Original Article

Symptomatic Outcome of CTDa In Multiple Myeloma Patients

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Abstract

Background: *Multiple Myeloma (MM) represents approximately 15% of all hematological malignancies. Despite the use of high-dose chemotherapy followed by stem cell rescue MM remains incurable at present. The goal is to control the disease as much as possible, providing the best quality of life to patients for the longest duration. Currently, CTDa (attenuated Cyclophosphamide, Thalidomide, Dexamethasone) is the best option of treatment as it is cost-effective, with no need for hospitalization with a good response.* ***Objective:*** *To find out the symptomatic responses and toxicities of CTDa in Multiple Myeloma patients.* ***Materials and Methods:*** *25 patients of newly diagnosed MM patients were treated in the Haematology Department,* Bangabandhu Sheikh Mujib Medical University *(BSMMU) from July 2016 to July 2017. The mean age of the patients was 54 years, Male female ratio was 1.5:1 and most of the patients were farmers. After induction of 4 to 6 cycles of CTDa all patients were followed up at 6th and 12th weeks. At follow up we evaluated improvement of weakness, bone pain, Hb%, ESR, monoclonal protein, ß2microglobulin, bone marrow plasma cells and serum calcium and albumin level. Adverse effects, such as peripheral neuropathy, thromboembolic events, hyperglycemia, constipation, rash, and somnolence were also assessed.* ***Results:*** *Among 25 patients, complete response achieved only 13 patients (52%), where 20% and 16% of patients belonged to partial or no response respectively. The death occurred in 2 cases (12%).* ***Conclusion:*** *CTDa is a gentle approach to treat an especially frail group of patients, since virtually all patients ultimately relapse.*

Key words: *Multiple Myeloma, CTDa, Monoclonal protein, ß2 microglobuli.*

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Introduction

Multiple myeloma (MM) is a clonal B-cell malignancy characterized by the marrow and usually secret monoclonal immunoglobulin or immunoglobulin light chains. It results in skeletal involvement, with osteolytic lesions, hypercalcaemia, anemia and/or soft tissue involvement. In addition, nephrotoxic monoclonal immunoglobulins can result in renal failure and the risk of life-threatening infections due to a lack of functional immunoglobulins.[1] It represents approximately 1% of all malignant diseases and 15% of all hematological malignancies. The median age of diagnosis is 65-70 years with 15% and 2% are younger than 50 and 40 yrs respectively. Despite the use of high-dose chemotherapy followed by stem cell rescue MM remains incurable at present. The goal is to control the disease as much as possible, providing the best quality of life to patients for the longest duration by judicious, intermittent use of available classes of active chemotherapeutic agents.[2] According to the British Journal of Haematology (BJH) guidelines for diagnosis and management of multiple myeloma induction regimens should contain at least one novel agent. For older and less fit patients in whom high dose therapy is not planned initial induction therapy should consist of either a thalidomide containing regimen in combination with an alkylating agent and steroid such as MPT or CTDa or bortezomib in combination with melphalan and prednisolone. CTD is the most widely used combination in UK.[3] Asbortezomib is very costly and can only be given IV route, CTD or CTDa can also be the most suitable induction regimen for MM patients in Bangladesh. Patients who underwent autologous stem cell transplantation (ASCT) after CTD

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therapy had higher success rates and longer survival.[4] Currently thal-dex is one of the standard treatments for newly diagnosed myeloma patients but is associated with high rate of blood clotting in the deep veins and negative effects on stem cell mobilization. In Bangladesh availability, cost-effectiveness, total duration and whether patients require hospital admission for the therapy must also be considered. As induction regimen 4 to 6 cycle can be given. CTDa is an oral regimen, so hospital admission is not required, cost effective for our general population with minimum 4 cycles that is completed within 4 months with high response rate. But in our country no organized and structured clinical trial of response of CTDa in MM patients has yet been carried out. This clinical study will reflect the response of CTDa in newly diagnosed patients of MM in Bangladesh.

Materials and Methods

It is a descriptive type of observational study carried out at the Haematology Department, Bangabandhu Sheikh Mujib Medical University (BSMMU) from July 2016 to July 2017. Thirty newly diagnosed MM patients 40 to 75 years of age, with a platelet count 100x109/L, ANC 1x109/L, normal renal function, liver function, cardiac function and coagulation study who willingly gave informed consent to take part in this study were included in this study. Relapsed or refractory MM patient with history of other malignancy, uncontrolled Diabetes, Grade-2 peripheral neuropathy were excluded. Among the 30 patients 5 discontinued treatment. So the sample size was 25. These patients got CTDa as follows.

CTDa schedule: 28 days cycle.

