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Original Paper

Dacarbazine–Vindesine Versus Dacarbazine–Vindesine–Cisplatin in Disseminated Malignant Melanoma. A Randomised Phase III Trial

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In a multicentre phase III study of disseminated malignant melanoma performed in Sweden and Norway, 326 patients were randomised to receive treatment with the combination dacarbazine [DTIC] (D) and vindesine (V) with or without the addition of cisplatin (P). D was given intravenously (i.v.) at a dose of 250 mg/m^2 days 1–5 every 4 weeks and V was given i.v. at a dose of 3.0 mg/m^2 day 1 weekly. P was given i.v. at a dose of 100 mg/m^2 day 1 every 4 weeks. There was no statistically significant difference in overall survival between the treatment arms ($P = 0.22$). Increased toxicity was observed in the treatment arm containing P of which leucopenia, alopecia and nausea/vomiting were the most pronounced. The median time to progression was significantly longer in patients treated with DVP (4.2 versus 2.2 months, $P = 0.007$). In conclusion, adding P to DV did not change overall survival but did significantly increase toxicity. **© 1998 Elsevier Science Ltd. All rights reserved.**

Key words: disseminated malignant melanoma, chemotherapy agents, survival, toxicity
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INTRODUCTION

CHEMOTHERAPY OF disseminated malignant melanoma has progressed slowly over the last 15 years. Treatment of advanced malignant melanoma is an increasing clinical problem worldwide because of the increase in incidence of malignant melanoma. The median survival for previously untreated patients with disseminated malignant melanoma is approximately 4 months [1].

Alkylating agents are the most frequently used drugs in chemotherapy regimens for the treatment of metastatic malignant melanoma. The most common drug in use is dacarbazine [DTIC] (D), a monofunctional alkylating agent [2–4] which induces objective responses in 15–20%. With vindesine (V), a semisynthetic vinca alkaloid, objective responses have been reported in 15–20% [5, 6]. In addition, patients with melanoma metastases resistant to D responded to treatment with V [7]. Cisplatin (P) as a single agent induces objective responses in 10% of melanoma patients [8, 9]. The mode of action of P is quite different to D or V as is the toxic spectrum [10]. The low degree of haematological toxicity with P makes it an interesting candidate to add to D and V.

Overall, single drug therapy of disseminated malignant melanoma has produced objective response rates of 10–20%, with few complete remissions [11]. A number of phase II studies with the combination DVP have demonstrated high objective response rates in disseminated malignant melanoma [12–17] ranging from 35 to 52%. The median response duration has not, however, exceeded more than a few months

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[12]. Thus far there have been no reports showing that cytostatic treatment is able to increase median survival time.

We now report a prospective randomised phase III trial in patients with disseminated malignant melanoma. The aim of the study was to investigate if the addition of P to the combination DV could increase survival.

PATIENTS AND METHODS

Patients

Patients were consecutively recruited from eight different geographic areas in Norway and Sweden. In total, 326 patients with measurable, metastatic malignant melanoma were randomised.

Inclusion criteria were histopathologically proven melanoma, no prior chemotherapy, surgery not feasible or inappropriate, measurable (in two dimensions) or evaluable (measurable in one dimension) disease with documented progression within 2 months prior to the start of the study, performance status (WHO) ≤ 2 and an estimated life expectancy of > 3 months, age < 75 years; white blood cell count $\geq 3.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, serum creatinine < 125 mol/l, and creatinine clearance > 60 ml/min. Skin, subcutaneous and superficial lymph node metastases were verified by fine needle aspiration biopsy before study entry.

The anatomical sites of primary tumours and metastases were registered in the following categories: skin, lymph nodes, lungs, liver, bones, central nervous system and other.

Response evaluations were carried out according to WHO classification [18], i.e. all tumour sites were investigated at the same time on two consecutive occasions at least 4 weeks apart. Response rates according to location and number of sites were determined in the majority of cases using one response evaluation only (best response), i.e. not fulfilling WHO criteria. Toxicity was evaluated according to WHO criteria.

