Research Article

Current Treatment Pattern and Outcome of Chemotherapy regimen in Multiple Myeloma Patients in Tertiary Care Cancer Hospital: A Prospective and Observational Study

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ABSTRACT

Multiple myeloma (MM): is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure or a cancer that starts in plasma cells. MM is the second most common haematological malignancy. Monitoring of prescriptions and drug utilization studies could identify the associated problems and provide feedback to prescribers. This study was aimed to describe the current treatment pattern and outcome of chemo-regimen in MM patients. This was a prospective and observational study during November 2018 to April 2019 all patients with proven diagnosis of MM were included in this study. The ethical approval was obtained from the hospital. The characteristics of patients, current treatment pattern and outcomes were analysed. A total of 52 patients, most of the patients were from geriatric age and were overweight. Bortezomib, thalidomide and dexamethaxone (VTD) regimen was the most frequently used therapy. Chemotherapy was effective in using plasma cell percentage (~50%). The kappa value is 74.54% and lambda value is 52.84%, significant increase in therapy response was observed. The side effects reported were less and mostly common. Once a rare disease, cancer is spreading fast in the modern world, the treatment opportunities are also tremendous. Based on these finding, we suggest that VTD is prescribed majorly in multiple myeloma patients and is effective and safe. Health professionals should be made aware of threats due to chemotherapy in multiple myeloma patients, so that the patient gets the best possible medical care and thus fight against this deadly disease. There is a 'can' in 'cancer' because we will beat it!

Keywords: Multiple myeloma, chemotherapy, plasma cells, M- protein.

INTRODUCTION

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure or multiple myeloma is a cancer that starts in plasma cells.[1] MM accounts for 1% of all cancers and approximately 10% of all hematologic malignancies. In India, incidence of MM varies from 1.2 to 1.8 per 100,000. Approximately, 50,000 new MM cases are diagnosed annually. Key differences in presentation include younger median age at diagnosis – 55 years with 12% of patients being less than 40 years of age, asymptomatic (1%), higher proportion of patients with anaemia (Hb ≤10G/dl-62%), serum creatinine (≥2 mg/dl, 31%) and ISS III stage (40%) and extra- medullary disease in about 20% of patients.[2] Males are predominantly affected by a median age of 70 years in Western countries, however, in some parts of the world, onset is seen in much younger age groups.[3,4]

MM is characterized by clonal expansion of plasma cells. Classic clinical manifestations include hypercalcemia, renal failure, anaemia, and lytic bone lesions as well as recurrent bacterial infections and extramedullary soft-tissue plasmacytomas.[5] When myeloma cells grow and spread throughout the bone marrow, it is called multiple myeloma. Like plasma cells, myeloma cells also make antibodies called monoclonal proteins or M- proteins. International staging system is widely used, which has recently been revised.[1] MM patients are initially treated with primary induction therapy followed by HDT/ASCT in eligible patients and then by maintenance therapy in intermediate and high risk groups.[6] There are several combinations available such as bortezomib, thalidomide plus dexamethasone (VTD), cyclophosphamide plus thalidomide and dexamethasone (CTD), lenalidomide, bortezomib, dexamethasone (RVD), thalidomide and dexamethasone (TD), melphalan combined with prednisone (MP), and melphalan–prednisone–thalidomide (MPT).[7] However, a 3-drug regimen is preferred. Bortezomib- based regimens are the first choice for patients with renal impairment.[8]

Several recommendations of MM diagnosis and treatment cannot be applied in low and middle income countries due to cost issues and availability of novel agents.[9] The therapeutic practice is expected to be primarily based on evidences provided by pre marketing clinical trials, but complementary data from post marketing period are needed to supply an adequate basis for improving drug therapy. Drug utilization studies are powerful exploratory studies to ascertain the role of drugs in society. Monitoring of drug utilization, safety and outcome studies could identify the associated problems and provide feedback to

prescribers. In this study, we investigated prescribing patterns, side effects and outcome of therapy in Multiple myeloma patients.

MATERIALS AND METHODS

Between November 2018 to April 2019, 52 cases of MM patients consecutively seen at Apollo Multi Speciality Hospital and Research Centre, Bengaluru who meets inclusion and exclusion criteria. Inclusion criteria were patients with either Multiple myeloma drugs, outpatients and inpatients, patient irrespective of gender aged above 15 years and exclusion criteria were pregnant and lactating women, patients who are not recorded with Multiple myeloma. This was a prospective and observational study to assess the current prescribing pattern, cost and outcome of chemotherapy regimen of MM patients in oncology one day care department. The ethical approval was obtained by the IECCS of hospital with registration nnumber ECR/320/Inst/KA/2013/RR-16. The patients who meet the criteria were included for the study and follow up was carried out till the discharge, the demographic datas and clinical datas were collected.

Determination of Prescribing pattern

The prescribing pattern of therapy was done by finding the number of chemo regimen prescribed and also the side effects were identified and noted by conducting the follow up of progress notes and laboratory investigation reports of patients.

