COMPARISON OF ADVERSE DRUG EVENTS IN MULTIPLE MYELOMA PATIENTS TREATED WITH CDT(CYCLOPHOSPHAMIDE DEXAMETHASONE THALIDOMIDE) AND BORTEZOMIB BASED REGIMENS: A PROSPECTIVE COHORT STUDY FROM TERTIARY CARE TEACHING HOSPITAL, KERALA

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ABSTRACT

Background and objectives: Chemotherapeutic drugs belongs to a group of drugs having verylean therapeutic index. Therefore the therapeutic response attaining substantiateharm to the body's neoplastic cells. No much published data exist related to the study of adverse drug events of chemotherapy drugs, especially which is used for hematological malignancies in Indian population. We evaluated whether ADRs vary in patients with Multiple Myeloma taking two different chemotherapy regimens in this prospective cohort study.**Methods:**patients who fulfilled the inclusion criteria were enlisted for the study and they were divided into two groups according the chemotherapy regimen they are taking. The patients who received Cyclophosphamide, Dexamethasone and Thalidomide were assigned to group CDT and those who received Bortezomib based regimenwere in group Bb. Adverse drug events weredetermined by direct interview with the patients and also by analyzing the patient's investigation reports.Then the adverse events were assessed as per NCI CTCAE guidelines.**Result and discussion:** A total of 54 patients were enrolled of which, 30 patients (55.6%) received Bb and 24 patients (44.4%) received Bb regimen. Among eleven system organ classification studied, ophthalmological disorder (P value=0.042) and nervous system disorder (P value=0.048)was statistically significant. Conjuctivitis was present in 6 subjects from Bb and no subjects from CDT had conjuctivitis. Severe peripheral neuropathy were present in 11 subjects from Bb and no one in CDT.6 subjects from CDT had dyspnoea and 1 subject from Bb. Generalised muscle weakness was observed from both Bb and CDT. Although hematological reactions were a few but most of them belongs to severe type. 10 from CDT and 4 from Bb had diarrhoea. 11 subjects from Bb and 10 subjects from CDT had weight loss and no one had weight gain.**Conclusion:**Both of the regimen were considerately well tolerated by the subjects.Serious (Grade 3 or 4) adverse effects were very uncommon. Most of the adverse effects were mild.

Keywords: Multiple Myeloma; Bortezomib; Cyclophosphamide; Dexamethasone; Thalidomide; Adverse drug reaction; NCI CTCAE

No: of Tables : 2 **No: of References: 14**

Introduction

There are 16,000 newly diagnosed Multiple Myeloma cases diagnosed in India each year which is very different from USA where it is 22,000. The reason for this may be difference in diet, life expectancy, rural vs. urban population, industrialization, use of chemicals and pesticides, under-reporting, genetics etc.Multiple myeloma is a hematogical malignancy caused by abnormality of plasma cells characterized by hypercalcemia, renal insufficiency or failure, bone pain and abnormal bone radiographs, anemia and a monoclonal protein in urine or serum or both. It begins in the form known as monoclonal gammopathy of undetermined significance(MGUS) and progresses to asymptomatic myeloma and then lastly to symptomatic myeloma. The three main domains in the understanding of pathophysiology are cytokines and cell signaling, bone Marrow Microenvironment and cell Cycle. Bifunctional alkylating agents like Melphalan and cyclophosphamide are considered as standard therapy for multiple myeloma. Patients who are chosen for stem cell transplantation can be treated with Lenalidomide, an immunomodulatory agent and an amino-substituted variant of Thalidomide. It is given along with dexamethasone. In stem cell therapy, the patients receive stem cells intravenously similar to the blood transfusion and this phase takes 1-5 hours. Since chemotherapy drugs comes under the class of drugs having narrow therapeutic index, the possibility of arousal of an adverse drug event is very high. Hence it is crucial when it comes to the study of adverse drug events. Multiple myeloma cannot be completely cured which makes patients to receive chemotherapy for considerable long period of time. This implies that there is a great significance in detail understanding of the both good and deleterious effects of the drugs used for the treatment of multiple myeloma.

This aim of the study was to assess whether ADRs varies in patients with multiple myeloma when treated with 2 different chemotherapy regimens. The two regimens coming under the study are Cyclophosphamide, Dexamethasone and Thalidomide (CDT) and Bortezomib based regimen.

Methodology

Study design and participants

This is a prospective cohort study which was conducted at Department of Hemato Oncology, Government Medical College, Kozhikode, India. Duration of the study was over a period of 6 months (March 2018-August 2018). All the patients with multiple myeloma who received chemotherapyCyclophosphamide, Dexamethasone and Thalidomide (CDT) and Bortezomib based regimen as out-patients in chemotherapy day care ward or in patients under Dept. of Hemato Oncology were included in the study. According to the formula a minimum of 25 subjects were needed in each study group.

