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Vincristine, doxorubicin and dexamethasone (VAD) administered as rapid intravenous infusion for first-line treatment in untreated multiple myeloma

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Summary. We examined the feasibility of achieving a rapid response in patients with previously untreated multiple myeloma by administering vincristine 0·4 mg and doxorubicin 9 mg/m^2 as a rapid intravenous infusion for 4 d together with intermittent high-dose dexamethasone 40 mg (VAD) for remission induction treatment in patients who were scheduled to receive high-dose therapy. 139 patients (86 male, 53 female; median age 53 years, range 32–65 years; Durie & Salmon stage IIA: 42, IIB: one, IIIA: 89, IIIB: seven) were included in a prospective multicentre study in which VAD was administered as remission induction treatment and was followed by intensified treatment. The response was evaluated according to the criteria of the Eastern Cooperative Oncology Group (ECOG). The results of treatment were evaluable in 134 patients. Five patients died before evaluation. 86 patients (62%) achieved a partial response (PR) and seven patients (5%) achieved a complete response (CR), which equates to a response rate of 67%. The main side-effect was mild neurotoxicity, which was observed in 18% of the patients. Fever or infections were reported in 27% of the patients. VAD administered as an outpatient regimen, based on rapid intravenous infusion, is an effective induction regimen for untreated myeloma with a 67% response rate and acceptable toxicity.

Keywords: multiple myeloma, induction treatment, chemotherapy, VAD, rapid infusion.

With the introduction of melphalan and prednisolone as remission induction therapy the median survival of patients with multiple myeloma improved from 17 months to 30–36 months (Gregory *et al*, 1992). Since then, several combination chemotherapy regimens have been used in an attempt to improve the survival and response rate in newly diagnosed patients with multiple myeloma which did not show superiority over melphalan and prednisolone (Gregory *et al*, 1992). The combination of vincristine and doxorubicin administered as a continuous infusion together with intermittent high-dose dexamethasone (VAD), a non-alkylating agent-based regimen, induces rapid and marked responses in newly diagnosed patients and in patients with relapsed or refractory myeloma (Alexanian *et al*, 1990; Barlogie *et al*, 1984). Usually vincristine and doxorubicin in this regimen are administered by a continuous infusion via an indwelling catheter, which imposes logistic problems for outpatient administration. We now report the feasibility of administering VAD as an outpatient schedule using 4 d of rapid intravenous infusion in patients with previously untreated multiple myeloma. This regimen was designed in order to investigate the feasibility of achieving a rapid response with outpatient treatment in newly diagnosed patients, while conserving the well-proven efficacy of continuous infusional VAD. In this study only patients <66 years of age were included who were scheduled to receive further intensified treatment. No elderly patients were studied.

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METHODS

Study design. From December 1995 to April 1998, 232

patients aged 15–65 years with previously untreated multiple myeloma were registered in a prospective multicentre study for intensified treatment following remission induction treatment. In this study three or four cycles of rapid intravenous VAD were given as standard remission induction treatment to all patients. Thereafter patients were randomized to receive either intensified treatment including peripheral blood stem cell transplantation followed by interferon-α maintenance or intensive chemotherapy without stem cell support followed by interferon-α maintenance. Patients with multiple myeloma stage II or III and younger than 66 years of age were included in the study. Patients with World Health Organization (W.H.O.) performance status of 4 and patients with concomitant severe cardiac, pulmonary, neurologic or metabolic disease were excluded from registration.

Patient characteristics. 139 patients (86 male and 53 female) who had at least 1 year of follow-up after VAD were included in this analysis. All patients received rapid intravenous infusion of VAD as remission induction regimen (Table I). All patients gave written informed consent. The study was performed according to the Helsinki agreement. The median age of the patients was 53 years, ranging from 32 to 65 years. According to the Salmon & Durie classification, 42 patients had stage IIA disease and 89 patients had stage IIIA disease, one patient had stage IIB and seven patients had stage IIIB disease (Durie & Salmon, 1975). 40 patients had IgA, 73 patients IgG and three patients had IgD myeloma. One patient had an IgM M-component and 18 patients had urinary light chain disease. Four patients had non-secretory myeloma.

Table I. Patient characteristics.