Treatments

D (DTIC, Dome/Hollister-Stier Leverküsen, Germany) was given at a dose of 250 mg/m^2 as a 30 min intravenous (i.v.) infusion for the first 5 days in a 28-day schedule. V (Eldesine, Eli Lilly, Indiana, Indianapolis, USA) was administered at a dose of 3 mg/m^2 as an i.v. bolus injection once weekly on days 1, 8, 15 and 22. After completion of the D infusion and after prehydration, P (Platinol, Bristol-Myers Squibb, New York, USA) was given at a dose of 100 mg/m^2 as a 30-min infusion on day 1 every 4 four weeks. Schedules for dose reduction, in case of haematological, renal or neurotoxicity were included in the protocol. It was decided to give a maximum of three cycles with P. Patients without tumour progression continued thereafter with DV treatment.

Ethical and quality assurance

Approvals from appropriate ethical review boards and regulatory authorities were obtained in the participating countries before initiation of the study. Informed consent was also obtained from patients before randomisation. Source data verification was carried out through the activity of monitoring the participating clinics. All documented complete and partial responses and severe toxicities were reviewed by an Oncology Review Board (ORB).

Statistical considerations

The median survival after 2 years was estimated to be approximately 15% after treatment with the DV combination. The minimal difference considered to be clinically relevant to detect between the study groups was set at 15%, i.e. the median overall survival after DVP treatment was estimated to be at least 30%, 2 years after treatment.

With an alpha of 0.05 and a beta of 0.20, calculated according to a two-sided statistical significant test, 2×120 evaluable patients were needed in order to detect a 15% difference between the treatment arms. The calculated number of patients required was estimated at 2×140 patients. At the time when the estimated number of patients (280) had been recruited, a decision was taken to continue enrolment, as no alternative treatment options were available.

Differences in response rates were tested using chi-square analysis. Differences in response duration and survival were plotted using the Kaplan–Meier method [19] and were compared by the log rank test [20]. The response duration for complete responders was calculated from the date that a complete response was first noted until the date of progressive disease or the date of last follow-up. The time to progression was calculated from the start date of treatment to the documented date of progressive disease or the date of last follow-up. Stratification parameters were participating regional hospitals, the presence of central nervous system metastases and prior chemotherapy. Logistic regression techniques with standard forward selection methods were used to determine factors predictive of survival [21, 22].

RESULTS

Patients

Patients' demographics are shown in Table 1, indicating that the two treatment groups were well balanced. The most common primary site was skin (80.4%), and lung was the most common site of distant metastasis (23.5%). The median time to distant metastasis after primary surgery was 32.7 months (0–325.5 months), with no significant difference between the two groups. The number of patients evaluable and reasons for exclusion are shown in Table 2 and Figure 1.

Dose intensity

The median number of administered cycles per patient was three (range 1–19) with more cycles for patients receiving DVP (60.8% versus 48.7%, $P = 0.043$). Regarding dose intensity (mg/m^2/week), the predetermined dose for D was 313 mg, for V 3 mg and for P 25 mg. The median received D dose was 294 mg for the total patient population. The DV group received 301 mg and the DVP group 284 mg, a statistically significant difference ($P = 0.032$).

The median received V dose was 1.8 mg in the total population. In the DV arm patients received 1.9 mg and the DVP arm 1.6 mg, a statistically significant difference ($P = 0.006$). The median received dose for P was 23 mg/m^2/week.

