British Journal of Haematology, 1992, **82**, 555–559

Modified adriamycin–vincristine–dexamethasone (m-VAD) in primary refractory and relapsed plasma cell myeloma: an NCI (Canada) pilot study

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Received 30 April 1992; accepted for publication 17 June 1992

Summary. The purpose of this single arm phase II study was to test a modified version of the three drug combination vincristine, adriamycin and dexamethasone (m-VAD), in which intravenous vincristine (0·4 mg/d) and adriamycin (9 mg/m^2 per day) infusions are administered for only 2 h on days 1–4 of each 28 d cycle, in patients with refractory multiple myeloma. In addition, only two 4 d courses of dexamethasone 40 mg/d was given during each cycle. The entry criteria for 44 patients included plasma cell myeloma and a measurable monoclonal peak, either refractory to initial treatment with melphalan and prednisone, or resistant to melphalan and prednisone after initially responding (resistant relapsed disease, 27 patients). Patients treated previously with chemotherapy other than melphalan and predisone were excluded. There were no complete responses. Of the 41 evaluable patients who completed at least one course of therapy 11 had a partial response (27%, 95% C.I. 14–40%). The response rates were 19% for primary refractory disease patients, and 32% for those with resistant relapsed disease. The median duration of response was 4 months. The median survival for all 44 patients was 7·6 months (5·5 months for primary refractory patients, and 10 months for relapsed resistant disease patients). Episodes of documented bacterial infection occurred in 12 patients, and 10 patients had minor viral infection. The dexamethasone dose was reduced in 12 patients. The median neutrophil nadir was $1{\cdot}2 \times 10^9$/l, and median platelet nadir was 147×10^9/l. Five deaths were judged as treatment related and occurred during marrow cytopenia. The results of this modified form of VAD are inferior to that reported previously for 4 d continuous infusions of vincristine and doxorubicin. This could be related to either patient selection factors, or to a reduction of the efficacy of the drug combination produced by either the shortened intravenous infusions and/or omission of one 4 d course of dexamethasone.

The combination of vincristine, adriamycin and dexamethasone (VAD) chemotherapy is one of the most promising second line regimens for multiple myeloma (Barlogie *et al*, 1984). Using the strict response criteria of the Southwest Oncology Group, the response rate in 29 patients (14 refractory, 15 relapsed) was 59±18% (95% confidence interval). Furthermore, at 15 months 60% of patients were alive and 45% were still in their first remission. Subsequently, the VAD regimen has been tested as first line therapy (Alexanian *et al*, 1990; Samson *et al*, 1989; Attal *et al*, 1992).

The National Cancer Institute of Canada (NCIC) Clinical Trials Group was also interested in determining whether VAD could be introduced for treatment of new patients, but we were concerned about the logistics and safety of 4 d continuous infusions in ambulatory patients. Therefore, we developed a modified version of the VAD protocol (m-VAD) which could be administered in the ambulatory setting. This report describes our experience with a phase II pilot study of

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m-VAD in patients with primary refractory and relapsed plasma cell myeloma.

METHODS

Study design. This was a single arm phase II trial designed to estimate the antitumour effect and toxicity of m-VAD in two cohorts of patients with primary melphalan-refractory or relapsed myeloma. The protocol was approved by the Institutional Review Boards of all participating centres. The primary outcome was tumour response defined as stabilization of blood counts and bone lesions without hypercalcaemia, and accompanied by at least 50% reduction of the baseline pretreatment serum monoclonal protein level for two measurements at least 1 month apart, or, when a urine protein only was present, at least 90% reduction of the baseline level (Chronic Leukemia-Myeloma Task Force, 1973).

Sample size was calculated to exclude a response rate below 45%. Survival was calculated using a life table method.

Patients. Eligible patients had to have a diagnosis of plasma cell myeloma confirmed by biopsy of an osteolytic or soft tissue lesion, or ≥ 10% plasma cells in the bone marrow, and a monoclonal protein in serum or urine. For patients with a urine monoclonal protein only, 24 h excretion had to be at least 500 mg. All patients had to be either clinically refractory to initial treatment with melphalan and prednisone (MP) (primary refractory disease), or resistant to a subsequent course of MP after an initial response (relapsed disease).

Criteria for exclusion were any one of the following: stable or responding myeloma while on MP, previous treatment with chemotherapy other than melphalan and a steroid, solitary plasmacytoma only, nonsecretory myeloma, IgM paraprotein, age >74 years, other malignancy except for basal cell carcinoma or cervical carcinoma *in situ*, active peptic ulcer disease, diabetes mellitus requiring insulin or oral hypoglycaemics, previous history of heart failure or on antifailure medications, history of multiple sclerosis or other symptomatic peripheral neuropathy, serum bilirubin > twice normal, inability or unwillingness to give signed informed consent.

