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Treatment of metastatic malignant melanoma with dacarbazine, vindesine and cisplatin

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Summary Twenty-seven patients with disseminated malignant melanoma were treated monthly with cisplatin (CDDP) 120 mg m^{-2} on day 1, vindesine (VDS) 3 mg m^{-2} on day 2 and dacarbazine (DTIC) 250 mg m^{-2} on days 2–6. None of them had received prior chemotherapy. All patients are evaluable for response and toxicity.

There were five (19%) complete (CR) and seven (26%) partial (PR) responses for a total response rate of 45%. We conclude that the combination of DTIC, VDS and CDDP is capable of producing a relatively high rate of response in patients with advanced metastatic malignant melanoma, but responses are short.

There is documented activity of vindesine (VDS) (Retsas *et al.*, 1980) and dacarbazine (DTIC) (Comis, 1976; Constanzi, 1976; Pritchard *et al.*, 1981) as single agents or in combination in malignant melanoma with objective response rates of 15–42% (Einhorn *et al.*, 1974; Hill *et al.*, 1984; Retsas *et al.*, 1985). Numerous attempts have been made to increase the response rate by combining various drugs. However, there is no evidence that any particular combination has improved these results (Einhorn *et al.*, 1974; Karakousis *et al.*, 1979). Cisplatin (CDDP) alone or in combination with other active agents has been tried in patients with advanced malignant melanoma and has resulted in a wide range of remission rates (Chary *et al.*, 1977; Nathanson *et al.*, 1981; Al-Sarraf *et al.*, 1982; York *et al.*, 1983; Retsas *et al.*, 1985; Wussow *et al.*, 1987).

Since DTIC, VDS and CDDP have different mode of action and toxicity, it was rational to combine these drugs in an effort to improve response rates and possibly response duration.

Patients and methods

From March 1984 to December 1986, 27 consecutive patients entered the trial. Entry criteria included histologically documented melanoma, age < 75 years, ECOG performance status of 0–2, predicted survival > 2 months, no prior chemotherapy and creatinine clearance > 60 ml min^{-1}.

Chemotherapy consisted of CDDP 120 mg m^{-2} as a 30 min infusion in 3% hypertonic saline with hydration and mannitol diuresis on day 1, VDS 3 mg m^{-2} (no more than 5 mg) on day 2 as an i.v. bolus and DTIC 250 mg m^{-2} on days 2–6 as an i.v. infusion over 30 min. The course was repeated every 4 weeks and doses were decreased according to the degree of haematological and renal toxicity of the preceding course.

Antiemetic treatment with metoclopramide 2 mg kg^{-1} 0.5 h before and 1.5, 3.5, 5.5 and 8 h after CDDP administration plus dexamethasone 8 mg 3 h before and 3, 6 and 9 h after CDDP administration was given. On days 2–6 metoclopramide 2 mg kg^{-1} plus dexamethasone 8 mg 0.5 h before and 3 h after DTIC administration were given.

Fourteen males and 13 females with a mean age of 54 years entered the trial. Patient characteristics are shown in Table I. The mean number of administered courses was four (range 1–8 courses). World Health Organization (WHO) response and toxicity criteria were used (WHO, 1979).

Table I Patient characteristics

Characteristic	*No. of patients (%)*
Total no. entered	27
Sex	
Male	14 (52)
Female	13 (48)
Age (years)	
Mean	54
Median	57
Range	36–72
ECOG performance status	
0	6 (22.3)
1	11 (40.7)
2	10 (37.0)
Site of metastases	
Subcutaneous and skin	14 (52)
Lymph nodes	15 (56)
Lung	14 (52)
Liver	1 (4)
Bone	2 (8)

