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Comparison of the Effects of Different Therapeutic Regimens in the Clinical Manifestations and Laboratory Parameters in Multiple Myeloma Patients

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ABSTRACT:
Multiple myeloma is the neoplasm of the plasma cells that affects approximately 6.5% per lakh population and is the second most common haematological malignancy. As the incidence of MM is increasing and the number of Indian studies is less, a meticulous study regarding the clinical improvements of MM patients along with an overall comparison of different therapeutic regimens was mandatory. The study was a retrospective clinically based cohort study in which the MM patients who received CyBorD, VD, VRD, TD and RD as their chemo regimens were enrolled in the study. Patients at the end of the study showed both clinical as well as statistical improvement in their lab parameters. Despite the retrospective nature of our study, limitation of a small geographical area and absence of clinical data, our study confirms that the survival and the quality of life cannot be attributed to a single therapeutic regimen alone. Future population based studies are essential to confirm these observations.

KEY WORDS: Multiple Myeloma, clinical manifestations , laboratory parameters

I. INTRODUCTION:

Multiple myeloma (MM), also known as Kahler's disease is an incurable hematological malignancy (plasma cell dyscrasia) of clonal B – cells of the plasma cells (a type of white blood cells in the bone marrow) which help to fight against the infections by the activation of immune complementary antigen – antibody response reactions. [1-4]. Multiple myeloma results in the accumulation of malignant plasma cells in the bone marrow and over production of these malignant plasma cells leads to end organ damages such as bone destruction and bone lesions. Approximately 6.5% per lakh population are affected with multiple myeloma and is the second most common hematological malignancy. The exact cause of MM is not established. Studies showed that various factors contribute to the etiology of MM, such as genetic causes, environmental or occupational causes and Monoclonal Gammopathy of Undefined Significance (MGUS) or Smoldering MM (SMM). [5]Staging of MM is done to know the location of malignant plasma B cells, extent of its spreading and whether it has affected other parts of the body . Staging can be done by durie-salmon system, the international staging system (ISS) etc.The first and foremost treatment goals of MM is to achieve a deep and long lasting clinical response, control of malignant cell growth and its spreading, to reduce complications of MM and to improve the quality of life in these patients. Commonly used drugs for MM are [6] Alkylating agents – Cyclophosphamide, Melphalan etc, Proteasome Inhibitor – Bortezomib, Carfilzomib, Ixazomib, Angiogenesis Inhibitor, Immunomodulator, Histone Deacetylase Inhibitor and Monoclonal Antibodies .

According to the US Cancer network, the world wide incidence rate of Multiple Myeloma as in the year 2016 was 2.1% per lakh persons and has shown a global increase of 126% during the year 1990 – 2016[6].As such there were no studies available regarding the clinical response, survival rate, toxicity profile and the improvements seen in the laboratory parameters of MM patients to the different therapeutic regimens in a clinical care setting in Kerala in the recent years. Therefore such a study was relevant and desirable in this setting.Our study aimed at comparing the effects of treatment regimens in the clinical manifestations and laboratory parameters.

II. METHODOLOGY :

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The study was a retrospective cohort study in which the comparison of different chemotherapeutic regimens used for the management of multiple myeloma and their clinical manifestations were analysed. The study was done for a period of 11 months (August 2019–July 2020). Data collection was done only for a period of 5 months (October 2019–February 2020) due to the Covid - 19 and the associated consequences. The study was carried out in the department of Oncology at Caritas Cancer Institute, Kottayam. Caritas Hospital is a tertiary care center with NABH accreditation. The hospital has specialized Institution departments such as Caritas Heart Institute and Caritas Cancer Institute with bed strength of more than 600 and is well equipped with 10 intensive care units, 18 operation theatres and other specialized departments. The multiple myeloma patients who have consulted the Caritas Cancer Institute of Caritas Hospital during the time period 2015 – 2019 and who have satisfied the inclusion and exclusion criteria were selected for the study.

INCLUSION CRITERIA: MM patients who have completed the following treatment regimens and a follow-up of at least 6 months.

o Cyclophosphamide – Bortezomib - Dexamethasone (CyBorD)
o Thalidomide – Dexamethasone (TD)
o Bortezomib – Lenalidomide - Dexamethasone (VRD)
o Lenalidomide - Dexamethasone (RD)
o Bortezomib – Dexamethasone (VD

EXCLUSION CRITERIA: Patients with other types of cancers and myeloma, pregnancy,other treatment regimens, patients who are in palliative care are excluded from the study population.

