Original Paper

ROLE OF VAD REGIMEN AS THE FIRST-LINE TREATMENT IN MULTIPLE MYELOMA

Mahmood SS[1], Abedin AKM[2], Islam H[3], Jubaida N[4], Kawsar NM[5], Hoque M[6]

Abstract

Introduction: Multiple myeloma is a deadly haematological malignancy and needs to be appropriately managed by a suitable chemotherapy protocol. VAD (Vincristine, Adriamycin, Dexamethasone) regimen can be used as a first-line treatment with good safety profile.

Objective: The study was carried out to explore the effectiveness, tolerability, prognostic importance, speed of response rate, safety versus toxicity profile of VAD regimen in achieving complete remission (CR) and over all event free survival in patients having multiple myeloma.

Method: VAD regimen was administered to 34 newly diagnosed cases of multiple myeloma from Haemato-oncology unit of Combined Military Hospital (CMH) Dhaka and Bangabandhu Sheikh Mujib Medical University (BSMMU) over a period of two years. The effects of VAD regimen were observed and documented. Among the 34 patients 21 were male and the rest 13 patients were female.

Result: The maximum number of patients belonged to 5th and 6th decade of life. Out of 34 enrolled patients 21 (61.76%) were male and 13 (38.24%) were female. The male to female ratio was 1.6:1. Moderate degree of anaemia was present in 21 (61.76%) patients. The majority (85.21%) of the patients had high ESR in the range of 101-150 mm in 1st hr (85.29% patients). Serum calcium was high in 23(67.65%) patients before therapy. Three (8.82%) patients died during different phases of treatment mainly due to associated co-morbidities. Twenty five (73.53%) patients showed definite improvement with the treatment, 5 (14.71%) patients showed partial response and 4 (11.76%) patients showed relapsed symptoms.

Conclusion: As an initial chemotherapy, VAD regimen is safe, well tolerated cytoreductive therapy with minor and acceptable toxicity profile in patients having multiple myeloma.

Key-words: Multiple myeloma, VAD regimen, first-line therapy

Introduction

Multiple myeloma is a deadly haematological malignancy and constitutes 1% of all cancers and accounts for 10% of haematological malignancies[1]. Multiple myeloma is a B-cell malignancy characterized by a monoclonal expansion and accumulation of abnormal plasma cells in the bone marrow compartment[2]. The clinical manifestations of myeloma are heterogeneous and include bone complications, symptoms of impaired haemopoiesis and hyperviscosity, renal dysfunction, infections, peripheral neuropathy etc[1].

The peak age of onset of multiple myeloma is 65-70 years of age. Statistics indicate both increasing and earlier age of onset. The etiology of multiple myeloma is unknown.

1. **Lt Col Syed Sabbir Mahmood**,MBBS,DCP,MCPS,FCPS (Haematology), Graded spl in Pathology, CMH, Savar Cantt. 2. **Brig Gen AK Md Mustafa Abedin**,MBBS,MPCS,FCPS (Haematology), Graded spl in pathology, Prof & Head of Blood Transfusion, AFMC, Dhaka Cantt. 3. **Lt Col Hafizul Islam**,MBBS,DCP,FCPS (Haematology), Assoc Prof of Haematology, AFMC, Dhaka Cantt. 4. **Lt Col Nishat Jubaida**,MBBS,DCP,FCPS (Mircobiology), Classified spl in Pathology, BGB Hospital. 5. **Lt Col Narjis Maliha Kawsar**,MBBS,DCP,FCPS (Microbiology), Assoc Prof of Microbiology, AFMC, Dhaka Cantt. 6. **Lt Col Monirul Hoque**,MBBS,MCPS,DCP,FCPS (Microbiology), Instructor of Pathology, AFMI, Dhaka Cantt.

Epidemiologic data suggest that age, genetic factors, chronic antigenic stimulation and some environmental or occupational factors may play a role in multiple myeloma[1,3].

Myeloma is usually a disseminated disease at presentation. Chemotherapy is the main treatment modality. Chemotherapy is continued until plateau phase is reached i.e. clinically and biochemically unchanged for 3 months with stable para-protein[4,5].