No. of patients	139
Age (years)	
Median	53
Range	32–65
Sex (male/female)	86/53
M-component	
Immunoglobulin G	73
Immunoglobulin A	40
Immunoglobulin D	3
Immunoglobulin M	1
Light-chain disease	18
Non-secretory myeloma	4
Stage	
IIA	42
IIB	1
IIIA	89
IIIB	7
Performance status (W.H.O.)	
0	46
1	64
2	17
3	8
Unknown	4

Before the start of treatment with VAD, 46 patients had a W.H.O. performance status of 0, 64 patients a status of 1, 17 patients a status of 2, and eight patients a status of 3. The performance status before VAD was not known in four patients.

Treatment regimen. The VAD regimen consisted of vincristine 0·4 mg and doxorubicin 9 mg/m^2, both administered in 100 ml NaCl 0·9% by intravenous rapid infusion (30 min each) for 4 consecutive days. Dexamethasone was given orally at a dose of 40 mg on days 1–4, 9–12 and 17–20 during uneven cycles of VAD. The treatment cycles were repeated at 4-week intervals. All patients received fluconazole 200 mg/d and trimethroprim sulphamethoxazole 960 mg twice daily as prophylaxis against infections. The use of anti-emetic drugs was allowed. Treatment was given in the outpatient clinic via a peripheral intravenous catheter.

Evaluation of response. The response to VAD was evaluated by follow-up bone marrow samples and follow-up serum and urine M-protein measurements 3–4 weeks after the last VAD cycle. The response to VAD was determined according to the criteria of the Eastern Cooperative Oncology Group (ECOG). Partial response (PR) was defined as a 50% or more decrease of M-protein in serum or urine or >50% reduction of bone marrow infiltration (in non-secretory myeloma). Complete response (CR) was defined as no M-protein measurable in serum and 10 times concentrated urine by immunofixation analysis and <5% plasma cells with no abnormal morphology in bone marrow smears. These plasma cells had to be polyclonal by immunofluorescence staining. The median duration of response was not analysed because induction treatment was directly followed by intensified treatment.

RESULTS

One hundred and thirty-nine patients received a total of 416 cycles of VAD. 117 patients received three cycles of VAD and 13 patients received four cycles. Nine patients received one or two cycles because of early death (four), no response (three) or progressive disease (two). In addition, 26 patients received local radiotherapy just before or during the VAD cycles because of local symptoms.

Ninety-three patients (67%) were responsive according to the ECOG criteria (Table II). 86 patients (62%) achieved a partial remission: 24 patients with stage IIA disease, 55 with

Table II. Response to VAD according to stage of disease.

Disease stage	No. patients	CR	PR	NR	ED	PD
IIA	42	4	24	12	1	1
IIB	1	0	0	1	0	0
IIIA	89	3	55	25	4	2
IIIB	7	0	7	0	0	0
Total	139	7	86	38	5	3

CR: complete remission; PR: partial remission; NR: no response; ED: early death; PD: progressive disease.

stage IIIA and seven with stage IIIB disease. Seven patients (5%) entered a complete remission: four patients with stage IIA and three patients with stage IIIA disease. 38 patients (27%) showed no response. Three patients were progressive. The response of five patients was not evaluable because of early death due to toxicity or concomitant disease.

After VAD, 34 patients (25%) had a better W.H.O. performance status than before treatment. In all patients with stage IIB and IIIB disease (median creatinine 269 μmol/l; range 183–814 μmol/l), the renal function normalized. 119 of the 139 patients (86%) were able to proceed to high-dose therapy.

In order to determine the toxicity of rapid intravenous infusion of VAD, the W.H.O. toxicity $\geqslant$2 was recorded during all 416 VAD cycles (Table III). Significant nausea and vomiting arose in nine cycles (2%). In 10 cycles (2%) patients developed mucositis grade 2 or 3. Liver toxicity maximum grade 3 was seen during eight cycles (2%), and in six cycles (1%) mild to moderate renal function disturbances developed. One patient developed severe renal insufficiency. Overall, neurotoxicity was present in 30/139 patients (22%). Six patients developed neurotoxicity W.H.O. grade 1 (4%), 12 patients neurotoxicity W.H.O. grade 2 (9%) and 12 patients neurotoxicity W.H.O. grade 3 (9%). One patient had cardiac dysrhythmias and one patient had a myocardial infarction. No phlebitis was seen. In two patients cutaneous toxicity W.H.O. grade 2 occurred due to extravasation.

Table III. W.H.O. toxicity $\geqslant$2 during VAD cycles.