Days	Drug	Dose	Route
1, 8, 15, 22	Cyclophosphamide	500mg/day	P/O
1-21	Thalidomide	100mg/day	P/O
1-4, 15-18	Dexamethasone	20mg/day	P/O

After induction of 4 to 6 cycles of CTDa all patients were followed up at 6th and 12th week. During follow up we observed and investigated the following things, such as, weakness, bone pain, serum calcium, serum albumin, ß2 microglobulin, Hb%, ESR, bone marrow plasma cells, monoclonal protein, osteolytic lesions, Bence Jones protein. Data were collected at pre-designed datasheet and analyzed by using SPSS version 16.

Results

The age ranged from 40-75 years. The mean age was 54.04 (SD±8.35) (Table I).

Table I: Age distribution of patients

Age (years)	Frequency	Percentage
40-50	09	36%
51-60	12	48%
61-70	03	12%
71-75	01	4%
Total	25	100%

Male was found 15 (60%) and female was 10 (40%). The male and female ratio was 1.5:1. (Table II)

Table II: Sex distribution of patients

Sex	Frequency	Percentage
Male	15	60%
Female	10	40%
Total	25	100%

Most of the patients were farmers. Other frequent occupation was service holders, housewives and others (Table III).

Table III: Occupation of patients

Occupation	Frequency	Percentage
Farmer	08	32%
Industrial worker	07	28%
Small traders	02	08%
House wife	06	24%
Service holder	02	08%
Total	25	100%

All patients had weakness (100%), most of the patients had anaemia (96%) and bone pain (88%). Weight loss, fever and neuropathy were 28%, 20% and 04% respectively (Table IV).

Table IV: Clinical presentation

Presentation	Frequency	Percentage
Weakness	25	100%
Anaemia	24	96%
Bone pain	22	88%
Weight loss	07	28%
Fever	05	20%
Neuropathy	01	04%

Weakness and bone pain reduced in 6 weeks and 12 weeks follow up (Table V).

Table V: Statistics of Clinical outcome

Presentation	Before Chemotherapy	Follow up	
		At 6 weeks	At 12 weeks
Weakness	25 (100%)	19 (76%)	10 (40%)
Bone pain	22 (88%)	08 (32%)	05 (20%)

The patients' mean Serum calcium before chemotherapy was 9.95 mg/L which gradually went down 9.18 mg/L and 9.02 mg/L at 6 and 12 weeks respectively. Mean S. albumin and ?2 Microglobulin was 29.12 g/L and 4.75 mg/L, but after chemotherapy at 12 weeks, it was 35.36 g/L and 2.7 mg/L respectively (Table VI).

Table VI: Mean Biochemical findings

Biochemical analysis (Mean)	Before Chemotherapy	Follow up At 6 weeks	At 12 weeks
Serum Calcium (mg/L)	9.95	9.18	9.02
Serum Albumin (g/L)	29.12	31.24	35.36
2 Microglobulin (mg/L)	4.75	3.27	2.7

Mean ESR before chemotherapy was 90.76 mm in 1st hour, whereas after treatment at 6 weeks and 12 weeks were 34mm in 1st hour and 18.30mm in 1st hour respectively. Before treatments, mean Hb concentration was only 8.36 g/dl which was increase to 10.87 g/dl and 11.85 g/dl at 6 and 12 week (Table VII).

Table VII: Mean Haematological findings

Haematological findings (Mean)	Before Chemotherapy	Follow up At 6 weeks	At 12 weeks
Hb% (g/dl)	8.9	10.87	11.85
ESR (mm in 1st hour)	90.76	34	18.30
Bone marrow plasma cell (%)	69%	Not done	19%

Out of 25 patients, 19 (76%) had serum monoclonal protein, which reduced to 48% at 6 week and 12% at 12 week (Table VIII).

Table VIII: Statistics of Monoclonal protein

Serum monoclonal protein		Frequency	Percentage
Before chemotherapy		19	76%
After chemotherapy	At 6 weeks	12	48%
	At 12 weeks	3	12%

In our study, we found 4 (16%) cases had bony lesions in the skull and chest and one (4%) had in dorso-lumber spine, which improved after chemotherapy (Table IX).

Table IX: Study of osteolytic lesions (radiological findings)

X-ray	Before Chemotherapy	Follow up At 6 weeks	At 12 weeks
Skull	04 (16%)	03 (12%)	02 (08%)
Chest	04 (16%)	03 (12%)	02 (08%)
Dorso-lumbar spine	01 (04%)	01 (04%)	01 (04%)

One patient (4%) had urinary Bence Jones protein which remained positive at 6 week but disappeared at 12 week of treatment.

During treatment, some patients developed Somnolence, peripheral neuropathy, constipation, hyperglycaemia, intracranial haemorrhage, rash/desquamation, cardiac arrest and electrolyte imbalance (Table X).