Inclusion criteria

- Multiple myeloma patients prescribed with any of the two chemotherapy regimen.
- Subjects with 18-80 years of age.
- Both males and females

Exclusion criteria

- Subjects with serious infections
- Subjects with End stage disease
- Blind patients
- Alzheimer's patients
- Psychiatric patients
- Pregnant/lactating patients

Materials

- NCI CTCAE Version 4.0
- Case sheet of patients.
- Laboratory reports.

Study procedure:A prospective cohort study of 6 months duration has been carried out in the Department of Hemato-Oncology, Govt. Medical College, Kozhikode. Subjects who fulfilled the eligibility criteria were enrolled for the study from March 2018 to August 2018. Demographic details of the patients like name, age, sex, residing area, education level, marital status, past medical history were obtained during interview. Chemotherapy details like regimen, mode of treatment were obtained from master file and individual case sheet. The collected data were entered to Data Collection Form (DCF). A total of 54 patients have been enrolled for the study out of which 30 patients with intake of bortezomib (group 1) and 24 patients with intake of CDT (Cyclophosphamide, Dexamethasone, Thalidomide) regimen (group 2). Quality of life was assessed by EORTC QLQ - C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire) and EORTC - MY20. All possible adverse drug events are assessed by NCI CTCAE (Common Terminology Criteria for Adverse Events) grading. All the collected data were entered to Microsoft Excel 2013 for the purpose of further statistical analysis.

Statistical analysis

PASW statistics 18, 2009 version was implemented to perform statistical analysis. Socio-demographic variables were analyzed first. Qualitative data were analyzed using frequency and percentage and qualitative data were analyzed by mean and standard deviation.Descriptives and cross tabs (chi-square test) was used to analyze the statistical difference in the ADR among two regimens was analyzed using. The level of significance was set at 0.05. All p values less than 0.05 were considered as significant. Results of the present study are illustrated in Tables 1-2.

Table 1 Baseline measures

Overall Subjects Analyzed [Units: Subjects]	Bb	CDT	P value
Age [Units: Years] Mean	67.14 ± 2.91	69.74 ± 6.45	0.006
Gender [Units: Subjects]			
Female	18	12	
Male	12	12	0.462
Education level			
Illeterate	6	5	
School level	22	18	
Graduate	2	1	0.923
Comorbidities			
Present	12	17	
Absent	18	7	0.190
Family history			
Present	4	2	
Absent	26	22	0.425
Social habits			
Nil	18	13	
Alcoholic	1	2	
Smoker	2	1	

Pan chewer	1	3	0.624
Ex-alcoholic	2	2	
Ex-smoker	5	1	
Multiple habits	1	2	
Residence			
Rural	27	21	0.771
Urban	3	3	

Table 2 Adverse Events (AE)

	Bb	**CDT**	**P value**
Total, SAE # Subjects affected/ at risk (%)	30 (100%)	24 (100%)	
Dermatological reactions			
Alopecia # Subjects affected/ at risk (%)	30 (100%)	24 (100%)	-
Dry skin # Subjects affected/ at risk (%)	11 (36.7%)	10 (41.7%)	0.708
Rash aceniform # Subjects affected/ at risk (%)	5 (16.7%)	5 (20.8%)	0695
Gastro intestinal reactions			
Abdominal distension # Subjects affected/ at risk (%)	8 (26.7%)	5 (20.8%)	0.618

Abdominal pain # Subjects affected/ at risk (%)	4 (13.3%)	6 (25%)	0.273
Diarrhoea # Subjects affected/ at risk (%)	4 (13.3%)	10 (41.7%)	0.050
Constipation # Subjects affected/ at risk (%)	14 (46.7%)	11 (45.8%)	0.951
Nausea # Subjects affected/ at risk (%)	13 (54.1%)	10 (41.7%)	0.661
Vomiting # Subjects affected/ at risk (%)	24 (80%)	17 (70.8%)	0.665
Investigation related disorders			
Neutrophil count decreased # Subjects affected/ at risk (%)	13 (43.3%)	20 (83.3%)	0.567
Weight gain # Subjects affected/ at risk (%)	0	0	-
Weight loss # Subjects affected/ at risk (%)	11 (36.7%)	10 (41.7%)	0.708
Hematological reactions			
Anemia # Subjects affected/ at risk (%)	16 (53.3%)	11 (45.8%)	0.584
Leucocytosis # Subjects affected/ at risk (%)	2 (6.7%)	3 (12.5%)	0.690
Lymph node pain # Subjects affected/ at risk (%)	4 (13.3%)	1 (4.7%)	0.248
Ophthalmological reactions			
Blurred vision # Subjects affected/ at risk (%)	0	1 (4.2%)	0.425
Conjuctivitis # Subjects affected/ at risk (%)	6 (20%)	0	0.049
General disorders			
Localized edema	3 (1%)	3 (12.5%)	0.771

