value
Age (years)	48 ± 7
Gender	
Male	23 (65.7%)
Female	12 (34.3%)
eGFR (ml/min)	**Mean (range)**
Pre-treatment	25 (4-55)
Post-treatment	71 (3.6-179)
Serum Creatinine (mg/dl)	**Mean ± SD**
Pre-treatment	4.3 ± 3.4
Post-treatment	2.2 ± 2.9
Dialysis	
Required	11 (31.5%)
Not Required	24 (68.6%)
International myeloma working group renal response criteria	**n (%)**
Complete response	19 (54.3%)
Partial response	8 (22.9%)
No response	8 (22.9%)
International Myeloma working group criteria of Myeloma response assessment	**n (%)**
Very good partial response	16 (45.7%)
Partial response	8 (22.9%)
Minimal response	4 (11.4%)
Progressive disease	1 (2.9%)
Died during therapy	4 (11.4%)
Lost to follow up	2 (5.7%)

patient (2.9%) each. The OS at 60 months was 37% for both groups of patients in whom creatinine levels normalized or remained abnormal. The median OS for patients in whom creatinine levels normalized and those in whom creatinine levels remained abnormal was 33 and 15 months respectively (fig-2A). The median PFS was 16 months for the entire cohort (fig-2B).

Among the patients who required dialysis initially, the median OS for those remaining dialysis-dependent and those coming off dialysis was 43 and 33 months respectively (fig-2C). As only three patients remained dialysis-dependent, the number is too small to draw any conclusions.
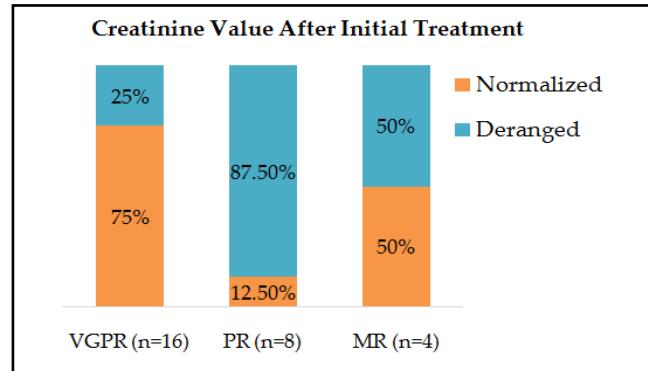

Figure: He relation between myeloma response and improvement in RI in terms of serum creatinine. VGPR: Very good partial response, PR: Partial response, MR: Minimal response.

DISCUSSION

Renal impairment is acommon complication of MM, which has a direct impact on survival[12]. In this study, we evaluated the recovery in kidney functions and its effect on survival after using first-line chemotherapy, which in the majority of our patients was CTD regimen.

In western population, the reported median age at diagnosis of MM is 66 years[9]. In comparison, we noted that median age of our patientsat diagnosis was much lower i.e 48 years. Similar younger median age at the diagnosis is reported in some of the publications in our region[2,13,14]. There was male predominance i.e 65%, which is also in line with what has been reported earlier[15].
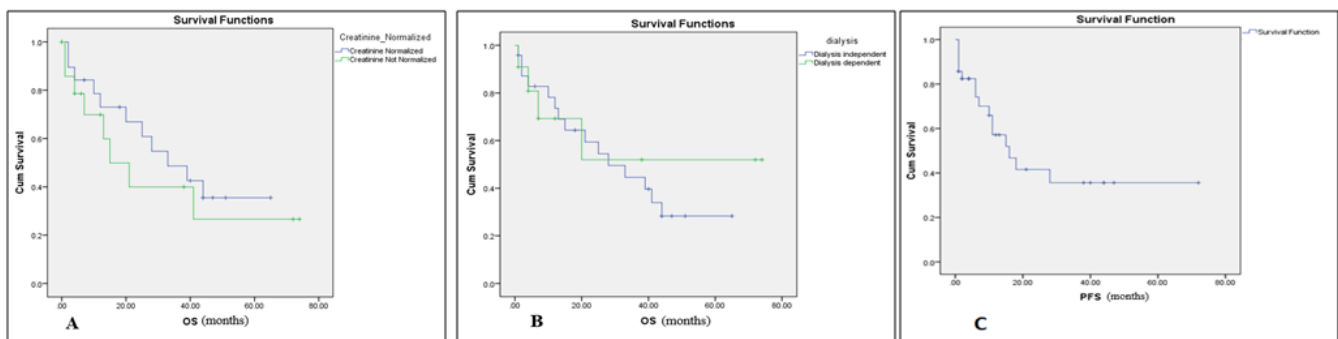

Figure-2A: Overall survival (OS) in reference to creatinine normalization. (B) Overall survival (OS) of patients receiving dialysis versus who got off dialysis. (C) Progression-free survival (PFS) of entire cohort.