Treatment. Patients received doxorubicin 9 mg/m^2 and vincristine 0·4 mg intravenously mixed together in 250 ml normal saline as a 2 h infusion through a central intravenous catheter or peripheral vein on days 1–4 every 28 d. Dexamethasone was given orally at a dose of 40 mg with breakfast on days 1–4 and 15–18 of each 28 d cycle.

Dose modifications and treatment delays for doxorubicin were based on granulocyte and platelet counts, stomatitis, and on serum bilirubin. Doxorubicin could be discontinued for clinical evidence of cardiac failure, marked EKG changes, a fall in cardiac ejection fraction below normal and bilirubin- > twice normal. Vincristine dose could be reduced by 50% for painful parasthesia or moderate constipation, and was temporarily discontinued for severe motor weakness, paralytic ileus, or severe constipation.

Patients were closely monitored for steroid-induced hyperglycaemia, myopathy, psychosis, symptoms of gastric irritation and hypertension, with dose adjustments if necessary. Dexamethasone could be tapered for severe symptoms of withdrawal. Scheduled treatments were delayed for episodes of active infection. All patients were to receive a histamine H_2 antagonist, oral antibacterial prophylaxis, allopurinol, and an oral antifungal agent throughout the treatment period.

Patients who responded were treated until maximum reduction of the monoclonal protein concentration and then for four additional cycles. Nonresponders with progressive disease were taken off treatment immediately, and those with stable disease were continued for at least six cycles and then were treated at the discretion of the attending physician.

Table I. Baseline characteristics of all eligible patients.

	No.	%
Age:		
<60 years	14	31·8
⩾60 years	30	68·2
Gender:		
males	26	59·1
females	18	40·9
ECOG performance status:		
0–2	31	70·5
>2	13	29·5
Primary refractory myeloma	17	38·6
Relapsed myeloma	27	61·4
Haemoglobin (g/dl):		
<10	21	48
⩾10	23	52
% bone marrow plasma cells:		
10–40	15	34·1
>40	29	65·9
Baseline serum calcium:		
hypercalcaemic	16	36·4
normal	28	63·6
Bone disease:		
generalized osteoporosis	1	2·3
1–3 lytic lesions	6	13·6
>3 lytic lesions	37	84·1

RESULTS

Patient population

Forty-five patients were registered from 14 centres between March 1987 and October 1989. One patient had not been shown to be clinically resistant to MP and was declared ineligible, leaving 44 eligible patients.

Seventeen patients were classified with primary refractory disease, and 27 had previously responded to MP and were clinically resistant at the time of trial entry. Criteria for clinical MP resistance included progressive rise of monoclonal protein (35 patients), hypercalcaemia (16 patients), and progression of skeletal lesions (33 patients) or enlargement of plasmacytomas (five patients) while on treatment. Of the 44 patients, 38 met more than one criterion for

Table II. Treatment response in evaluable patients.

Resistance type	Responses	Stable	Nonresponse*	Progressive	Total
Primary refractory	3	1	1	11	16
Relapse	8	5	2	10	25
Total	11	6	3	21	41

* Patients who completed at least one course of m-VAD and either discontinued therapy because of toxicity or died of toxicity before response status verified. Included in the primary analysis as nonresponders.

progressive disease. Of the six patients who qualified with only one criterion, four had a progressive rise in the monoclonal protein and two had an increase in the number or size of plasmacytomas.

Table I summarizes clinical and tumour related baseline characteristics for all 44 eligible patients. The median age was 62·1 years with 59% males. 13 patients (30%) had ECOG performance status >2, and 66% had >40% plasma cells in the bone marrow at study entry. Hypercalcaemia was present in 36% of patients, 48% had a haemoglobin level <10 g/dl, and 84% had extensive bone involvement.

Treatment response and survival

To be assessable for response patients had to complete at least one course of therapy. Patients who withdrew because of toxicity, or who died of toxicity before then, are not assessable for response. Patients who completed at least one course of treatment and who died of toxicity subsequently, before response status could be determined, are included as nonresponders in the primary analysis. A secondary analysis was also performed in which these patients were excluded. All patients were included in the survival analysis.

According to these criteria, 41 patients are assessable for the primary analysis of response. In two patients, treatment was discontinued before completion of the first cycle because of complications or side-effects, and one patient died on day 17.