# Subjects affected/ at risk (%)			
Malaise # Subjects affected/ at risk (%)	8 (26.7%)	12 (50%)	0.078
Fever # Subjects affected/ at risk (%)	9 (30%)	3 (12.5%)	0.124
Fatigue # Subjects affected/ at risk (%)	30 (100%)	24 (100%)	-
Musculo skeletal reactions			
Generalized muscle weakness # Subjects affected/ at risk (%)	30 (100%)	24 (100%)	-
Myalgia # Subjects affected/ at risk (%)	4 (13.3%)	3 (12.5%0	0.928
Arthralgia # Subjects affected/ at risk (%)	8 (26.7%)	7 (29.2%)	0.839
Metabolism and nutrition related disorders			
Hypocalcemia # Subjects affected/ at risk (%)	4 (13.3%)	6 (25%)	0.273
Hypoglycemia # Subjects affected/ at risk (%)	4 (13.3%)	2 (8.3%)	0.561
Nervous system disorders			
Somnolence # Subjects affected/ at risk (%)	3 (10%)	5 (20.8%)	0.695
Peripheral neuropathy # Subjects affected/ at risk (%)	11 (36.7%)	0	0.001
Respiratory disorders			
Dyspnoea # Subjects affected/ at risk (%)	1 (3.3%)	6 (25%)	0.019
Psychiatric disorders			
Depression # Subjects affected/ at risk (%)	6 (20%)	5 (20.8%)	0.940

Discussion

Baseline characteristics of the subjects

Prevalenceof multiple myeloma was high in elderly patients especially who areunder the age group of 61-70 and majority of the population aged between 51 and 60from all the groups. Multiple myeloma is the more common amongst women in both developed and developing countries. Among 54 patients, 30 (55.6%) subjects were female and 24 subjects (44.4%) were male. Multiple myeloma accounts for 1% of all neoplastic disorders and 10% of all hematological malignancies.[2]A Ravindranet al[11] point out that the proportion of multiple myeloma was higher among women than in men.

Adverse drug reactions

All the reported adverse drug events were categorized under 11 SOC. Nervous system disorders ophthalmological reactions were significant among all the SOCs. ADRs were analyzed as per NCI CTCAE criteria version 4.03. All the subjects experienced any of the ADR. Dermatological reactions, gastro intestinal reactions and general disorders were present in all enrolled subjects.

Dermatological reactions: Dry skin were present in 11 subjects from Bb and 10 subjects in CDT and rash acneiform were seen in 5 subjects in Bb group and 5 subjects in CDT group. They showed no statistical significance. Alopecia present in every subjects was common and appeared early (days to week).

Gastro intestinal reactions:A significant difference among the study groups were seen when diarrhea is considered. Here 10 subjects (41.7%) from CDT had diarrhoea. Majority of the reported gastro intestinal ADRs were mild among the groups. Constipation, vomiting and abdominal pain was comparable among the groups with no significant difference similar to study conducted by Kirthi C et al.[12]

Investigations: No significant difference among the study groups where seen when investigation related disorders was considered.

Hematological reactions: All hematological reactions were statistically insignificant among the study groups.

Ophthalmological reactions: A significant difference among the study groups where seen when conjunctivitis is considered. Here, 6 subjects (20%) from Bb group had conjunctivitis.

General disorders: When consideringgeneral disorderstheir comparison among the study groups where statistically insignificant.

Musculo-skeletal reactions: When considering musculo-skeletal disorders their comparison among the study groups where statistically insignificant.

Metabolism and nutrition related disorders: There is no significant difference in the study groups when metabolism and nutrition related disorders was considered. This is in line with the study conducted by SneegdhaPoddaret al.[47]

Nervous system disorders: A significant relation between Peripheral neuropathy

and chemotherapy were clearly seen from the study. Peripheral neuropathy appeared as higher in Bb group(36.7%).AndreasA et al[53]conducted a study which showed similar result and it showed it is is increasingly recognized that BIPN (Bortezomib induced peripheral neuropathy) producea primarily a painful, axonal, sensory distal neuropathy. Incidence of BIPN is associated with various risk factors which includes cumulative dose and evidence of any preexisting neuropathy.

Respiratory disorders: When considering respiratory disorders their comparison among the study groups where statistically significant (P=0.019). 6 subjects of CDT group had dyspnea and 1 subject from Bortezomib group had dyspnea.

Limitations of this study

Since the study is of a short span the late showing drug effects cannot be determined and included in the study results. Hepatic, renal, hematological, neurological and occular-toxicity mainly takes several months and years to appear after completing the treatment. Even though our study reveal that there is no significant difference when using two different regimens for multiple myeloma, there are many psychological aspects of the patients to be considered which they are reluctant to reveal. More studies have to be conducted on this aspect.

Conclusion

The Adverse events of the chemotherapy drugs used for multiple myeloma were assessed during a period of 6 months. The results shows all the patients receiving chemotherapy encountered one or more adverse events. Nausea, diarrhea, anemia, vomiting, weight loss, alopecia, anemia, anorexia and constipation were the most frequent adverse events. Most of the adverse drug events were mild and subsided with the supportive treatment. Peripheral neuropathy was seen in patients receiving bortezomib based regimen. Eventhoughpremedications were used, the incidence of adverse effects was relatively high. Inorder to minimize the adverse eventsther should be more light to be throwed on to appropriate interventions, rational use of premedications and non-pharmacological treatments.

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