Original article

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Prospective randomized comparison of vincristine, doxorubicin and dexamethasone (VAD) administered as intravenous bolus injection and VAD with liposomal doxorubicin as first-line treatment in multiple myeloma

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Background: The combination of vincristine and doxorubicin administered as a continuous infusion via an indwelling catheter together with intermittent high-dose dexamethasone (VAD) is an effective primary treatment for patients with symptomatic multiple myeloma. In order to avoid the need for an indwelling catheter, which imposes logistic problems for outpatient administration, several phase II studies have explored the feasibility and efficacy of VAD-like outpatient regimens. We designed a prospective randomized study to compare the objective response rates of two VAD-like outpatient regimens as primary treatment for symptomatic patients with multiple myeloma.

Patients and methods: Patients were entered in a randomized study regardless of age, performance status and renal function. One hundred and twenty-seven patients received VAD bolus, which consisted of vincristine 0.4 mg i.v., doxorubicin 9 mg/m^2 i.v. and dexamethasone 40 mg p.o. daily for four consecutive days and 132 patients received VAD doxil, which consisted of vincristine 2 mg i.v. and liposomal doxorubicin 40 mg/m^2 i.v. on day 1 and dexamethasone 40 mg p.o. daily for 4 days. The two regimens were administered every 28 days for four courses and in courses 1 and 3, in both arms, dexamethasone was also given on days 9–12 and 17–20.

Results: An objective response was documented in 61.4% and 61.3% of patients treated with VAD bolus and VAD doxil, respectively. Hematological and non-hematological toxicities were mild or moderate and equally distributed between the two treatment arms with the exception of alopecia, which was more common after VAD bolus, and of palmar–plantar erythrodysesthesia, which was more common after VAD doxil.

Conclusions: Our multicenter trial, which included an unselected patient population, indicated that both VAD bolus and VAD doxil can be administered to outpatients and can provide an equal opportunity of rapid response in many patients with multiple myeloma.

Key words: chemotherapy, liposomal doxorubicin, multiple myeloma

Introduction

The administration of melphalan and prednisone, introduced as primary treatment 35 years ago, can induce objective responses in about 50% of patients with multiple myeloma, and the subsequent median survival is 2–3 years [1]. Since then several combination chemotherapy regimens have been used in an attempt to improve the response rate and the survival of patients with multiple myeloma but they do not show superiority over melphalan and prednisone [2]. The combination of vincristine and doxorubicin administered as a continuous infusion via an indwelling catheter together with intermittent high-dose dexamethasone (VAD) was shown to be an effective regimen for patients with refractory and relapsed myeloma [3]. When VAD was administered to previously untreated patients objective responses were noted in approximately two-thirds of patients. Responses were rapid, reaching near-maximum

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after two courses of treatment [4, 5]. In order to avoid the need for an indwelling catheter, which imposes logistic problems for outpatient administration, Segeren et al. [6] reported recently a large phase II study in which VAD was administered on an outpatient basis using 4 days of rapid i.v. infusion (VAD bolus). This study showed that the VAD bolus regimen was associated with a 67% objective response rate and the toxicity was acceptable. Recently, doxorubicin has been encapsulated in 'stealth' liposomes. Liposomal doxorubicin, because of its longer half-life, can be administered once in each treatment cycle and is considered less toxic than doxorubicin, especially as far as cardiotoxicity is concerned. Furthermore, liposomal doxorubicin may be preferentially delivered to sites of leaky blood vessels such as those elaborated in tumor neo-angiogenesis [7]. A preliminary phase II study of VAD with liposomal doxorubicin (VAD doxil) as primary outpatient treatment in patients with multiple myeloma produced objective responses in 88% of patients including a complete response (CR) rate of 15% [8]. Based on the above-mentioned phase II studies we designed a prospective multicenter randomized trial in order to compare the activity of these two VAD-like outpatient regimens as first-line treatment in multiple myeloma.

Patients and methods

Study design

This was a prospective multicenter randomized phase III trial open to all patients with previously untreated multiple myeloma who were considered candidates for systemic treatment. The patients provided informed consent according to institutional guidelines. A center randomization office randomly allocated the patients. Random permuted blocks were used to ensure balance between the two arms. The randomization was stratified for each participating center and the patient's age (≤65 or >65 years). The patients were randomly assigned to receive either VAD bolus or VAD doxil and the primary end point of the study was objective response and toxicity after four courses of treatment. Patients with asymptomatic stage I multiple myeloma were not included in this trial. Patients were included regardless of age, renal function and performance status. The follow-up was performed according to protocol guidelines, on a monthly basis while on treatment, to record treatment-related toxicity and antitumor effects.

