

## VAD Regimen as Front Line Therapy in Multiple Myeloma

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### ABSTRACT

**Purpose:** We have planned this study to evaluate the response and toxicity of VAD regimen as a front line therapy in 35 newly diagnosed symptomatic myeloma patients.

**Methods & Materials:** All patients were subjected to the following: complete history, clinical examination, routine laboratory investigations, radiological investigations, and specific investigations including plasma viscosity determination, immunoglobulin and cryoglobulin quantitation, immunoelectrophoresis and immuno-fixation. All patients were treated with VAD regimen which consisted of vincristine 0.4 mg/day and doxorubicin 9 mg/m<sup>2</sup> administered by continuous infusion for 4 days with oral dexamethasone 40 mg/day for days 1-4, 9-12 and 17-20 for the first cycle only to be repeated every 28 days for 4 cycles then reevaluation to determine the response to therapy based on the degree of reduction of M-component.

**Results:** Our results showed that the frequency of Ig isotypes was IgG (57.1%), IgA (37.1%) and light chain disease (5.7%). For light chain type: Kappa (54.3%), Lambda (31.4%), Kappa and free Kappa (2.9%), Lambda and free Lambda (5.6%), free Kappa and free Lambda each 2.9%. All studied parameters showed significant changes after 4 cycles of VAD regimen including elevation of hemoglobin level, platelet count and S. albumin and reduction of ESR level, S. creatinine, S. calcium, CRP, LDH and M-band. Monoclonal immunoglobulin was reduced with elevation of other normal immunoglobulins. The overall response was 85.7% (30/35) with CR2 in 5 patients (14.3%) and PR2 in 25 patients (71.4%). The response was rapid occurring after 2 cycles of VAD. Median response duration was 20 months. The estimated median survival for all patients was 42 months, with 79% 2 years overall survival. Toxicity was acceptable; only side effects due to steroid were noticed.

**Conclusion:** So, we can conclude that the high response rate and lack of toxicity of VAD regimen as a primary therapy for multiple myeloma patients are promising and warrants further evaluation and modification although other strategies will be necessary to prolong the duration of response.

**Key Words:** M. Myeloma - Chemotherapy.

### INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic cancer and represents approximately 1% of all cancers and 2% of all cancer deaths. Although, the peak age of onset of MM is 65-70 years of age, statistics indicate both increasing and earlier age of onset [16].

Therapeutic progress has been slow in myeloma, oral melphalan and prednisone, introduced over 30 years ago, have remained standard therapy providing control of symptoms and/or tumor mass reduction by no more than 50% in one half of patients treated [2].

Various chemotherapeutic combinations have been investigated in myeloma, include VBMCP or VMCP/VBAP, all achieved similar response rate and event free survival and overall survival when compared with melphalan and prednisone [7].

High dose dexamethasone was evaluated in combination with vincristine and adriamycin for the treatment of MM (VAD regimen), more than 50% of refractory myeloma patients showed rapid and marked response, defined as greater than 75% cytoreduction. The advantages of this combination (VAD regimen) includes quick response, effectiveness in hypercalcemia, quick relief of bone pain, applicability in patients with renal failure and no cumulative bone marrow stem cell damage, allowing subsequent successful mobilization of stem cells [1].

### PATIENTS AND METHODS

Between July 1997 and March 2000, 35 patients with newly diagnosed MM were included (Table 1).

Table (1): Patients characteristics (n=35).

Characteristic	Number (%)
<i>Age (years):</i>	
Range	35-85
Median	58
<i>Sex:</i>	
Male	22 (62.8)
Female	13 (37.2)
<i>Clinical stage:</i>	
IIA	10 (28.5)
IIB	5 (14.3)
IIIA	8 (22.8)
IIb	12 (34.3)

All patients underwent the followings: complete history and clinical examination, routine investigations including CBC, ESR, s. total protein, s. albumin, s. alkaline phosphatase, s. urea, s. creatinine, s. uric acid, s. LDH, s. electrolytes, c-reactive protein level, serum protein electrophoresis on cellulose acetate and bence jones protein in urine by heating method. Radiological investigations including plain X-ray, C.T. scan and MRI when needed according to the symptoms of the patients and specific investigations including:

- 1- Plasma viscosity measured by simple red pipette method [21].
- 2- Cryoglobulin screening by cryocrite and quantitation of it [14].
- 3- Serum immunoglobulins quantitation of IgM, IgG, IgA by turbidometric method using turbidimeter from Dade Bohring inc., Newark, DE 19714 USA [15].
- 4- Serum protein immunoelectrophoresis by Graber and William technique, 1953 using IEP kit from Helena laboratories, Tyne and wear NEII OLH, UK.
- 5- Serum protein immunofixation [3] using IF kit from Helena laboratories, Tyne and wear NEII OLH, UK.
- 6- Detection of free light chain type (Kappa or Lambda) in urine by immuno-diffusion using human proteinuria screening bind a RID kit from Binding site limited P.O. Box 4073, Birmingham B29 6AT United Kingdom.