Survival analysis

The survival analysis included all randomised patients. No significant difference ($P = 0.22$) between the treatment groups regarding overall survival was observed according to the log rank test (Figure 2). The median time from treatment start to the date of death or the date of last follow-up was 6.5 months. Previous chemotherapy had been delivered to 36 patients, equally distributed between the treatment arms. Survival in this subgroup did not differ from patients without previous treatment (data not shown). No differences were

Table 1. *Patient demographics at inclusion (*326 *patients)*

	DV ($n=165$) *n* (%)	DVP ($n=161$) *n* (%)
Gender		
Male	105 (63.6)	104 (64.6)
Female	60 (36.4)	57 (35.4)
WHO index		
Median	0	0
Range	0–3	0–4
Age (years)		
Median	53.0	53.6
Range	14.1–74.3	20.8–73.8
Primary tumour site		
Skin	138 (83.6)	124 (77.0)
Eye	12 (7.3)	10 (6.2)
Genitals	3 (1.8)	1 (0.6)
Unknown	11 (6.7)	25 (15.5)
Other	1 (0.6)	1 (0.6)
First recurrence		
Local recurrence	16 (9.7)	10 (6.2)
Regional skin metastases	17 (10.3)	17 (10.6)
Regional lymph nodes metastases	67 (40.6)	74 (48.0)
Distant metastasis	64 (38.8)	58 (36.5)
Unknown	1 (0.6)	2 (1.2)
Prior chemotherapy	19 (11.5)	17 (10.6)
Distribution of metastatic sites at start of treatment		
Skin	61 (37.0)	66 (41.0)
Lymph nodes	81 (49.1)	75 (46.6)
Lungs	89 (53.9)	74 (46.0)
Liver	58 (35.2)	43 (26.7)
Bones	18 (10.9)	13 (8.1)
Brain	22 (13.3)	26 (16.1)
Other	31 (18.8)	35 (21.7)
Unknown	1 (0.6)	1 (0.6)
Total	361*	333**
Number of metastatic sites per patient		
1	45 (27.3)	52 (32.3)
2	57 (34.5)	64 (39.8)
3	49 (29.7)	28 (17.4)
4	11 (6.7)	12 (7.5)
5	2 (1.2)	4 (2.5)
Unknown	1 (0.6)	1 (0.6)
Months from diagnosis to first recurrence		
Median	24.6	21.2
Range	0.9–240.7	0.0–322.8
Months from first recurrence to metastatic disease		
Median	6.4	6.7
Range	0.0–179.7	0.0–74.3
Months from diagnosis to metastatic disease		
Median	32.2	33.5
Range	0.0–283.2	0.3–325.5

*Multiple sites in 119 patients. **Multiple sites in 108 patients. D, dacarbazine; V, vindesine, P, cisplatin.

observed between participating centres (data not shown). The presence of brain metastases at inclusion strongly correlated ($P<0.0001$) with a survival disadvantage (Figure 2). There was a statistically significant trend ($P<0.0001$, log rank test) between the number of involved sites at inclusion and survival. Patients with fewer metastatic sites lived longer.

Response evaluation

Response was a secondary objective in this study resulting in a total of 216 patients being evaluable with 110 patients being excluded (Table 2). Of the 216 patients, 111 received treatment with DV and 105 DVP. With the DV treatment, 11 (10%) patients obtained complete remission and 12 (11%) patients partial remission (Table 3). With the DVP regimen 17 (16%) patients obtained complete remission and 16 (15%) partial remission. The overall response rate (complete plus partial remission) for the DV arm was 21 (95% confidence interval 13.9–29.7) and for the DVP arm 31% (95% confidence interval 22.9–41.3), but the difference was not statistically significant ($P=0.10$).

A comparison of the two treatment arms showed significantly higher response rates for patients who received DVP when metastases were located in the skin DVP 25/53 versus DV 11/52, ($P=0.009$) and lymph nodes DVP 32/64 versus CV 18/64 ($P=0.018$). No significant differences were noted at other sites. Patients with fewer metastatic sites had a higher response rate ($P=0.04$) but there was no significant difference between the two treatment groups.

The median response duration for complete responders according to the Kaplan–Meier estimate was 6.0 months for the whole study population. The median time to progression (Kaplan–Meier estimate) among evaluable patients was 2.8 months. When the treatments were compared, the median time to progression in the DVP arm was 4.2 months and in the DV arm 2.2 months, a statistically significant difference (log rank test $P=0.007$) (Figure 3).