Multiple myeloma is a neoplasm of malignant plasma cells invading bone marrow, causing widespread skeletal destruction, bone marrow failure, and problems related to quantitatively abnormal serum or urinary M proteins[5]. For the vast majority of myeloma patients, the rational goals of treatment are meaningful prolongation of life with durable relief of pain and other disease symptoms and protection of normal performance status and quality of life for as long as possible. These are usually achieved through reduction of the myeloma tumour burden by establishing a plateau phase and delaying disease progression[6] .The strategy, therefore, is to select a safe and well-tolerated treatment that can reliably produce objective response of long duration or can at least delay relapse or progression for many years[6,7].

Skeletal destruction is a major cause of morbidity, functional loss, and mortality in multiple myeloma. Bone pain is a frequent clinical indication of bone lesions and is the hallmark of bone metastases[7,8]. Patients typically present with intractable bone pain that may be constant or intermittent. Current treatment options for skeletal complications of malignancy include bisphosphonates, radiation therapy, surgery and analgesics. Intravenous bisphosphonates are the standard treatment for hypercalcaemia in malignancy (HCM) and have become integral part of the current treatment of skeletal metastases, reducing the incidence of skeletal complications and delaying their onset[8]. Bisphosphonate therapy can also reduce the need for radiation and surgery to bone.

Materials and Methods

The study was carried out in the Haemato-oncology unit of Combined Military Hospital (CMH) Dhaka and Bangabandhu Sheikh Mujib Medical University (BSMMU) over a period of two years starting from January 2006 to December 2007. Total 48 patients of multiple myeloma were diagnosed in these two Haemato-oncology units, out of these 48 patients 34 patients were enrolled in this study because the remaining 14 patients were dropped out due to their failure to fulfill the selection criteria. Informed consents were taken from all the 34 patients prior to commencement of the study. The disease pattern and subsequent consequences with complications of the therapy were informed in details in their understandable languages to the patients and their relatives. Detailed history, clinical examination and relevant investigations were carried out to confirm the diagnosis and possible course of the disease. Patients were included irrespective of age, sex, race, occupation and body configuration with reasonable economic background to support the chemotherapy and other adjuvant supportive measures. Before initiating chemotherapy all relevant routine investigations were carried out to see the suitability and tolerability of the patients for chemotherapy.

All patients enrolled in the present study were given 06 cycles of VAD regimen following standard dose and duration. Each cycle was repeated at every 04 weeks interval. All the patients were followed up to minimum one year after the completion of six cycles of chemotherapy. During follow up patients were examined both physically and by laboratory investigations. General and systemic examinations including individual performance status were done. Laboratory investigations included complete haematological profiles including ESR, measurement of myeloma protein in every three months.

Patient' selection criteria:

Inclusion Criteria[9,10]:

- Diagnosed case of multiple myeloma.
- Patients with bone pain, osteolytic lesions, increased calcium level, pathological fracture etc.
- Informed consent.

Exclusion criteria[9,10]:

- Asymptomatic multiple myeloma patients.
- Variants of multiple myeloma i.e. monoclonal gammopathy of undetermined significance, smouldering myeloma, solitary plasmacytoma, other lymphoproliferative disorders etc.
- Patients having diabetes mellitus, hypertension, abnormal ECG findings, abnormal liver function test (LFT) and abnormal renal function tests.

Results

In this study 34 patients received VAD regimen. Table-I shows the distribution of age and sex of the enrolled patients. Maximum number of patients belonged to the 5th and 6th decade of life in the present study. Out of 34 patients, 21 (61.76%) were male and 13 (38.24%) were female. The male to female ratio was 1.6:1.

Table-I: Distribution of patients according to age and sex (n=34)

Age group(in years)	Male (n=21)	Female (n=13)	Total (n=34)
31-40	2 (9.52%)	1(7.69%)	3(8.82%)
41-50	3 (14.29%)	3 (23.08%)	6(17.65%)
51-60	9 (42.86%)	5 (38.46%)	14(41.18%)
61-70	4 (19.05%)	4 (30.77%)	8(23.53%)
71-80	3 (14.29%)	-	3(8.82%)
Total	21 (61.76%)	13(38.24%)	34(100%)

The most common and persistent symptom was generalized weakness on fatigue (100%). Severe body ache was present in 27 (79.41%) patients. The other noteworthy difficulties experienced by the patients were inability to walk independently, bone tenderness and backache.