Determination of Outcome

The diagnostic criteria as recommended were based on clinical information such as serum monoclonal protein, serum free light chain (kappa and lambda). During the monthly cycle of treatment patients were followed of physical examination, blood count, renal and liver function test. Bone marrow aspiration and biopsy with serum were performed at intervals when patient's monoclonal components had reached maximum reduction and the outcome of chemotherapy regimen was done by using European Group for Blood and Marrow Transplant (EBMT) criteria. The M protein is taken under consideration to be measurable if it's ≥1gm/dL within the serum and or ≥200 mg/day within the urine. The M protein level is monitored by serum and urine protein electrophoresis to assess treatment response monthly while on therapy, and every 3–4 months when off-therapy.

Statistical methods

The statistical descriptive analysis has been carried out in the present study. Chi square test has been used to find the significance of study parameters on categorical finding among the different groups.

P value or significant considerations: Actual range (0.01-0.1)

*Strongly Significant if P value is = 0.01

*Significant if P value is </= 0.05

*Moderately Significant if P value is > 0.05 and <0.1

*Not Significant if P value is >/= 0.01

The statistical software called SPSS (IBM) version 1.0 was used for the analysis. Microsoft word and excel are used to generate tables and graphs respectively.

RESULTS AND DISCUSSION

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure or multiple myeloma is a cancer that starts in plasma cells.[1] MM accounts for 1% of all cancers and approximately 10% of all hematologic malignancies. In India, incidence of MM varies from 1.2 to 1.8 per 100,000. Clinical pharmacist as a part of health care team as the opportunity to improve the knowledge and the experience for better pharmaceutical care. Health care professionals needs to carefully assess the prescribing pattern of chemotherapy based on cancer and patient characteristics. This is a field of study in which a clinical pharmacist knowledge and experience is needed and appreciated by other health care professionals and the general public.

Out of 52 patients involved in the study, the majority of the patients were male (67%) and females patients (32%) were less in number. Among 52 patients of various age groups studied, 1.92% patients were in the age group of <29 years, 5.76% patients were in the age group of 30-39 years, 9.6% patients were in between 40-49 years 17% were from the age group of 50-59 years and 65.38% of subjects were from the age group of ≥60 years. It is also found that the, majority of subjects are diagnosed with stage 1 (65.38%) followed by stage 3 (21.15%) and stage 2 (13.46%). BMI show that majority of the subjects are overweight 46.15% followed by which 28.84% of subjects are of normal weight,11.53% are obese and 5.30% are under weight. The evaluation of side effects revealed that 53.85% of patients were found to be well tolerated and free of side effect. Among 46.15% of subjects with side effects, it is found that anaemia (46.15%), headache (26.92%), cough (17.30), vomiting (15.38) and alopecia (13.46%) are the most commonly observed side effects. Characteristics of patients are summarized in Table 1 and 1a.

Among the 52 subject, most of patients were prescribed with dexamethasone (52), bortizomib (48), thalidomide (44) and cyclophosphamide (04) which reveals that, corticosteroids and proteasome inhibitors class of drugs is preferably prescribed among all other class of chemotherapy drugs (Table 2).

In the evaluation of outcome of chemotherapy regimen, it is found that chemotherapy was effective in reducing the plasma cell percentage in bone marrow by 32.30% in males and 15.37% in females. Therefore the overall percentage of reduction in plasma cell range is 47.67% (Approx. 50%). This implies that the therapy is effective in reducing the plasma cell range by approximately 50% in our study (Table 3)

Table 1: Patients, disease, and side effect characteristic

Variable	Level	Number of subjects	Percentage
Gender	Male	35	67
	Female	17	32
Age	<29	01	1.92
	30-39	03	5.76
	40-49	05	9.6
	50-59	09	17
	≥60	34	65.38
ISS staging	Stage 1	34	65.38
	Stage 2	07	13.46
	Stage 3	11	21.15
Side effects	Anaemia	24	46.15
	Headache	14	26.92
	GI discomfort	7	13.46
	Cough	9	17.30
	Vomiting	8	15.38
	LRTI	6	11.53
	Gum swelling	4	07.69
	Alopecia	7	13.46
	Cytopenia ..mostly seen	5	09.61

Table 1a: Body Mass Index BMI (Kg/m^2), Classification based on weight

BMI	Under weight (<18.5)	Norma Weight (18.5-24.9)	Over weight (25-30)	Obese (>30)	Total	%
Male	6	11	15	3	35	13.46
Female	1	4	9	3	17	28.84
Total	**7**	**15**	**24**	**6**	**52**	100

P=0.062, Moderately Significant, Chi-Square test

Table 2: Class wise distribution of chemotherapy agents

Class of Drug	Drug name	Subject
Proteasome Inhibitors	Bortizomib	48
	Carfilzomib	02
Coricosteroids	Dexamethasone	52
Bisphosphonates	Zoledronic Acid	07
	Ibandronate	02
Immunomodulatory Drugs	Thalidomide	44
	Lenalidomide	05
	Pomalidomide	01
Cytogenic Agents	Cyclophosphamide	04
Vinca Alkaloids	Vincristine	01

Table 3: Distribution of average serum M-Protein (Kappa and Lambda) values before and after initiation of chemotherapy.