We noted that 25% of our patients presenting with MM had renal impairment. Most of the international data also reports similar figures of 20-40% of patients with MM presenting with RI. In addition, around 50% of MM patients advance to RI at some time during the disease course[3].

There is considerable variability in the reported reversibility of renal impairment. In our study, renal functions recovered in 19 (54.2%) patients which is comparable to what is reported. Pönisch *et al*, for example, showed that there is 20-80% recovery of renal functions after starting chemotherapy[16]. The average time for reversibility of renal functions in study was 1.5 months, with two cycles of chemotherapy. This is also comparable to published data. For example, the time to reversibility of renal impairment reported by Blade *et al*. is also around 1.5-1.6 months[17].

We noted that 11 (31.5%) of our patients required dialysis earlier in the course of the disease. Of these, 3 (27.3%) came off from dialysis after first-line therapy, and remaining 8 (72.7%) remained dialysis-dependent. The international data suggests that up to 10% of patients require dialysis at presentation, and death occurs in 30% of cases during the first two months of dialysis[4]. In our study, 2 out of 11(18%) patients died during the first two months of therapy. Although our reported early mortality is less than what has been reported, firm conclusions cannot be drawn as the sample size is small. The median OS of patients who remained dialysis-dependent was 43 months as compared to those patients who became dialysis independent (33 months). Again, due to small numbers, firm conclusions cannot be drawn. However, in a study by Kastritis *et al*. it was reported that with irreversible RI requiring permanent dialysis in MM, the median survival was about two years while 30% survived more than three years[4]. These findings suggest that those who have permanent renal impairment and become dialysis dependent, prolonged survivals can still be acheived[4].

The treatment and outcomes of multiple myeloma have changed significantly since the advent of newer drugs namely bortezomib and thalidomide[4,18]. In our study, the median OS of patients with MM having RI on presentation was 33 months for those in which creatinine levels normalized. Internationally before the year 2000, the median OS was 18-19 months for patients of MM with RI who had age >65 years. This median OS increased to 32 months after 2005. However, MM patients <65 years old with severe RI have had the best reported improvement in median OS of over 60 months[18]. This has been attributed mainly to the introduction of bortezomib which was not possible in our centre because of cost constraints as our hospital is charity based and offers free of cost treatment to majority of the patients. However, thalidomide based treatment was readily available.

Hence, the regimen most commonly used as the first line in our patients was CTD (30-85.7% patients) patients, while only three patients receiving bortezomib based treatment as first-line. Bortezomib based treatments are reported to induce early CR and VGPR according to IMWG myeloma response assessment criteria[19]. Better PFS and OS have been reported when bortezomib based regimens are used as compared to CTD regimen. In one study, 78% of patients underwent autologous stem cell transplantation (ASCT) after bortezomib based VCD induction chemotherapy as compared to 48% when CTD was used[19]. Despite usage of CTD regimen in majority of our patients, comparable early CR and PR according to IMWG renal response assessment were seen.

LIMITATION OF STUDY

This study has a few limitations, first and foremost being limited number of patients. Secondly, due to cost and availability issues, the bortezomib based treatment was offered only a few patients. Therefore, the exact survival comparisons are not possible. The cytogenetic studies were not done in any of our patients at that time due to laboratory limitation. The cytogenetic studies not only give us an idea about standard, intermediate and high-risk categories but also help us in estimating survival, choosing induction chemotherapies and maintenance therapies[9].

CONCLUSION

Prompt recognition and initiation of treatment, in patients of MM with RI, is of utmost importance as the prognosis of patients who get complete renal function recovery have improved survival significantly. Although regimens having bortezomib are now standard care for first-line treatment of MM especially with RI, regimens such as CTD provide a reasonable alternative with improved outcomes.