Visual upset and mental slowing were present in only two male patients as shown in Table-II.

Table-II: Distribution of important signs/symptoms of the patients (n=34)

Symptoms/signs	Male(n=21) No. (%)	Female(n=13) No. (%)	Total (n=34) No. (%)
Generalized weakness and fatigue	21 (100)	13 (100)	34 (100)
Severe bodyache	16(76.19)	11(84.62)	27 (79.41)
Inability to walk	7 (33.33)	4(30.77)	11(32.35)
Bony tenderness	17(80.95)	10(76.92)	27(79.49)
Backache	9(42.86)	5(38.46)	14(41.18)
Fever	8(38.1)	6(46.15)	14(41.18)
Weight loss	5(23.81)	7(53.84)	12(35.29)
Respiratory tract infection	11(52.38)	7(53.84)	18(52.94)
Visual upset & mental slowing	2(9.52)	--	2(9.52)

All the patients had variable degree of anaemia as indicated by the haemoglobin level at the time of diagnosis. Eight (23.53%) patients had mild, twenty one (61.76%) had moderate and five (14.71%) patients had severe anaemia as shown in Table-III.

Table-III: Distribution of Anaemia/haemoglobin level before commencement of therapy (n=34)

Anaemia/haemoglobin level	Male (n=21) No (%)	Female (=13) No. (%)	Total No. (%)
Mild (9-12 gm/dL)	5(23.81)	3(23.08)	8 (23.53%)
Moderate (6-9 gm/dL)	14(66.67)	7(53.85)	21(61.76%)
Severe (<6 gm/dL)	2 (9.52)	3(23.08)	5(14.71%)

Table-IV: Distribution of haemoglobin level after therapy (n=34)

Haemoglobin level	After 3rd cycle of chemotherapy	After 6th cycle of chemotherapy
Normal haemoglobin >12 gm /dL	3	7
9-12 gm/dL (Mild anaemia)	17	15
6-9 gm/dL (Moderate anaemia)	11	10
< 6 gm/dL (Severe anaemia)	3	2

Table-IV shows improvement of haemoglobin level after completion of 3rd and 6th cycles of chemotherapy.

In the majority of patients ESR was very high before commencement of therapy as shown in Table-V.

Table-V: Distribution of ESR level (n=34)

ESR	Before starting treatment	After 3 months of chemotherapy	After 6 months of chemotherapy
0-50 mm	-	2(5.88%)	09 (26.47%)
51-100 mm	02(5.88%)	14(41.18%)	25(73.53%)
101-150 mm	29(85.29%)	18(52.94%)	-
151-180 mm	03(8.82%)	-	-

Twenty nine (85.29%) patients had 101-150 mm in the first hour and 3(8.82%) patients had more than 151 mm in 1st hour. Reduction of ESR level was remarkable after 3rd and 6th cycles of therapy in a significant number of patients.

Serum calcium level was high in 24(70.59%) patients. Reduction of serum calcium level was observed after 3rd and 6th cycles of therapy in all patients (Table-VI). Osteolytic lesions without pathological fractures were present in 31 (91.18%) patients and only 3(8.82%) patients had pathological fractures as well as multiple osteolytic lesions. Table VII shows the distribution of osteolytic lesions.

Table-VI: Distribution of serum calcium level (n=34)

Normal range (9-11mg/dL)	Before chemotherapy No. (%)	After 3 cycle of chemotherapy No. (%)	After 6 cycle of c chemotherapy No. (%)
(9-11mg/dL)	10(29.41))	16(47.06)	23(67.65)
11.1-12 mg/dL	13(38.24)	09(26.47)	07(20.58)
12.1-14mg/dL	11(32.35)	09(26.47)	04(11.76)

Table-VII: Distribution of Radiological evidence of disease (n=34)

Changes in skeleton	Male (n=21) No. (%)	Female (n=13) No. (%)	Total(n=34) No. (%)
Osteolytic lesion	19(90.48)	12(92.31)	31(91.18)
without fracture			
Osteolytic lesion	2(9.52)	1(7.69)	3(8.82)
with fracture			

Before the treatment bone marrow examination showed that more than 39% of plasma cells were having typical and atypical morphological appearances. Marrow examination after 3rd and 6th cycles of chemotherapy showed significant reduction of plasma cells.