Average	Kappa (3.3-19.4 Mg/L)		Lambda (5.71-26.3 Mg/L)	
	Male	**Female**	**Male**	**Female**
Before	66	31.91	62.5	38.93
After	22.89	18.72	27.2	29.67
Mean	34.88		39.57	
Mean+/-SD	21.46		7.00	
Total percentage change	74.54%		52.84%	

P=0.072, Moderately Significant, Chi-Square test

The evaluation of effectiveness was done by collecting the laboratory data and test were M- protein and the response was categorized according to EBMT (European Society for Blood and Marrow Transplantation) criteria. Out of 52 patients, the evaluation of response obtained shows that the majority of the patients were found to have partial

response (82.69%) and (13.46%) of subjects showed complete response. Mortality rate of MM in 6 months was found to be (3.84%) (Figure 1).

Figure 1: Evaluation of response obtained
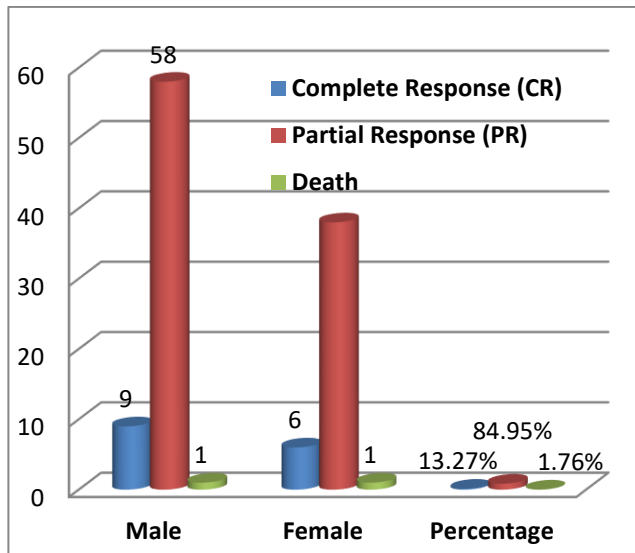
P=0.99, Non significant, Chi-square test

In the current study, we studied patients of various age group and found maximum participation of patients in the age of ≥ 60yrs (65.38%). This shows that the prevalence of MM is high in geriatric age group which may be due to age related immune suppression to fight against infection. Similar finding was found in the study of Carla M et al.[10] We also found that, there were a greater number of male patients compared to female patients enrolled in the study. Similar findings were found in the study conducted by the Caroline E O et al.[11] We evaluated for the BMI, which shows that majority of the subjects are overweight (46.15%) and obese (11.53%). This implies that weight is one of the risk factors for acquiring various disorders indicating the deviation from healthy life style among the population. Out of 52 patients, majority of the patients were under stage 1(60.17%). In the treatment of cancer the occurrence of side effects are common due to suppressed immune system and novel agents, therefore we evaluated for side effects and we found that the most commonly seen were anaemia, headache, alopecia and cough.

The therapy of individual patients is based on several factors including age, symptoms, laboratory parameters, cytogenic, goals of treatment, previous myeloma treatment, quality of life and personal reference. Paradigm of MM management evolved by introducing novel drugs including proteasome inhibitors and immunomodulatory drug. These agents have increased the response rates before and after ASCT.[12] Bortezomib, thalidomide, or lenalidomide – based regimens followed by ASCT are the standard approaches for transplant eligible patients. Combination therapy with melphan and prednisone with either thalidomide, lenalidomide or bortezomib is recommended in the transplant ineligible patients.[13] In our study we found that bortezomib, thalidomide and

dexamethasone (VTD) were the most frequently used first line regimen to treat MM due to the improved survival rate in patients. Similar findings were found in the study conducted by Kaladada I et al.[14] The effectiveness of therapeutic agents in MM patients based on the changes in the parameters (M–Protein, ie; Kappa and Lambda) and found that the overall percentage change in kappa and lambda value which implies that there is 50% reduction and serum and protein, the response obtained shows that the majority of the patients were found to have partial response. Similar findings were found in the Caroline E O et al.[11]

The limitations of the study were less sample size, short study duration and single centre study. Moreover, we did not look at the effects of different factors on progression free survival (PFS) and overall survival (OS).

CONCLUSION

Based on our results, onset of MM occurs more in geriatric male patients (≥ 60yrs), most of them were overweight and the majority of the patients with first stage of MM. Bortezomib, thalidomide and dexamethasone (VTD) were the most frequently used first line regimen to treat MM due to the improved survival rate in patients. The most common side effects reported in our study were anaemia, headache, alopecia and cough. The changes in M- protein (kappa and lambda) were significant suggesting chemo regimen has been effective. Based on these finding, we suggest that VTD is prescribed majorly in multiple myeloma patients and is effective and safe.

There is a need to take serious measures in under resourced countries to improve care provided to MM patients. The treatment opportunities are also tremendous, yet side effects of the chemotherapy cannot be ruled completely. Cost availability of novel agent in the developing world is all major obstacles in providing high quality care. Thus, health professionals should be made aware of threats due to chemotherapy in multiple myeloma patients, so that the patient gets the best possible medical care and thus fight against this deadly disease.

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