Table X: Table of toxicity after treatment

Toxicity	Frequency	Percentage
Peripheral neuropathy	05	20%
Constipation	03	12%
Hyperglycaemia	01	04%
Somnolence	06	24%
Rash/Desquamation	01	04%
Intracranial haemorrhage	02	08%
Cardiac arrest	01	04%
Electrolyte imbalance	01	04%
Thromboembolism	00	00%

Among 25 patients, complete response achieved only 13 patients (52%), where 20% and 16% of patients belonged to partial or no response respectively. The death occurred in 2 cases (12%) (Table XI).

Table XI: Statistics of treatment outcome

Treatment outcome	Frequency	Percentage
Complete response	13	52%
Partial response	05	20%
No response	04	16%
Death	03	12%

Discussion

Baseline data of 25 newly diagnosed MM patients were recorded before treatment and follow up were recorded at 6th and 12th weeks after completion of chemotherapy.

The mean age was 54.04, ranged from 40-75 years. The mean age of the study was lower than other studies. Dingli et al.[5] found the mean age 65, ranged 38-83 years, Rajkumar et al.[6] found mean age 57, ranged 34-65 years, Lokhorst et al.[7] found mean age 66, ranged 36-78 years and Deok-Hwan et al.[8] found mean age 62.5, raged 38-70 years.5-8 In our study male-female ratio was 1.5:1, which widely varies from other studies such as 1:1, 2:1, 1:1 and 1.2:1 respectively.5-8 Most of the patients in this study were, farmer (32%), others were industrial worker (28%), housewife (24%), small traders (08%) and service holders (08%). In a study done by Eriksson and Karlsson, found that among 275 patients 151 (54.9%) were farmer, 58 (21.1%) were worker, 17 (6.1%) were driver and others were service holders and businessman.[9]

All of the patients presented with weakness followed by bone pain in 88%, weight loss 28%, fever 20%, neuropathy 04% and anaemic were 96%. WhereasLokhorst et al. in their study, showed 100% of patient had bone pain, 77% anaemic and 41% patients had infection.[7]

The mean Hb concentration was 8.36 g/dl before treatment which increased 10.87 g/dl and 11.85 g/dl at 6th and 12th weeks respectively after treatment. Mean ESR before chemotherapy was 90.76 mm in 1st hour, where after treatment at 6th weeks and 12th weeks were 34 mm in 1st hour and 18.30 mm in 1st hour respectively. Whereas Jagannath et al. in his study showed 82% of patients had Hb<10 g/dl and 86.4% had high ESR >85 mm in 1st hour.[10] In this short period of study bone marrow was done two times to evaluate the plasma cell percentage as it is a costly and invasive procedure. The mean bone marrow plasma cell percentage before chemotherapy was 69% and after chemotherapy was 19% at 12th weeks.

Among the patients, the mean Serum Calcium before chemotherapy was 9.95 mg/dl which gradually fell down 9.18 mg/dl and 9.02 mg/dl at 6th weeks and 12th weeks respectively. At diagnosis mean Serum Albumin and B2 Microglobulin were 29.12 g/L and 4.75 mg/L respectively. In our study only 18% of patients had hypercalcaemia. This result matched with the study of Khan et al. who found almost the same result.[11]

During treatment 24% of patient suffered from somnolence, 20% had peripheral neuropathy, 12% complained of constipation and 4% suffered from hyperglycaemia, rash, cardiac arrest and electrolyte imbalance. Life-threatening intracranial haemorrhage occurred in 8% of patients. Jagannath et al. in their study the most common adverse events were sensory neuropathy 31%, constipation 28%, myalgia 28% and fatigue 25%.[10]

At induction therapy, the rate of thromboembolism in this study was nil but in some study where showed that the adverse events of thromboembolism may occur 12%-13% in the course of treatment.[12] They suggested the use of anticoagulation therapy to decrease thromboembolic events dramatically. Deok-Hwan et al. showed 5.9% thromboembolic events including DVT and 2.9% atrial fibrillation.[8]

A direct comparison between the efficacy of our CTDa and the CTDa schemes used by other authors is not easy due to the use of a variety of doses as well as doses schemes.[13] Their result also indicates that the CTDa regimen shows significant benefits in elderly patients; however, the relevance of this study's findings may be limited because of the increased use of novel agents, such as Bortezomib and Lenalidomide for the initial treatment of myeloma.[14]

Among 25 patients, 13 (52%) achieved complete response, 5 (20%) patients achieved partial response and 4 (16%) patient achieved no response. Three (12%) patients died during treatment, 2 (8%) due to intracranial haemorrhage and 1 (4%) for cardiac arrest. Morgan et al. in their study showed,overall response rate (>partial response) for the intent-to-treat population was significantly higher with CTD, that is 82.5% and the complete response rates were13.0%.[15] Study done by Deok-Hwan et al.[8] showed over all response rate who completed cycles of CTDa was 87.7% including complete response of 32.3%.[8]

Conclusion

There are multiple options for treating MM, CTDa is one of them. It is cost effective, orally taken with satisfactory response in elderly newly diagnosed MM patients.

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