All patients were treated with VAD regimen consists of vincristine 0.4 mg/day and doxorubicin 9 mg/m<sup>2</sup> administered by continuous infusion for 4 days with oral dexamethasone 40 mg/day for days 1-4, 9-12 and 17-20 first cycle

only to be repeated, every 28 days for 4 doses, then reevaluation. Routine hematological and biochemical tests were done before each course of treatment. Prophylactic H<sub>2</sub>-blockers were given during dexamethasone treatment but prophylactic antibiotics were not routinely given. We used the reduction of M-component as a guide for detection of degree of response according to Lahuerta et al. [13].

Criteria	Abbreviations	Definition
<i>Response</i>		
Complete remission	CR	> 50% reduction unmeasurable by EP, sustained 6 weeks
<i>New definition:</i>		
Type I CR	CR1	No detection by EP and IF
Type II CR	CR2	No detection by EP but positive IF
Partial response	PR	> 50% reduction, +ve EP, stable for 1 month
<i>New definition:</i>		
Very good PR	PR1	90-99% reduction
Partial response	PR2	50-90% reduction
No response		< 50% reduction
Stable disease	SD	0-50% decline
Progressive disease	PD	Increase

#### *Statistical analysis:*

Data were entered and analyzed using Epi-INFO version 6.1 Software. Response duration and survival were estimated by the Kaplan-Meier method. A *p*-value of < 0.05 was considered significant [8].

## RESULTS

Table (2) shows the mean±SD of studied parameters in multiple myeloma patients before and after treatment with VAD regimen where most of the parameters showed significant difference after VAD regimen.

Table (3) shows comparison between immunoglobulins level in multiple myeloma before and after treatment with VAD regimen where malignant isotypes were significantly reduced and the other normal immunoglobulins were significantly increased in levels after VAD regimen.

Table (4) shows frequency of heavy chain and light chain types, where IgG was the commonest isotype, it represent 57.1% of total cas-

es, IgA was the second commonest isotype (37.1%) and there were 2 cases only (5.7%) showed no heavy chain in their serum but free monoclonal light chain was discovered in serum by immunoelectrophoresis and in urine by immunodiffusion against anti Kappa and anti Lambda antibodies.

There were 3 primary treatment failures, all in stage III patients and 2 other patients died of disease also in stage III. The remaining 30 patients all responded giving overall response rate of (85.7%). Five of these patients went into CR2, the remaining 25 patients went into PR2. Patients with advanced disease were less likely than those with less advanced disease to respond, but likely to go into CR as were these with less advanced disease. One of the striking features of response was the rapidity of tumor reduction; with near maximum response occurring after 2 courses of VAD regimen. The medi-

an duration of response was 20 months (Table 5).

The median follow-up duration was 26 months (range: 6 to 50). The estimated median survival duration for all patients was 42 months with 79% 2 years overall survival rate (Fig. 1).

#### Toxicity:

Alopecia and mild peripheral neuropathy (loss of reflex) were common, but the main side effects were related to steroid therapy. Infective episodes occurred in 18 patients, in 12 patients, there were minor infections-mainly oral herpes or candida, however, in 6 patients, they were serious (2 patients died from bronchopneumonia). Myopathy occurred in 3 patients and moderate mood changes in 3 patients. Altogether 12 of the 30 responders required treatment modification due to steroid-related toxicity. No myelotoxicity or cardiac toxicity was observed.

Table (2): Mean±SD of studied parameters in multiple myeloma patients before and after treatment with VDA regimen (n=35).