Table II shows that of the 41 evaluable patients there were 11 responders (27%, 95% C.I. 14–40%), with no complete responses. 21 patients had progression of disease while on therapy, and in six patients the disease remained stable. Among the 16 patients with primary refractory disease there were only three responders (19%), and among those with relapsed disease the response rate was 32% (8/25). When patients who discontinued therapy, or died after one cycle because of toxicity are excluded, the overall response rate in the remaining 38 patients is still only 29% (95% C.I. 13–43%).

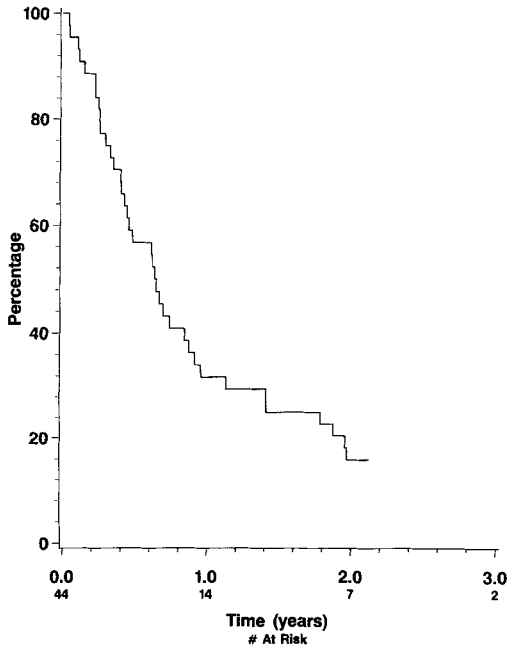

Fig 1. Overall survival of 44 eligible patients.

Table III. Toxicity in m-VAD treated patients.

Toxicity	No. patients
Nausea	9
Alopecia	5
Febrile neutropenia	8
Documented: bacterial infection	12
gram positive bacteraemia	(1)
gram negative bacteraemia	(3)
pneumonia	(8)
Stomatitis:	17
soreness only	(10)
ulcers, able to eat	(6)
ulcers, unable to eat	(1)
Neuropathy:	23
mild	(13)
severe	(10)
Liver enzyme elevation	7
Gastric irritation	3
Myopathy	3
Hypoglycaemia	1
Depression	1

Table IV. Description of treatment related deaths.

Patient	Resistance type	Cause of death
K1	Refractory	66-year-old male developed fatal pneumonia during pancytopenia in cycle 3
K2	Refractory	57-year-old female died of sepsis and gastrointestinal bleeding during an episode of pancytopenia in cycle 2
M3	Relapse	70-year-old female died of sepsis during pancytopenia in cycle 1
V1	Refractory	66-year-old male died of pneumonia during neutropenia in cycle 2
V2	Relapse	69-year-old male died of sudden massive haemorrhage of tracheostomy site during thrombocytopenia after biopsy of a benign subglottic mass following cycle 1

At the time of analysis there were 36 deaths of which 31 were attributed to progressive myeloma only. For the 11 patients who responded, the median duration of response was 4 months, and all patients relapsed from m-VAD therapy by 20 months. Median survival for all 44 patients was 7·6 months (Fig 1). Median survival was 5·5 months for primary refractory patients and 10 months for relapsed patients. At 1 year, only 30% of patients were alive.

Toxicity

A total of 206 courses of treatment were delivered to 44 patients evaluable for toxicity. 34 patients received at least three courses of therapy, three patients received two courses, and seven patients received only one course.

Table III summarizes the observed toxic events and their frequency. 10 patients had non life-threatening viral infections (6 localized herpes simplex, 1 localized herpes zoster, 3 upper respiratory tract infection). Bacterial infection was documented in 12 patients (8 pneumonia, 3 gram negative bacteraemia, 1 gram positive bacteraemia). No patient was diagnosed with systemic fungal infection. Severe stomatitis occurred in one patient, and severe neuropathy occurred in 10 patients (4 constipation, 1 parasthesia, 3 motor weakness, 1 bladder dysfunction, and 1 radial neuropathy). Transient mild elevation of liver enzymes occurred in seven patients.

Dexamethasone dosage was reduced in 12 patients: reasons were gastric irritation (three patients), myopathy (three patients), and hyperglycaemia, depression, neutropenia, steroid withdrawal symptoms, suspected infection, and severe parasthesia in one patient each. Dexamethasone was discontinued in three patients for myopathy.

Weekly neutrophil counts were recorded for 137 cycles of therapy, and platelets in 147 cycles. The median neutrophil nadir was $1{\cdot}2 \times 10^9$/l, and the nadir fell below $0{\cdot}5 \times 10^9$/l in 17 cycles (12%), and below $1{\cdot}0 \times 10^9$/l in 50 cycles (36%). The median platelet nadir was 147×10^9/l, and the nadir fell below 50×10^9/l in 13 of 147 evaluable cycles (9%).