Prognostic factors

When analysing prognostic factors, the univariate analyses were based on Kaplan–Meier log rank values for survival. There was a strong correlation between survival time and the number of metastatic sites at study entry, (1 versus 2–5, $P<0.0001$) complete remission (complete remission versus not complete remission, $P<0.0001$), the absence of liver and central nervous system metastases at study entry (absent versus present, $P<0.0001$) and the number of received treatment courses (4 versus <4, $P<0.0001$). The absence of distant metastatic disease at first recurrence ($P=0.002$) and long median time (≥ 32.2 months) from primary diagnosis to the start of study treatment ($P=0.043$) also correlated to a longer survival time.

A logistic regression analysis was performed on 317 patients, at two intervals. The first analysis was carried out at 6 months, representing approximately the median survival time (6.5 months) of the total patient population and at 18 months, representing long-time survivors. Negative independent prognostic factors at 6 months were the presence of central nervous system, bone, liver metastases and short time interval (<32.2 months) from diagnosis to metastatic disease. Positive independent prognostic factors at 18 months were no more than one metastatic site and the absence of liver metastases.

Table 2. Number of evaluable patients and reasons for exclusion from tumour response evaluation according to the WHO criteria

	DV	DVP	Total
Number randomised			
Evaluable for survival (= all patients)	165	161	326
Evaluable for toxicity	160	153	313
Evaluable for WHO response	111	105	216
Number excluded (%)			
Incomplete response evaluation	38 (23.0%)	33 (20.5%)	71 (21.8%)
Early death	5 (3.0%)	6 (3.7%)	11 (3.4%)
Wrong inclusion	5 (3.0%)	8 (5.0%)	13 (4.0%)
Never received study treatment	5 (3.0%)	8 (5.0%)	13 (4.0%)
Major protocol violations	1 (0.6%)	1 (0.6%)	2 (0.6%)
Total	54 (32.7%)	56 (34.8%)	110 (33.7%)

D, dacarbazine; V, vindesine; P, cisplatin.