Serum protein electrophoresis showed monoclonal gammopathy in all the patients before treatment. After treatment with VAD regimen concentration of M-protein had reduced in significant number of patients.

Three (8.82%) patients died during different phases of treatment due to disease process and associated severe co-morbidities. Twenty five (73.53%) patients showed definite improvement with the treatment and 5 (14.71%) patients showed partial response and 4 (11.76%) patients had relapse after completion of treatment.

Discussion

A total number of 34 patients of diagnosed cases of multiple myeloma were included in our study. Out of 34 patients, 21 were male and 13 were female. The average age of the patients was 61 years and 09 patients were in the 5th and 6th decade of life. The findings of this study correspond with other studies[6]. The enrolled patients belonged to either stage-II or stage-III disease according to Durie and Salmon Staging System[9].

Multiple myeloma is a widely disseminated malignant disease at presentation. Conventional chemotherapy cannot cure the disease, it can effect a temporary remission[6,7].Bone marrow transplantation or autologous stem cell transplantation offer prolonged survival compared with conventional chemotherapy. But transplant related mortality is very high due to high toxicity (about 30%)[1,7].Moreover stem cell transplantation is not suitable for older patients (age>50 years). So, appropriate and optimum treatment protocol should be selected in individual clinical setting. The aim of treatment is to control the disease, to maximize quality of life and to prolong survival. Chemotherapy and good supportive care are both essential to achieve these aims[10,11,12].

The combination of Melphalan and Prednisolone (MP) has been historically used since 1960[12,13].It produced responses in approximately 50% of patients and a progression-free survival of about 15 months[14].

This combination (MP) was considered as gold standard in the management of multiple myeloma until 2000. With the explosion of knowledge and understanding about the disease process, a good number of new regimens were formulated and these drugs are still under trial. As an induction therapy Melphalan plus Prednisolone has lost its credibility and as such abandoned in the Western world[15].

A complete response to therapy is considered when the reduction of 75% serum myeloma proteins takes place and partial response is reduction of 50-75% serum myeloma proteins. In our study, 25 (73.53%) patients showed definitive improvement with rapid response rate and 5 (14.71%) patients demonstrated partial response with VAD regimen. These findings correlate with other study[16,17]. Most of the investigators studying MP and VAD regimens found significant response rate and overall survival index with VAD regimen[14,17].

A randomized study by South West Oncology Group (SWOG) had shown that for induction therapy patients received alternating combinations of vincristine, melphalan, cyclophosphamide and prednisolone (VMCP) and vincristine, cyclophosphamide, adriamycin and prednisolone (VCAP) showed response rate of 54%[17]. In our study the response rate is much higher than the SWOG study. The higher response rate may be due to effects of VAD regimen itself and better supportive management rendered to the patients. Supportive drugs such as bisphosphonates for hypercalcaemia, G-CSF for neutropenic patients and transfusion of blood and blood products were used as and when required. Recombinant erythropoietin was also used in few cases for correction of anaemia in addition to blood products.

The positive responses were gradually evident after 3rd course of chemotherapy and full response was evident after 6th cycle of therapy. Finally after completion of six cycles of therapy 4 patients were found to be non-responders to VAD regimen and they were given palliative care.

Among the non-responders having relapsed symptoms, 3 patients died due to bacterial infection related to neutropenia, bone marrow suppression by disease process and chemotherapy.

Conclusion

A recent explosion of knowledge about pathobiology and pathogenetics of multiple myeloma associated with growing chemotherapeutic armamentarium allow us to rationally select optimum therapy taking into cognizance of every facets of disease in individual cases. From this study, it is clearly evident that VAD therapy is able to bring about rapid response rate, prolong the remission state and improve the quality of life in significant percentage of newly diagnosed patients with multiple myeloma. VAD therapy was initially used in resistant and refractory myeloma cases but as an initial therapy it has produced impressive results[18].Treatment of multiple myeloma is still not optimum in Bangladesh due to absence of bone marrow and stem cell transplantation[19].However, judicious use of novel agents available here can improve the survival and quality of life of the myeloma patients.

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