Parameter	Before treatment Mean±SD (Range)	After treatment Mean±SD (Range)	p-value
Hemoglobin (g/dl)	7.9±1.4 (4.0-10.5)	10.5±1.2 (8.0-13.5)	< 0.01
TLC x10 <sup>3</sup> /cmm	5.4±5.2 (1.9-30.0)	6.9±2.1 (4.5-12.5)	> 0.05
Platelets count x 10 <sup>3</sup> /cmm	110.5±46.7 (35.0-250)	219.4±43.4 (142-327)	< 0.01
ESR (mm/h)	99.7±27.3 (50-160)	33.7±10.4 (15-63)	< 0.01
Total protein (g/dl)	9.7±1.7 (6.0-15.5)	7.7±0.8 (6.0-9.6)	< 0.01
S. Albumin (g/dl)	2.8±0.5 (1.9-3.8)	4.0±0.6 (3.0-5.3)	< 0.01
Alk. Phosphatase (U/l)	178.5±76.4 (67.0-370)	183.7±53.4 (107-288)	> 0.05
S. Urea (mg/dl)	63.9±30.6 (16.0-150)	41.2±16.8 (13.7-80.0)	< 0.01
S. Creatinine (mg/dl)	2.3±1.5 (0.68-6.2)	1.0±0.5 (0.5-2.6)	< 0.01
Uric acid (mg/dl)	7.9±2.4 (4.0-13.5)	5.3±1.6 (2.2-8.2)	< 0.01
C-reactive protein (mg/l)	70.6±73.1 (6.0-192)	8.2±6.1 (1.0-24)	< 0.01
LDH U/l	586.8±220.3 (185-950)	239±120.2 (68-550)	< 0.01
S. Calcium (mg/dl)	11.1±1.2 (9.0-13.5)	8.7±0.6 (7.3-9.8)	< 0.01
S. Phosphorus (mg/dl)	4.2±0.6 (2.9-5.5)	4.9±0.6 (2.9-6.5)	< 0.01
S. Sodium (mmol/l)	138.8±4.4 (130-148)	138.6±3.0 (132-145)	> 0.05
S. Potassium (mmol/l)	4.3±0.55 (3.5-5.3)	3.9±0.3 (3.4-4.7)	< 0.01
M-Band (g/dl)	4.5±1.8 (0.0-9.5)	1.5±0.8 (0.0-2.95)	< 0.01
Cryoglobulin (ug/ml)	2191±1576.5 (360-6000)	194.2±107.2 (68-500)	< 0.01
Plasma viscosity	3.1±1.4 (1.2-6.0)	2.1±0.9 (1.0-4.5)	< 0.01

Table (3): Comparison between immunoglobulin level before and after treatment with VAD regimen (n=35).

Isotypes	Igs	Before treatment Mean±SD (Range)	After treatment Mean±SD (Range)	p-value
Ig G Monoclonal gammopathy	Ig G	5026±1506 (198-7850)	2580±1022 (1258-4658)	< 0.01
	Ig A	125.5±120.5 (32-545)	484.6±127 (382-895)	< 0.01
	Ig M	93.4±60 (30-267)	340.6±146 (242-890)	< 0.01
Ig A Monoclonal gammopathy	Ig G	585.3±240 (230-480)	1327±2407 (1020-3400)	< 0.01
	Ig A	4043±965 (260-5480)	2237±762 (382-895)	< 0.01
	Ig M	91.1±92.8 (25-301)	311±92.8 (245-521)	< 0.05

Table (4): Frequency of heavy chain and light chain types.

Heavy chain type	No.	%
Ig G	20	57.1
Ig A	13	37.1
No (light chain disease)	2	5.7
Light chain type	No.	%
Kappa	19	54.3
Lambda	11	31.4
Kappa & free Kappa	1	2.9
Lambda & free Lambda	2	5.6
Free Kappa (light chain disease)	1	2.9
Free Lambda (light chain disease)	1	2.9

Table (5): Effect of disease stage on response to VAD regimen.

Response	All patients n=35	Stage IIA n=10	Stage IIB/III n=25
Number responding	30	10	20
Number of failure	5	0	5
Number in CR <sub>2</sub>	5	3	2
Number in PR <sub>2</sub>	25	10	15
Median duration of response	20 mo	20 mo	20 mo

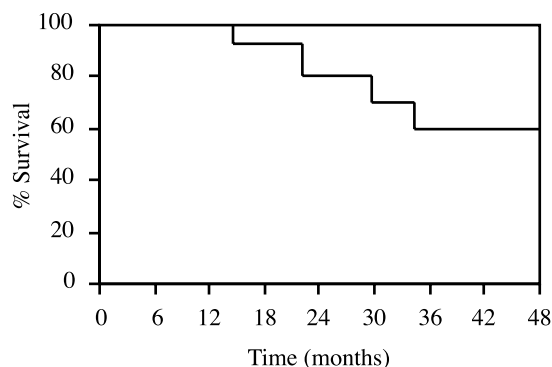


Fig. (1): Overall survival rate in 35 MM patients.

## DISCUSSION

In contrast to the great diversity of normal immunoglobulins, in monoclonal gammopathies a single abnormal cell line predominates (or in rare cases two or three). The abnormal cells may produce an intact immunoglobulins, free light chains without heavy chains (often both intact and free) and rarely only heavy chains each abnormal cell line produces only  $\kappa$  chain or  $\lambda$  chain, never both [4].