In our study we had 5 arms and are as follows: Patients treated with different treatment regimens such as - CyBorD, VD, VRD, RD and TD. More than 150 MM patients consulted Caritas Cancer Institute during the time period 2015–2019 and out of them we could only include 87 patients in the study as the result of COVID–19 outbreak and its subsequent consequences. Relevant details of the patient were collected from the patient's case file from the Medical Records Department (MRD). The collected data was then entered into the data collection form. The data regarding the patient's chief complaint at the time of diagnosis, stage and date of diagnosis, past medical and medication history, details of the treatment cycle, details of the treatment modifications (if any) and clinical manifestation of each treatment regimen and the current status of the patient were collected and analysed in this retrospective study. The clinical manifestations were analyzed in these patients after 4 cycles of their treatment regimens (after 4 months) and at the end of the therapy.The baseline characteristics needed for the outcome assessment of MM patients were recorded at the time of diagnosis, after 6 months of the chemotherapy and at the end of the treatment period. Effects of treatment regimens in clinical manifestations and laboratory parameters were also noted and compared. Descriptive statistics for the quantitative variables were represented by the mean and the standard deviation and the descriptive statistics for the categorical variables were represented as number (%). P values were two tailed and a significance level of 5% was used. Bar diagrams, Pie charts and scatter diagrams were used for visualization of these findings. The clinical manifestations were analysed as variations in lab parameters and improvement in symptoms.

III. RESULTS AND DISCUSSION:

The aim of the study was to find the improvement in the clinical manifestations of multiple myeloma patients treated with different therapeutic regimens. The study was conducted in the Cancer Care Institute of a tertiary care hospital among 87 multiple myeloma patients. Even though our predetermined sample size was 94, we could only collect data from 87 MM patients due to the Covid–19 pandemic and its associated consequences. Demographic details such as age, gender, duration of multiple myeloma, stage at the time of diagnosis, CRAB symptoms and the baseline lab parameters of MM patients were collected from the patient records. We could see a slight male predominance and most of the people about 56 (64.37%) of them were above 60 years of age. The mean age years of the patients were found to be 64 ± 11.8. 73 (83.90%) patients showed MM duration of less than 2 years. Staging of MM patients was done accordingly by using the Durie–salmon staging of MM. Among 87 patients, 53 (60.92%) patients were diagnosed at their 1st stage of MM, 28 (32.18%) patients were diagnosed at their 2nd stage and 6 (6.90%) of them were diagnosed at the 3rd stage of MM.Patients with haemoglobin ≤ 10 and > 10 were found to be 49 (56.30%) and 38 (43.70%), patients with calcium ≤ 8 and > 8 were 38 (43.70%) and 49 (56.30%), patients whose serum creatinine ≤ 1.5 and > 1.5 were 61 (70.10%) and 26 (29.90%) respectively. 44

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(50.60%) among 87 showed a baseline value of WBC ≤ 6000 while the rest 43 (49.40%) showed a base line of >6000. About 53 (60.90%) patients showed a baseline value of platelet count as ≤ 2.5 lakhs and the rest 34 (39.10%) showed a base line of > 2.5 lakhs.

Clinical manifestations of MM are as follows: [7]

I. CRAB features:

- Hypercalcaemia (Ca ≥ 12 mg/dL)
- Renal Insufficiency (Creatinine ≥ 2.0 mg/dL),
- Anemia (Hb ≤ 10)
- Bone Lesions - Back pain, painful bone lesions (other than spine) pathologic fractures (other than spine)

II. Non-CRAB features:

- Neuropathy,
- Spinal cord compression,
- Nerve root compression/plexopathy,
- Peripheral neuropathy.

As the study was done retrospectively, the assessment of improvement in these clinical manifestations was not feasible and we assessed the improvement in the clinical manifestations by looking into the improvement shown by the patient's blood levels.

Table 1. Improvement seen in the clinical manifestations and lab parameters of the patients after all treatment cycles.

CLINICAL MANIFESTATIONS AND LAB PARAMETERS	Baseline value (mean)	At the end of all treatment cycles (mean)	Number of patients improved n (%)
Hemoglobin	10.17 ± 2.22	11.31 ± 1.68	45 (51.72)
Calcium	8.46 ± 0.83	9.05 ± 1.19	55 (63.22)
Creatinine	1.50 ± 1.14	1.12 ± 0.53	60 (68.96)
WBC	5885.34 ± 2587.14	7154.92 ± 2891.05	65 (74.71)
Platelet count	2.35 L ± 1.04 L	2.64 L ± 1.73 L	68 (78.16)

Clinical manifestations such as fatigue and weakness, anemia are reflected in the blood hemoglobin levels and the renal complications are reflected in the serum creatinine levels. Improvement in the lab parameters such as blood hemoglobin, calcium, serum creatinine, WBC and platelet count were analysed by comparing the mean of baseline values and the mean values of these parameters at the end of the study period. Clinically as well as statistically significant improvement in the clinical manifestations and lab parameters of the MM patients was seen at the end of their study period. Thus we could say that the therapeutic regimens received by the patients showed improvement of their disease condition.