Statistical analysis

The primary objective was to compare the overall response rates of the two regimens. The null hypothesis was that the VAD doxil regimen should show a response rate of at most 15% lower than that of the VAD bolus regimen. No statistically different responses would lead to the conclusion that the VAD doxil regimen was equivalent to (or better than) VAD bolus regarding antitumor effectiveness. According to previous experience the expected response to VAD was considered to be 70%. To show such a difference by a one-sided hypothesis test based on a χ^2 distribution with a continuity correction (significance level $\alpha = 5\%$; power 80%), the inclusion of 128 patients in each treatment arm was required. Performing an intention-to-treat analysis a total of 256 eligible patients would be needed to reach the desired power. To account for patients lost to follow-up, ~5% were added to the above-calculated sample size.

All case report forms were reviewed by the Data Monitor for completeness, accuracy, eligibility criteria and assessment of the outcome variables. All data were entered into a computerized database and analyzed with the SAS and SPSS version 8.0 programs.

Table 1. Patients and disease characteristics

	VAD bolus	VAD doxil
No. of patients	127	132
Age (years)		
Median	66	65
Range	37–88	37–88
Male/female	67/59	77/55
Percent of patients with		
Myeloma type		
IgG	57	56
IgA	24	26
Light-chain disease	17	15
Non-secretory	2	3
Salmon–Durie stage		
II	28	36
III	72	64
Performance status (WHO)		
0	18	9
1	37	46
2	32	27
3	13	18
Hemoglobin <8.5 g/dl	26	28
Calcium >11.5 mg/dl	10	7
Creatinine >2.0 mg/dl	23	20
β2-microglobulin >2.5 mg/dl	73	75
Albumin <3.0 g/dl	29	28

VAD bolus, vincristine, doxorubicin and dexamethasone; VAD doxil, VAD with liposomal doxorubicin.

Response rates were compared using the χ^2 test. Comparison of treatment groups according to all toxicity categories was done by Wilcoxon rank-sum test. Time to progression and overall survival were estimated by the non-parametric method of Kaplan–Meier and were compared by the log-rank test.

Patient characteristics

Between February 1999 and June 2001, 272 patients were randomly allocated, 136 to each arm. Thirteen patients never received either regimen and 259 patients received treatment and were evaluable for toxicity and response; 127 patients received VAD bolus and 132 patients received VAD doxil. Patients and disease features are shown in Table 1. Staging was performed according to Durie and Salmon [9]. The majority of patients had poor prognostic features, which were equally balanced between the two treatment groups (Table 1).

Treatment regimens

For both VAD bolus and VAD doxil we adopted the doses from the original phase II studies [6, 8]. The VAD bolus regimen consisted of vincristine 0.4 mg and doxorubicin 9 mg/m^2, both administered in 100 ml NaCl 0.9% by i.v. rapid infusion and dexamethasone 40 mg p.o. daily for 4 consecutive days. The VAD doxil regimen consisted of vincristine 2 mg in 100 ml NaCl 0.9% day 1, liposomal doxorubicin (doxil) 40 mg/m^2 in 500 ml 5% dextrose in water i.v.

Table 2. Response to treatment

	VAD bolus	VAD doxil	*P* value
Complete response	16 (12.6%)	17 (12.9%)	
Partial response	62 (48.8%)	64 (48.4%)	0.993
No response	49 (38.6%)	51 (38.7%)	
Total	127	132	–

VAD bolus, vincristine, doxorubicin and dexamethasone; VAD doxil, VAD with liposomal doxorubicin.

Table 3. Toxicity after treatment according to WHO criteria

	VAD bolus (%)	VAD doxil (%)	*P* value
Neutropenia ≥2	20	15	0.7
Thrombocytopenia ≥2	10	5	0.2
Nausea/vomiting ≥2	4	5	0.8
Alopecia ≥1	55	37	<0.001
Mucositis ≥2	7	15	0.3
Erythrodysesthesia ≥2	2	13	0.03
Neurotoxicity ≥2	13	15	0.9

VAD bolus, vincristine, doxorubicin and dexamethasone; VAD doxil, VAD with liposomal doxorubicin.

over 1 h on day 1 and dexamethasone 40 mg p.o. daily for 4 days. The two regimens were administered every 28 days for four courses. In courses 1 and 3, in both arms, dexamethasone was also given on days 9–12 and 17–20.