This study confirms that if treatment is initiated early, the RI in MM is reversible and patients have improved outcomes.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Gastelum ZN, Biggs DM, Scott A. Multiple myeloma presenting as acute renal failure in the absence of other characteristic features. Cureus 2017; 9(9): e1703-08.
2. Sultan S, Irfan SM, Parveen S, Ali H, Basharat M. Multiple Myeloma: A retrospective analysis of 61 patients from a tertiary care center. Asian Pac J Cancer Prev 2016; 17(4): 1833-35.
3. Jung SH, Ahn JS, Yang DH, Cho MS, Kim JY, Ahn SY. Oliguria as an early indicator of mortality risk in patients with multiple myeloma and renal impairment. Blood Res 2015; 50(3): 167-72.
4. Kastritis E, Terpos E, Dimopoulos MA. Current treatments for renal failure due to multiple myeloma. Expert Opin Pharm 2013; 14(11): 1477-95.
5. Dimopoulos MA, Sonneveld P, Leung N, Merlini G, Ludwig H, Kastritis E, et al. International myeloma working group recommendations for the diagnosis and management of myeloma-related renal impairment. J Clin Oncol 2016; 34(13): 1544-57.
6. Faiman B, Tariman JD, Mangan PA, Spong J. Renal complications in multiple myeloma and related disorders: survivorship care plan of the IMF Nurse Leadership Board. Clin J Oncol Nurs 2011; 15(Supply-1): 66-69.
7. Heher EC, Rennke HG, Laubach JP. Kidney disease and multiple myeloma. Clin J Am Soc Nephrol 2013; 8(11): 2007-17.
8. Bozic B, Hölbling S, Völkel V, Sebesta C. Renal insufficiency in patients with multiple myeloma. Memo 2017; 10(3): 151-58.
9. Rajkumar SV, Kyle RA, editors. Multiple myeloma: diagnosis and treatment. Mayo Clin Proc; 2005: Elsevier.
10. Dimopoulos M, Kastritis E, Rosinol L, Blade J, Ludwig H. Pathogenesis and treatment of renal failure in multiple myeloma. Leuk 2008; 22(8): 1485-93.
11. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International myeloma working group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016; 17(8): e328-e46.
12. Laforet M, Jourde-Chiche N, Haddad F, Sallee M, Stoppa A, Brunet P, et al. Evolution in the treatment of multiple myeloma and impact on dialysis independence: data from a French cohort from 1999 to 2014. Blood Cancer J 2016; 6(3): e409-412e.
13. Hameed A, Ali J, Munawar K, Arshad F, Badar F, Siddiqui N. Characteristics and outcomes of patients with multiple myeloma: Data from a developing country. Med J Islam Repub Iran 2018; 32(1): 1-5.
14. Lu J, Chen W, Huo Y, Huang X, Hou J. Clinical features and treatment outcome in newly diagnosed Chinese patients with multiple myeloma: results of a multicenter analysis. Blood Cancer J 2014; 4(8): e239-242e.
15. Weil C, Gelerstein S, Moser SS, Chodick G, Ben-David NB, Shalev V, et al. Real-world epidemiology, treatment patterns and survival of multiple myeloma patients in a large nationwide health plan. Leuk Res 2019; 85(2): 106219-23.
16. Pönisch W, Andrea M, Wagner I, Hammerschmidt D, Kreibich U, Schwarzer A. Successful treatment of patients with newly diagnosed/untreated multiple myeloma and advanced renal failure using bortezomib in combination with bendamustine and prednisone. J Cancer Res Clin Oncol 2012; 138(8): 1405-12.
17. Bladé J, Rosiñol L, Cibeira MT, Fernández de Larrea C. Treatment of relapsed myeloma in a patient with renal insufficiency. J Clin Oncol 2018; 36(20): 2012-16.
18. Dimopoulos M, Delimpasi S, Katodritou E, Vassou A, Kyrtsonis M, Repousis P, et al. Significant improvement in the survival of patients with multiple myeloma presenting with severe renal impairment after the introduction of novel agents. Ann Oncol 2014; 25(1): 195-200.
19. Vigolo S, Zuckermann J, Bittencourt RI, Silla L, Pilger DA. Comparison of cyclophosphamide–thalidomide–dexamethasone to bortezomib–cyclophosphamide–dexamethasone as induction therapy for multiple myeloma patients in Brazil. Hematol Oncol Stem Cell Ther 2017; 10(3): 135-42.

....