In the present study, we investigated 35 patients with multiple myelomas. The median age was 58 years and the frequency of sex was 62.8% males and 37.2% females, these criteria agreed with the medical records of Mayo Clinic in which the median age of patients was 64 years, only 4% were younger than 40 years and one third were 70 years or older, 58% were males and 42% were females [11].

As regard the laboratory finding in our study, the mean value of hemoglobin level before treatment was  $7.9 \pm 1.4$  g/dL. The R.B.Cs in most patients are normochromic and normocytic due to bone marrow infiltration in most cases. Another cause was increased plasma volume in cases associated with hyperviscosity, due to osmotic effect of a large amount of M-protein [12]. Also, the mean value of platelet count was  $110.5 \pm 46.7 \times 10^3$ /cmm this may be due to bone marrow infiltration and shortened platelets survival [9].

The high level of ESR before treatment ( $99.7 \pm 27.3$  mm/h) was related to the presence of paraproteins result in an enhancement of erythrocyte aggregation and rouleaux formation. Increased erythrocyte aggregation may be

either a result of direct cell binding by paraproteins, neutralization of the negative erythrocyte surface charge or the formation of an adhesive layer over the erythrocytes membrane [17]. After 4 cycles of VAD regimen, there were significant changes with elevation of hemoglobin level ( $10.5 \pm 1.2$  g/dL), elevation of platelet count ( $219.4 \pm 43.4 \times 10^3$ /Cmm) and reduction of ESR level ( $33.7 \pm 10.4$  g/dL).

Serum urea and creatinine were high in our patients due to nephrotoxic bence jones protein and the presence of hypercalcemia. There were 48.5% of patients had renal insufficiency at presentation, also the two cases of light chain disease had renal failure from the start. In one large study by Kundsén et al. [10], they found that the prevalence of renal failure was 31% of cases under study and it was greater with light chain disease, hypercalcemia and advanced disease.

LDH and C-reactive protein levels were elevated in our patients and showed significant reduction after 4 cycles of VAD regimen. The cases with progressive disease were associated with very high levels of LDH and C-reactive protein [6].

As regards specific techniques, immunofixation and immunoelectrophoresis, the statistical analysis of our results showed that the most prevalent type of heavy chain was IgG (57.1%) followed by IgA (37.1%) of all cases. Waldmann and Strober [20] found that the distribution of various Ig classes among M-protein is roughly proportional to the concentration of their normal counterparts in serum or, more accurately the rate at which each Ig class is synthesized by healthy individuals. Our results showed that the common type was Kappa light chain (54.3%), Lambda light chain (31.4%), Kappa and free kappa (2.9%), Lambda and free Lambda (5.6%) and free Kappa and free Lambda each (2.9%) of all cases; in agreement with Thakar et al. [19].

Therapeutic progress has been slow in myeloma, oral melphalan and prednisone, introduced over 30 years ago, have remained standard therapy providing control of symptoms and/or tumor mass reduction by no more than 50% in one half of patients treated [2]. Various chemotherapeutic combinations have been investigated in myeloma, include VBMCP or

VMCP/VBAP, all achieved similar response rate and event free survival and overall survival when compared with melphalan and prednisone [7].

The role of high dose glucocorticoid therapy was conducted first as part of the VAD regimen, combining continuous infusions of vincristine, doxorubicin and 4-day pulses of high dose dexamethasone at 40 mg daily [5].

In our study, the overall response rate was 85.7%, 5 of these patients went into CR2, 25 patients went into PR2. Samson et al. [18] reported that therapy with VAD regimen produced response in 84% of previously untreated myeloma patients. In our study, patients with primary treatment failures were 70 years old, showed very low hemoglobin and serum albumin levels, hypercalcemia and high M-band with elevation of CRP and LDH at time of first presentation.

Our results showed rapid response rate to VAD regimen with near maximum response occurring after 2 courses of treatment. The rapidity of the response to VAD is clearly important, both in terms of improvement in clinical status and marrow function and because survival will be improved if early deaths due to progressive disease are prevented [18].

In the present study, the main side effects of VAD regimen were related to steroid therapy, no myelotoxicity or cardiac toxicity was observed. Samson et al. [18] reported the same findings.

In conclusion, the high response rate to VAD regimen together with rapid response rate and acceptable toxicity can lead to recommendation that VAD is the most effective way to achieve rapid response in newly diagnosed myeloma patients. Several centers are evaluating the role of high dose chemotherapy with stem cell support after initial cytoreductive therapy [18].

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