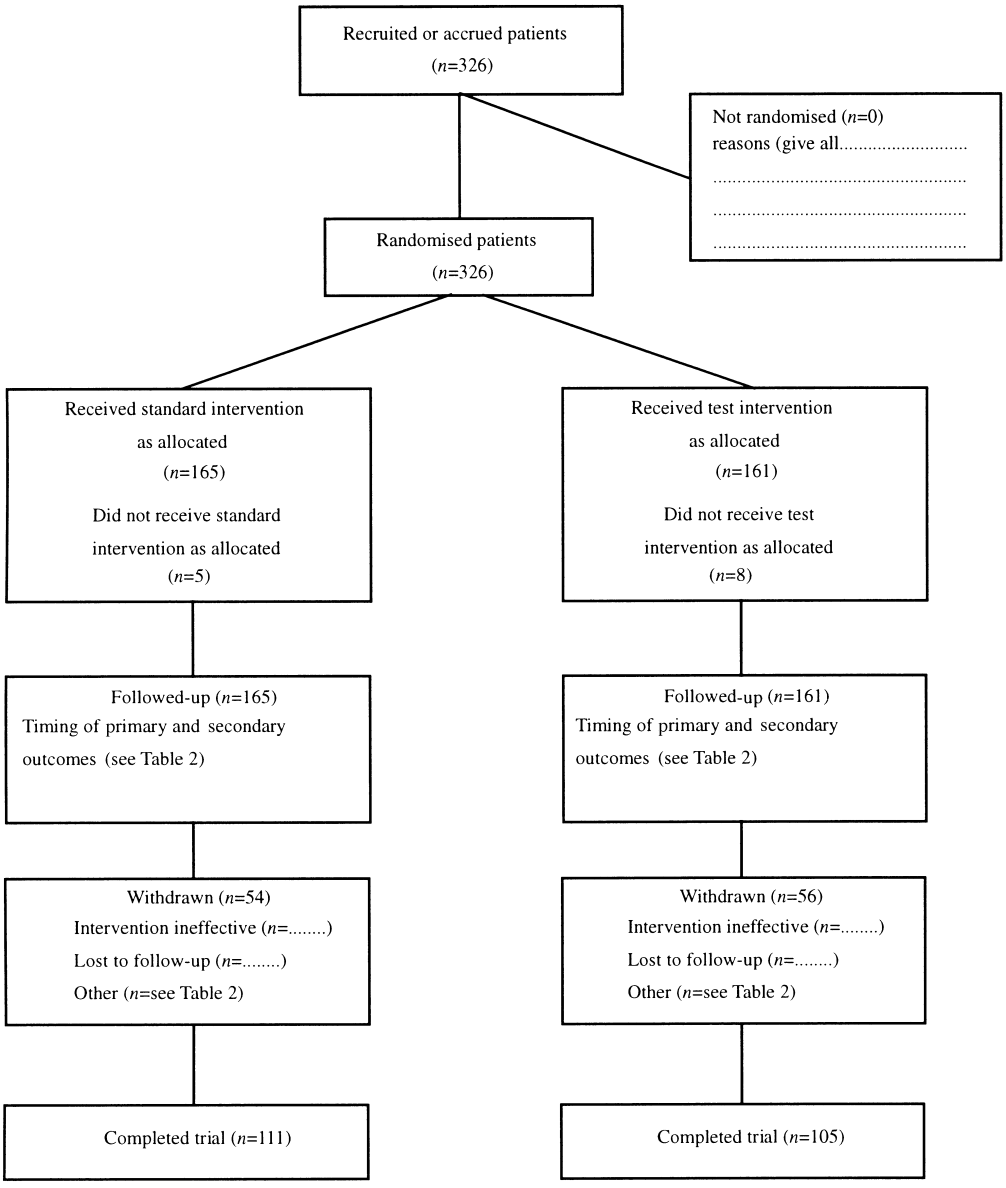

Figure 1. Flow chart of the progress of patients through the trial.

Toxicity

Toxicity was assessed according to WHO grading and was significantly more pronounced in patients treated with DVP. Toxicity was more pronounced among non-responders even though the number of cycles was less compared with responders.

Haematological toxicity

Anaemia, requiring transfusions (haemoglobin < 80 g/l) was observed in 11% of patients in the DVP group, and 5% in the DV group ($P = 0.077$). Grade 3–4 leucopenia (leucocytes $< 2.0 \times 10^9$/l) was observed in 38% of patients in the DVP group as compared with 13% in the DV group ($P < 0.0001$). 3 patients in the DVP group developed treatment-induced septicaemia. Grade 3–4 thrombocytopenia ($< 50 \times 10^9$/l) occurred in 6% in the DV group and in 11% of patients in the DVP group ($P = 0.19$). 1 patient in the DV group developed a grade IV thrombocytopenia with generalised petechias and a nadir of 6×10^9/l.

Non-haematological toxicity

Overall, non-haematological toxicity was less pronounced in the DV group (Table 4). Grade 3–4 alopecia occurred in both treatment groups, but was significantly ($P < 0.0001$) more common in the DVP group (45%) compared with the DV group (19%). Grade 3–4 nausea and vomiting was more commonly observed in the DVP group than in the DV group (35 versus 18%, $P = 0.0011$). Renal toxicity, defined as S-creatinine ≥ 125 μmol/l, was seen in only 3.1% of patients in the DVP group, but in 13.7% in the DVP group ($P = 0.0015$). Ototoxicity (subjective and/or objective) was observed in