No. of cycles		
Nausea and vomiting	9	(2%)
Mucositis	10	(2%)
Liver	8	(2%)
Renal	7	(1%)
Cardiac	2	(0–1%)
No. of patients		
Neurotoxicity	24	(18%)
Infections	37	(27%)

Forty-two infection episodes W.H.O. grade $\geqslant$2 were reported in 37 patients (27%). Five patients had an infection during two cycles of VAD. Pulmonary infections were most common occurring in 14 episodes. Documented bacteraemia was observed in seven episodes. There were six cases of bacteraemia caused by Gram-positive micro-organisms and one case with a Gram-negative bacteraemia. 31 episodes required oral antibiotics and 11 episodes intravenous antibiotics.

Five patients died during VAD treatment. One patient developed plasma cell leukaemia and died of progressive disease. Two patients died of septic shock with acute tubulus necrosis in one patient. One patient died of respiratory insufficiency due to cardiac insufficiency. One patient died of congestive heart failure following myocardial infarction.

DISCUSSION

The VAD regimen was first used in patients with multiple myeloma refractory to alkylating agents by Barlogie *et al* (1984). In successive studies VAD was used as first-line treatment in previously untreated myeloma patients or as remission induction treatment prior to high-dose therapy and autologous bone marrow transplantation (Alexanian *et al*, 1990; Anderson *et al*, 1995; Attal *et al*, 1992; Samson *et al*, 1989). The rationale of continuous VAD regimen was based on the assumption that the addition of corticosteroid pulses in high dosage improved the response rate in patients with refractory myeloma and on *in vitro* data which showed that a better tumour reduction was achieved in myeloma cells by prolonged exposure when compared to short exposure to vincristine (Alexanian *et al*, 1983, 1990; Barlogie *et al*, 1984; Drewinko *et al*, 1981; Jackson *et al*, 1981). In addition, the peak serum concentrations of vincristine and doxorubicin with VAD administered as continuous infusion are low. This fact has been regarded as a major reason why the risk of side-effects such as polyneuropathy and cardiomyopathy is relatively low, and an optimal anti-tumour effect is maintained (Barlogie *et al*, 1984; Koskela *et al*, 1993); however, it remains to be established if this results in a better anti-tumour efficacy. In contrast to multiple myeloma, in non-Hodgkin's lymphoma it is attempted to achieve a rapid response by rapid intravenous infusion of the same agents in the CHOP regimen (Gottlieb *et al*, 1973).

A disadvantage of the administration of VAD as continuous infusion is the necessity of a central venous catheter, which makes outpatient administration difficult, and it is associated with catheter-related problems such as sepsis and thrombosis in 24% of the patients treated with VAD as a remission induction therapy (Anderson *et al*, 1995).

In order to evaluate the feasibility and efficacy of VAD application in a more convenient schedule we administered vincristine and doxorubicin as a rapid intravenous infusion in a large cohort of unselected patients. Potential advantages of this approach were that no central venous catheter was necessary during remission induction, that outpatient administration was routinely possible, and that catheter-related infections could be avoided. Thus, the insertion of a central venous catheter could be delayed in patients receiving an autologous stem cell transplantation. VAD was chosen as a remission induction regimen prior to subsequent intensive treatment because it induces rapid responses and is not excessively myelosuppresive.

The response rate on remission induction treatment with only three or four cycles of VAD administered as rapid infusion was 67%. No direct comparison with continuous infusion of VAD is possible because of the absence of randomization for route of administration. Although this study is not fully comparable with earlier studies with respect to number of VAD cycles (six or seven courses versus three or four courses in our study) and inclusion criteria (median age 53–57 years *v* 53 years in our study), it is known that

continuous infusion of VAD may result in a 55–84% response rate in previously untreated patients (Alexanian *et al*, 1990; Anderson *et al*, 1995; Samson *et al*, 1989). In relapsed and refractory patients the response rate may vary from 50% to 70% (Barlogie *et al*, 1984; Collin *et al*, 1987; Lokhorst *et al*, 1989). Thus, rapid intravenous VAD (three or four cycles) results in the same response rate as with continuous infusion. From the present study, no conclusions can be drawn about survival of these patients, since they continued with further treatment. However, the primary aim in these patients was to obtain a rapid response and to clear the clinical symptoms for which three or four cycles seem to be sufficient.