There were four deaths judged as treatment related only, and one judged as due to both disease and treatment. Details for these five patients are described in Table IV.

DISCUSSION

In the original report of VAD chemotherapy for multiple myeloma, the response rate in patients with relapsed disease was higher (73%) than in patients with primary refractory myeloma (43%). Infection (four bacterial and four viral) was the most important complication (Barlogie *et al*, 1984).

In the current study, the overall response rate in 41 evaluable patients was only 27%, and in those with relapsed disease only 31% responded. Also, overall survival was poorer for m-VAD, compared with the original VAD patients (Barlogie *et al*, 1984).

The disappointing performance of m-VAD compared with the published results for VAD could be attributed to two main factors: (i) patient selection, and (ii) treatment differences. Because we did not perform a randomized comparison, we cannot rule out that the population studied by us, and that reported by Barlogie *et al* (1984) differed systematically with respect to important prognostic factors that influenced either response or survival. The most important prognostic variable for both studies, and for other reports of second line myeloma therapy, seems to be the nature of the drug resistant disease (Alexanian *et al*, 1986, 1990; Finnish Leukaemia Group, 1990). Patients with primary refractory myeloma respond less frequently than those with relapse. On this criterion, our study population has a more favourable prognosis, with only 39% of patients having primary refractory disease, compared with 48% in the study of Barlogie *et al* (1984). Also, the baseline haemoglobin was <10 g/dl in 52% of patients treated by Barlogie *et al* (1984) compared with 48% of our patients. Our eligibility criteria restricted entry to patients who were exposed to MP only, while patients in the original VAD study were exposed previously to more drugs, including other alkylating agents and anthracylines (Barlogie *et al*, 1984). According to these criteria, the patients reported in this study do not appear to have had an inherently worse prognosis than those in the original VAD report (Barlogie *et al*, 1984).

Thirty-six per cent of our patients were hypercalcaemic at the time of entry, 66% had $>40\%$ plasma cells in the marrow, and 84% had $>$ three lytic bone lesions. The original report of VAD therapy does not provide sufficient information on these baseline data to allow comparison (Barlogie *et al*, 1984).

Our patients were treated with a modified version of the VAD protocol (Barlogie *et al*, 1984). Although the drug doses were the same, instead of using continuous infusions of vincristine and adriamycin over each 4 d treatment period, we infused the drugs for 2 h on 4 consecutive days. This modification was based on a physician survey that indicated resistance to accepting continuous 4 d infusions through

indwelling catheters. The rationale for the use of a 2 h adriamycin infusion was based on studies indicating that a 2 h infusion produces a pharmacokinetic profile similar to a 24 h infusion (Greene *et al*, 1983). Vincristine was administered also for 2 h for convenience, but based on a phase II study that vincristine alone as a 24 h infusion produced a very low response rate in drug resistant myeloma, we did not feel that this modification would jeopardize efficacy (Jackson *et al*, 1985). However, it is possible that use of 2 h infusions interfered with potential synergism between the two drugs (Zeller *et al*, 1979). Despite the change in infusion duration, the median granulocyte and platelet nadirs achieved in our study ($1{\cdot}2 \times 10^9$/l and 147×10^9/l respectively) were similar to that reported for the longer duration infusions ($1{\cdot}7 \times 10^9$/l and 138×10^9/l), suggesting that myelotoxicity was equivalent.

We also altered the schedule of dexamethasone therapy. Dexamethasone was administered for 4 d starting on days 1 and 15 of each cycle. The original VAD report recommended that three 4 d treatments be abandoned because of the high infection rates (Barlogie *et al*, 1984). Subsequently, the original VAD regimen was altered to reduce the dexamethasone exposure (Alexanian *et al*, 1990). Our schedule provides for consistent treatment on each cycle, and achieves the same recommended total dose after every two complete cycles of therapy.

In summary, this phase II study of a modified version of VAD for drug resistant myeloma failed to reproduce the promising results of the original protocol. We were able to confirm the finding of other similar studies that patients with primary refractory myeloma respond less well and have a poorer prognosis than those with drug resistant relapsed disease. Due to the study design we are unable to determine whether these disappointing results reflect differences in the treatments employed or patient selection factors. Also, it is not possible to determine whether the response differences observed between this and other studies may reflect chance variation. On the basis of this study we cannot recommend m-VAD as a substitute for VAD chemotherapy in drug resistant myeloma.

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