Evaluation of response

Routine hematological and biochemical tests, serum monoclonal protein concentration and/or urinary light chain excretion and β2-microglobulin were performed at the beginning of each course of treatment and every 3–4 months thereafter. Bone marrow aspirate and/or bone marrow biopsy were performed before the first course of treatment and 4–6 weeks after administration of the fourth course of treatment.

Response criteria were adapted from those used by Samson et al. [4]. CR required a negative serum and urine immunofixation and <5% bone marrow plasma cells. Partial response (PR) required a reduction of serum and/or urine monoclonal protein by ≥50% along with reduction of bone marrow plasmacytosis by ≥50%. The condition of CR or PR required evidence of sustained response for at least 1 month. Lack of at least PR was considered as no response. All patients who discontinued treatment after the first course of treatment because of death, toxicity or the patient's wish were rated as non-responders. Disease progression was for patients in PR an increase in monoclonal protein of 50% above plateau on two samples 4 weeks apart, and for patients in CR reappearance of detectable monoclonal protein and/or recurrence of bone marrow plasmacytosis. Bone marrow examination was not mandatory in patients with obvious reappearance of monoclonal protein of the same type as the initial one. The time to progression was calculated from the date of diagnosis to the date of disease progression for responders. Overall survival was defined from the date of diagnosis to the date of death due to any cause. Early death was considered death <4 months after the start of treatment due to toxicity or progressive disease.

Results

Among the 127 patients who were randomly assigned and actually started treatment with VAD bolus, 117 patients received two courses, 103 received three courses and 98 received the planned four courses. Less than four courses of VAD bolus were given because of early death (11 patients), toxicity or patient's refusal (seven patients) or disease progression (11 patients). Among the 132 patients who started VAD doxil, 118 received two courses, 111 received three courses and 98 received the planned four courses. Less than four courses of VAD bolus were given because of early death (14 patients), toxicity or patient's refusal (six patients) or disease progression (14 patients).

The objective response rate to either regimen is shown in Table 2. The objective response rate (i.e. CRs and PRs) was 61.4% for VAD bolus and 61.3% for VAD doxil. As expected, the time to response was short and, with either regimen, at least 50% reduction of monoclonal protein was noted within 2 months of treatment in 80% of patients. In responding patients, monoclonal protein response was confirmed by a repeat bone marrow examination after four cycles of treatment. We subsequently assessed the objective response rate in subsets of patients with adverse prognostic factors such as stage III, severe anemia, hypercalcemia, renal impairment, hypoalbuminemia and elevated serum β2-microglobulin levels. There was no evidence that either regimen was more or less effective in any subset of patients (data not shown).

The toxicities recorded during all VAD bolus and VAD doxil regimen are shown in Table 3. The hematological toxicity was similar in both regimens. VAD bolus was associated more often with alopecia and VAD doxil caused erythrodysesthesia more often than VAD bolus. Steroid-related side-effects occurred with equal frequency in both arms; Cushingoid features were noted in approximately one-fifth of patients, hyperglycemia in 15% of patients treated with VAD bolus and in 12% treated with VAD doxil, mood changes in ~10% of patients in each arm and peptic ulcer disease, hiccups and proximal muscle weakness each occurred in <5% of patients. Infections, which required treatment with oral or i.v. antibiotics, including neutropenic fever, were noted in 17% of patients treated with VAD bolus and 18% treated with VAD doxil. Eleven patients (8.7%) in the VAD bolus arm and 14 (10.6%) in the VAD doxil arm died within the first 4 months of treatment. Among the 11 patients treated with VAD bolus, four deaths were considered to be related to progressive myeloma, three were due to infections, two were due to heart failure and/or myocardial infarction and in two the cause of death was unclear. Of the 14 early deaths in the VAD doxil arm, five were considered to be related to progressive disease, four were due to infections, three were due to heart failure and/or myocardial infarction and in two the cause of death was unclear. A causal relationship could not be established between either treatment and congestive heart failure or myocardial infarction.