Treatment with VAD is often associated with a high incidence of bacterial infections, which are frequently catheter-related and are facilitated by high-dose steroids. The fact that a central venous catheter is not required for rapid intravenous infusion of VAD and prophylactic antibiotics were administered may have contributed to the significantly lower incidence of serious infections in our study as compared with earlier studies (27% *v* 54% with antibiotic prophylaxis and 60% without antibiotic prophylaxis) (Anderson *et al*, 1995; Samson *et al*, 1989). Mild to moderate neuropathy also occurred less frequently than the incidence described in patients treated with continuous infusion of VAD (22% *v* 100%) (Alexanian *et al*, 1990; Samson *et al*, 1989). In this study the upper limit of age was 65 years. However, elderly patients with multiple myeloma are even more vulnerable to (bacterial) infections and neurotoxicity. Therefore the use of this regimen may also benefit patients >65 years of age.

We conclude that VAD administered as a rapid intravenous infusion is as effective as continuous infusion for remission treatment in previously untreated multiple myeloma. The most notable toxicities associated with VAD, i.e. serious infections and neurotoxicity, had a significantly lower incidence with this regimen. Therefore it can be recommended for convenient outpatient administration in stage II and III multiple myeloma.

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REFERENCES

Alexanian, R., Barlogie, B. & Tucker, S. (1990) VAD-based regimens as primary treatment for multiple myeloma. *American Journal of Hematology*, 33, 86–89.

Alexanian, R., Yap, B.S. & Bodey, G.P. (1983) Prednisone pulse therapy for refractory multiple myeloma. *Blood*, 62, 572–577.

Anderson, H., Scarffe, J.H., Ranson, M., Young, R., Wieringa, G.S., Morgenstern, G.R., Fitzsimmons, L. & Ryder, D. (1995) VAD chemotherapy as remission induction for multiple myeloma. *British Journal of Cancer*, 71, 326–330.

Attal, M., Huguet, F., Schlaifer, D., Payen, C., Laroche, M., Fournie, B., Mazieres, B., Pris, J. & Laurant, G. (1992) Intensive combined therapy for previously untreated aggressive myeloma. *Blood*, 79, 1130–1136.

Barlogie, B., Smith, L. & Alexanian, R. (1984) Effective treatment of advanced multiple myeloma refractory to alkylating agents. *New England Journal of Medicine*, 310, 1353–1358.

Collin, R., Greaves, M. & Preston, F. (1987) Potential value of vincristine–adriamycin–dexamethasone combination chemotherapy (VAD) in refractory and rapidly progressive myeloma. *European Journal of Haematology*, 39, 203–208.

Drewinko, B., Alexanian, R., Boyer, H., Barlogie, B. & Rubinow, S.I. (1981) The growth fraction of human myeloma cells. *Blood*, 57, 333–338.

Durie, B. & Salmon, S.E. (1975) A clinical staging system for multiple myeloma. *Cancer*, 36, 842–854.

Gottlieb, J.A., Gutterman, J.U., McCredie, K.B., Rodriguez, V. & Frei, E. (1973) Chemotherapy of malignant lymphoma with adriamycin. *Cancer Research*, 33, 3024–3028.

Gregory, W.M., Richards, M.A. & Malpas, J.S. (1992) Combination chemotherapy versus melphalan and prednisolone in the treatment of multiple myeloma: an overview of published trials. *Journal of Clinical Oncology*, 10, 334–342.

Jackson, D.V., Jr, Sethi, V.S., Spurr, C.L., White, D.R., Richards, F., Stuart, J.J., Muss, H.B., Cooper, M.R. & Castle, M.C. (1981) Pharmacokinetics of vincristine infusion. *Cancer Treatment Reports*, 65, 1043–1048.

Koskela, K., Pelliniemi, T. & Remes, K. (1993) VAD regimen in the treatment of resistant multiple myeloma: slow or fast infusion? *Leukemia and Lymphoma*, 10, 347–351.

Lokhorst, H.M., Meuwissen, O.J.A.T., Bast, E.J.E.G. & Dekker, A.W. (1989) VAD chemotherapy for refractory multiple myeloma. *British Journal of Haematology*, 71, 25–30.

Samson, D., Newland, A., Kearney, J., Joyner, M., Mitchell, T., Barrett, A.J., Gaminara, E., Van De Pette, J., McCarthy, D., Aston, L., Hamon, M. & Evans, M. (1989) Infusion of vincristine and doxorubicin with oral dexamethasone as first-line therapy for multiple myeloma. *Lancet*, ii, 882–885.