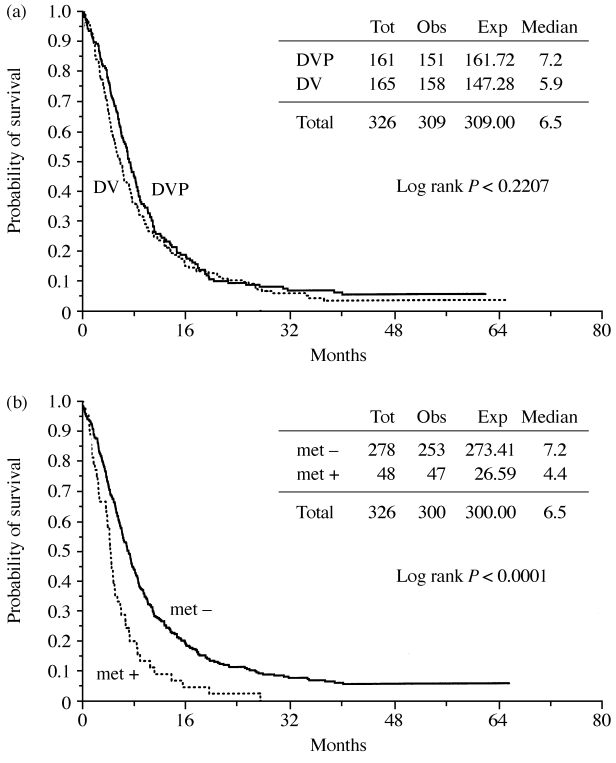

Figure 2. Overall projected probability of survival (from the start date of treatment to the date of death or the date of last follow-up) of (a) 326 patients with disseminated malignant melanoma treated with either dacarbazine–vindesine (DV) or dacarbazine–vindesine–cisplatin (DVP); (b) patients with brain metastases (met+) or without brain metastases (met−).

Table 3. *Response evaluation according to WHO criteria*

	DV ($n = 111$)	DVP ($n = 105$)
Complete response	11 (10%)	17 (16%)
Partial response	12 (11%)	16 (15%)
Stable disease	26 (23%)	36 (34%)
Progressive disease	62 (56%)	36 (34%)

Overall response rate for DV = 21% (95% CI 13.9–29.7). Overall response rate for DVP = 31.4% (95% CI 22.9–41.3). Responders DVP versus responders DV: chi-square, not statistically significant. D, dacarbazine; V, vindesine; P, cisplatin.

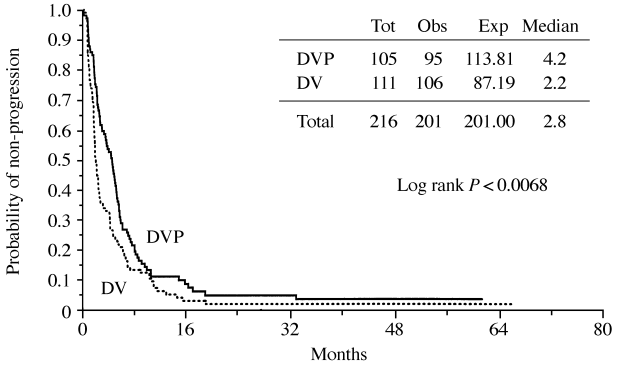

Figure 3. Overall projected probability of time to progression (from the start date of treatment to the documented date of progressive disease or the date of last follow-up) in patients treated with either dacarbazine–vindesine (DV) or dacarbazine–vindesine–cisplatin (DVP).

Table 4. *Haematological and non-haematological toxicity—worst event per patient*

WHO grade	DV	DVP
Anaemia		
0–2	151 (95%)	136 (89%)
3–4	8 (5%)	17 (11%)
Total	159 (100%)	153 (100%)
Leucopenia		
0–2	139 (87%)	95 (62%)
3–4	20 (13%)	58* (38%)
Total	159 (100%)	153 (100%)
Thrombocytopenia		
0–2	149 (94%)	136 (89%)
3–4	10 (6%)	17 (11%)
Total	159 (100%)	153 (100%)
Alopecia		
0–2	105 (81%)	68 (55%)
3–4	25 (19%)	56 (45%)
Total	130 (100%)	124 (100%)
Nausea and vomiting		
0–2	118 (83%)	90 (65%)
3–4	25 (17%)	49** (35%)
Total	143 (100%)	139 (100%)

D, dacarbazine; V, vindesine; P, cisplatin. *$P < 0.0001$ DVP versus DV. **$P = 0.0011$ DVP versus DV.