The median time to progression for responders was 23.93 months [95% confidence interval (CI) 16.92–30.94] and 24.30 months (95% CI 16.76–31.84) in VAD bolus and VAD doxil groups, respectively ($P = 0.58$) (Figure 1). Among the patients who responded to VAD bolus, 27% received consolidation with high-dose therapy and autologous stem cell transplantation, 37% received maintenance with interferon-α, or with dexamethasone

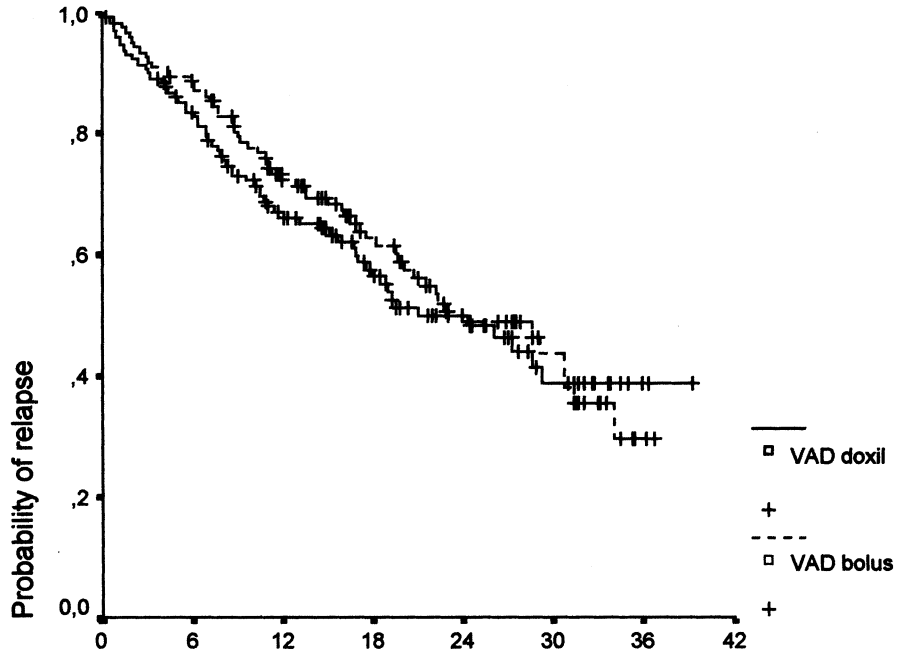

Figure 1. Time to progression after treatment with vincristine, doxorubicin and dexamethasone (VAD bolus) or VAD with liposomal doxorubicin (VAD doxil).

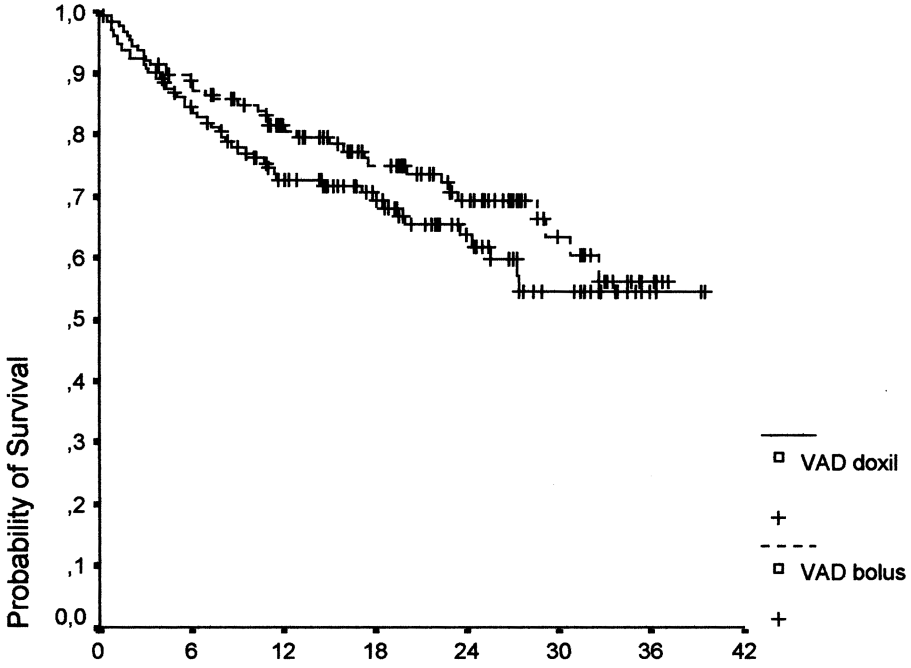

Figure 2. Overall survival after treatment vincristine, doxorubicin and dexamethasone (VAD bolus) or VAD with liposomal doxorubicin (VAD doxil).

or with both agents, 24% received post-remission treatment for several months with standard chemotherapy and 12% received no further treatment after VAD bolus. Among the patients who responded to VAD doxil, 31% received consolidation with high-dose therapy and autologous stem cell transplantation, 40% received maintenance with interferon-α or with dexamethasone or with both agents, 19% received several courses of standard chemotherapy and 10% received no further treatment after VAD doxil. The median overall survival has not been reached yet and is expected to exceed 40 months without obvious differences between the two treatment arms (Figure 2).