On assessing the clinical manifestations and lab parameters of MM patients after all treatment cycles, significant improvement was shown by most of the patients. Table 1 shows improvement seen in the clinical manifestations and lab parameters at the end of all treatment cycles. Out of 87 patients, about 45 (51.72%) patients had improvement in their Haemoglobin level from a mean baseline value of 10.17 ± 2.21 to a mean value of 11.34 ± 1.79 at the end of all treatment cycles, improvement in the calcium levels for 55 (63.22%) patients were seen from a mean baseline value of 8.46 ± 0.73 to a mean value of 9.05 ± 0.66 at the end of all treatment cycles, 60 (68.96%) of them showed improvement in their serum creatinine level with a mean baseline value of 1.50 ± 1.06 to a mean value of 1.12 ± 0.78 at the end of their therapy. 64 (73.56%) of them had improvement in their WBC count with a mean baseline value of 5885.46 ± 2611.74 to a mean value of 7154.68 ± 2058.77 at the end of all treatment cycles. 68 (78.16%) of them showed improvement in the platelet count with a mean baseline value of 2.35 L ± 79313.74 to a mean value of 2.60 L ± 86796.79 at the end of their therapy or at the end of the study period. The p value derived from the Paired t–test showed a statistically significant improvement for all of the above lab parameters. Thus we could find that the improvement in the clinical manifestations and lab parameters shown by the patients was both clinically as well as statistically significant.

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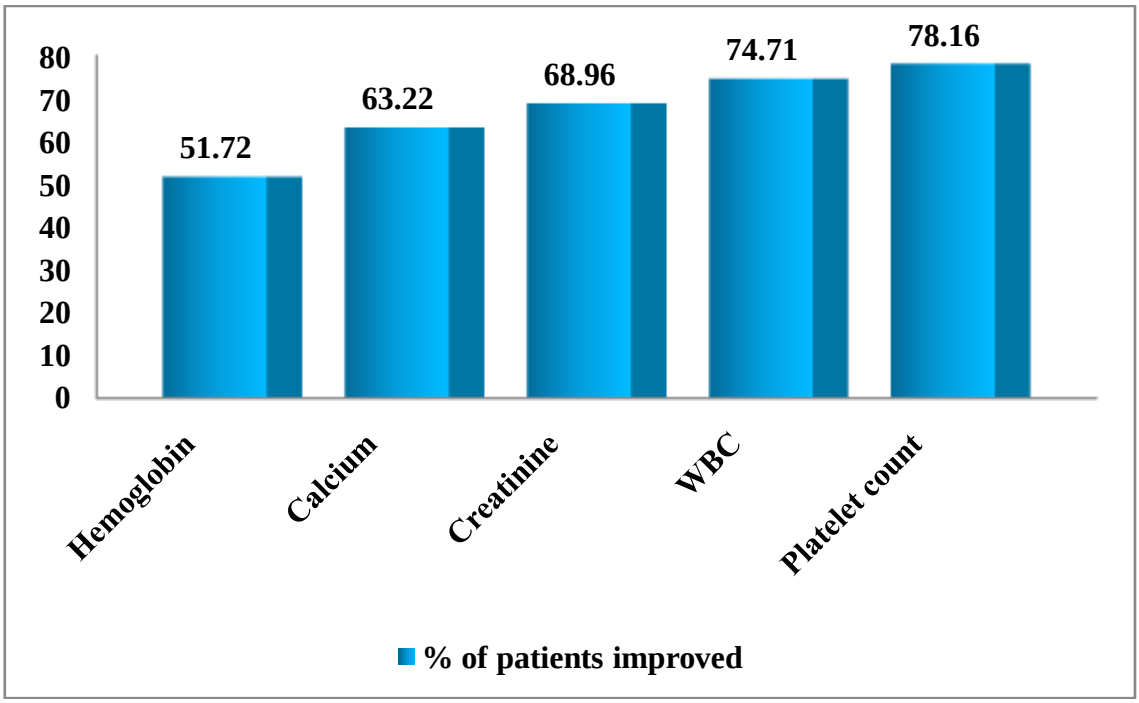

Figure 1. Percentage of patients who have shown improvement in their clinical manifestations and lab parameters at the end of their therapy.

Figure 1. shows the percentage of patients who have shown improvement in their clinical manifestations and lab parameters at the end of all treatment cycles. The percentage of patients who showed improvement in the blood hemoglobin, calcium, serum creatinine, WBC and platelet count was found to be 51.72%, 63.22%, 68.96%, 74.71% and 78.16% respectively.

IV. CONCLUSION:

Since the study was done retrospectively, the assessment of improvement in the clinical manifestations was not feasible and therefore it was obtained from blood levels of MM patients. More than half of the patients showed improvement in their platelet, WBC and creatinine levels. As anemia and other symptoms were corrected, it has led to the improvement of patient's quality of life. In a comparative study A. Riccardi et al. showed that the percentage of recently diagnosed patients who had symptoms related to multiple myeloma was reduced, while the percentage of asymptomatic patients diagnosed by chance was increased [8]. Patients at the end of the study showed both clinical as well as statistical improvement in their lab parameters. In conclusion, despite the retrospective nature of our study, the limitation of a small geographical area and absence of clinical data such as supportive care, our study confirms that the survival of the MM patients and the quality of life cannot be attributed to a single therapeutic regimen alone. Future population based studies are essential to confirm these observations.

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