21.7% in the DVP group and not at all in the DV group ($P < 0.0001$). The frequency and grade of neurotoxicity was equally distributed between the treatment groups, and was severe in 20.8% of patients.

DISCUSSION

The aim of this study was to investigate if an increased objective response rate obtained with the combination DVP might influence survival of melanoma patients with disseminated disease. As indicated in phase II trials, the addition of P to DV most probably increases the response rate [12–17], but it is questionable if this translates into survival benefit. Until October 1995, no randomised data had been published on this topic. The result of this study did not demonstrate any increased survival with the DVP regimen compared with DV.

Whether the three drug combination induced a significantly higher level of responses as compared with the two drug combination is an important question. A total of 216 of 326 patients were available for response evaluation (66%). This points to a serious problem with multicentre clinical trials. Although long experience with multicentre trials exists in the Scandinavian countries, the Oncology Review Board rejected a large number of cases from the response evaluation (Table 2). The main cause of exclusion was insufficient follow-up investigations due to the fact that patients had heavy tumour burden in multiple anatomical sites which often required different tumour evaluation methods. Required evaluations were, therefore, difficult to perform in daily clinical work within the time limits demanded by the protocol. Another reason was that patients often received treatment in different hospitals. The treatment was often initiated at the regional hospital, while follow-up treatment (two out of every three cycles) and some of the tumour evaluations were also performed at local hospitals. This method of reducing healthcare costs resulted in increased difficulties in following up and confirming objective responses, but did not affect the primary objective of the study (i.e. survival).

A comparison of the response rates for the two treatment arms showed, however, a trend favouring the three-drug combination. When the response rates were compared for different anatomical sites, the addition of P significantly increased the response rates of skin and lymph node metastases. We also calculated response rates and included patients without confirmation of response according to WHO criteria ('best response'). The difference between the two treatment arms increased when analysed for 'best response' and a statistical significance was reached (42.5% versus 22.7%, $P = 0.002$). Furthermore, the time to progression was significantly longer for patients in the DVP treatment arm (Figure 3). In our opinion, the addition of P to DV most probably increased the objective response rate. However, this did not significantly influence survival.

The response rate was estimated in patients with different numbers of metastatic sites. Patients with one or two metastatic sites responded significantly better. Thus, an increase in tumour volume might increase drug resistance. This may also be related to the size of metastases. Most probably, drugs more easily reach the tumour cells in small metastases. A decreased response rate may also be related to acquired resistance against cytostatic drugs due to up-regulation of drug resistance factors.

This study clearly demonstrated a significant increase in toxicity in the DVP treatment arm (Table 4). Haematological toxicity was generally moderate in both treatment groups, with statistically significant differences between the treatment arms in favour of the DV regimen. Peripheral neuropathy was common and equally distributed between the treatment arms. Alopecia was frequent and more pronounced in the DVP group. Renal toxicity was not a major problem, with only a few cases of severe episodes (S-creatinine > 150 μmol/l; with 7 patients in the DVP treatment arm and 1 patient in the DV treatment arm).

In conclusion, the addition of P to DV treatment of disseminated malignant melanoma did not show a prolongation of overall survival in this study. There was a numerical increase in the overall response rate favouring the DVP regimen, but it was not statistically significant. We conclude that the DVP combination does not merit further use in patients with disseminated malignant melanoma due to a statistically significant proven increase in toxicity and to the lack of evidence of increased survival. However, in some patients, the DVP regimen has apparently been of value, as time to progression was prolonged.

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