Discussion

The VAD regimen was introduced almost 20 years ago and was shown to be the first effective salvage treatment for multiple mye-

loma that was resistant to alkylating agents [3]. The rationale of continuous i.v. administration of vincristine and of doxorubicin was based on *in vitro* data, which indicated a more pronounced antimyeloma effect by the prolonged exposure of myeloma cells to these agents [10, 11]. In addition, when vincristine and doxorubicin are being administered by a continuous infusion the peak serum concentrations of these agents are low. This fact may be associated with a lower risk of important side-effects such as polyneuropathy and cardiomyopathy [3, 12]. Furthermore, a unique feature of the VAD regimen is the intermittent administration of high-dose corticosteroids, which have been shown to represent an active treatment for refractory myeloma [13].

These data prompted many investigators to use VAD as first-line treatment in patients with multiple myeloma. Objective response rates ranging between 50% and 80% were reported, and these differences could be explained by different patient characteristics [4, 5, 14, 15]. Furthermore, remission rates and survival times were similar to those achieved by standard alkylating agent-based regimens. All these studies confirmed rapid onset of response. Indeed in one study, all patients responding to primary VAD, which included repeated courses of dexamethasone, showed a tumor-halving time of 1.4 months or less, permitting the recognition of response after only one course of treatment [5]. Thus a VAD-based regimen seems better for newly diagnosed patients when rapid control of multiple myeloma is necessary.

A disadvantage of the administration of VAD as continuous infusions is the necessity for a central venous catheter, which makes outpatient administration difficult and is associated with catheter-related problems such as infections and thrombosis in 24% of patients [16]. In order to evaluate the feasibility and efficacy of VAD in a more convenient schedule, Segeren et al. [6] administered vincristine and doxorubicin as a rapid i.v. infusion in a large cohort of previously untreated patients ≤65 years of age and observed a 67% objective response rate. Our data confirmed the activity of VAD bolus in the context of a prospective randomized trial since we documented objective responses in 61.4% of patients. Furthermore, we observed that the VAD bolus regimen was equally effective in patients less or more than 65 years of age and we demonstrated that this regimen can be administered even to octogenarians.

Doxil is a stealth liposomal formulation of doxorubicin in which segments of hydrophilic methoxypolyethylene glycol are grafted onto the surface of each liposome. This technology provides several pharmacological benefits such as reduced uptake by the immune system and the heart, slow and steady plasma drug level, and enhanced extravasation through endothelial gaps in tumors [7]. Two phase II studies of VAD doxil as primary treatment for multiple myeloma indicated that this regimen induced objective responses in at least 80% of patients [17, 18]. Our prospective multicenter trial confirmed the activity of VAD doxil for previously untreated patients with multiple myeloma, albeit at a lower response rate of 61.3%. Furthermore, we observed that PR and CR rates after VAD bolus and VAD doxil were identical with either regimen and that four courses of treatment were adequate to induce a response. Thus limited primary treatment with such a regimen may avoid excessive myelosuppression and immunosupression and may reduce the severity of side-effects from long-term exposure to corticosteroids. Furthermore, this approach may also provide the best opportunity to collect adequate numbers of stem cells for patients who are candidates for high-dose therapy. From the present study, no conclusions can be drawn regarding time to progression and survival of our patients, since most patients received some form of maintenance or consolidation treatment. Nevertheless, we noted that the median time to progression was similar and that the survival curves appeared identical.

Despite the fact that at least one-half of our patients were ≥65 years of age both regimens were relatively well-tolerated. Approximately 75% of patients completed the planned four courses of treatment with either regimen. The degree of myelosuppression was similar between the two regimens. Early deaths that could be attributed to the toxicity of chemotherapy were observed in ~5% of patients. Approximately one-fifth of patients treated with either regimen developed an infectious complication. Palmar–plantar erythrodysesthesia was more common with VAD doxil and alopecia occurred more frequently after VAD bolus.

We conclude that, to the best of our knowledge, our study is the first multicenter trial to compare prospectively two outpatient VAD-like regimens. We did not use restrictions as far as age, performance status and renal function were concerned and we believe that our patient population was representative of myeloma patients in Greece. Our prospective randomized study indicated that these two VAD-like regimens can be administered on an outpatient basis and can provide an equal opportunity for a rapid response in many patients with symptomatic myeloma. We also confirmed that a limited number of cycles with either VAD bolus or VAD doxil is needed to induce a response.

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