Results

Response to therapy

The response to therapy was as follows: complete response (CR) five (19%) patients, partial response (PR) seven (26%), stable (SD) or progressive disease (PD) 15 (55%). The median duration of CR was 4+ months (4,4,4,4.5,9+) and of PR 8 months (3,4.5,5.5,8,10,11,18). Tumour responses by site are shown in Table II. Metastases in the lungs, lymph nodes, subcutaneous tissues and skin were more responsive to chemotherapy. As shown in Table II, CRs were seen in three patients with lung, subcutaneous and lymph node metastases and in two patients with lung and lymph node metastases. The seven patients responding partially to chemotherapy were: one with lung metastases, one with lung and lymph nodes metastases, two with subcutaneous and skin disease, two with lymph nodes metastases and one with lymph node, subcutaneous and skin metastases. There were only four patients with visceral metastatic deposits. Of these there were one PR and three SD or PD. Of the 12 patients with non-visceral disease, five responded partially and seven had SD or PD.

Toxicity

This schedule was well tolerated with moderate toxicity. The toxic effects are summarised in Table III. Three patients developed grade III and IV leucopenia and one of these developed severe lung infection, which was successfully treated with broad spectrum antibiotics. There were no

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Table II Metastatic sites

Response	Subcutaneous skin	Lymph nodes	Lung	Subcutaneous skin + bones	Lung + lymph nodes	Lung + subcutaneous skin	Liver + lung	Lung + bones	Subcutaneous skin + lymph nodes	Subcutaneous skin + lymph nodes + lung	Total
CR	–	–	–	–	2	–	–	–	–	3	5
PR	2	2	1	–	1	–	–	–	1	–	7
SD or PD	3	2	1	1	2	2	1	1	2	–	15

Only visceral metastatic disease, 4: 1 PR, 3 SD or PD.
Only non-visceral metastatic disease, 12: 5 PR, 7 SD or PD.

Table III Toxicity

	Grade				
	0	I	II	III	IV
Anaemia	15	12	0	0	0
Leucopenia	9	7	8	2	1
Thrombocytopenia	23	3	1	0	0
nausea/vomiting	0	1	5	12	9
Nephrotoxicity	9	12	6	0	0
Neurotoxicity	25	2	0	0	0
Hearing impairement	27	0	0	0	0

treatment-related deaths. Despite hydration and mannitol diuresis 18 patients developed transient and reversible nephrotoxicity of grade I and II (increased urea and/or creatinine). Two patients developed peripheral neuropathy, with symptomatic paresthesias and sensory deficit. Nausea and vomiting were nearly universal, but manageable. No patient developed socially noticeable hearing loss.

Discussion

Although the prognosis of patients with disseminated malignant melanoma remains poor, intensive chemotherapy may produce remissions in a small number of patients. The antitumour effect of VDS in advanced malignant melanoma is at least comparable with, and probably superior to, DTIC (Retsas *et al.*, 1980). It has been reported that the response rate in disseminated malignant melanoma with CDDP alone or in combination with DTIC was no better than the rate obtained with DTIC alone (Friedman *et al.*, 1979; Oratz *et al.*, 1987).

The VBD (vinblastine, bleomycin, cisplatin) combination has been reported to give objective responses ranging from 0% (York *et al.*, 1983) to 43% (Nathanson *et al.*, 1981). Other investigators reported response rates in the intermediate range 10–41% (Creagan *et al.*, 1981; Canadian Melanoma Group, 1984; Luikart *et al.*, 1984; Mechl *et al.*, 1985). Carey *et al.* (1986) reported 25% CR + PR in previously untreated patients with metastatic malignant melanoma by using the VDD (vinblastine, dacarbazine, cisplatin) regime. The (B) DPV_3 (Retsas *et al.*, 1985) (cisplatin, vinblastine, vindesine ± bleomycin alternating with dacarbazine, vincristine) regime gave a 29% response rate despite more advanced disease at the onset of treatment. It was concluded that the addition of bleomycin to the DPV_3 regime had no effect on response.

The response rate of 45% (CR + PR) for DVP combination in our study is slightly lower than that recently reported by Wussow *et al.* (1987). Toxicity encountered in our patients was similar to those reported by Wussow *et al.* (1987), who used an almost identical regime. The major difference between the previous studies and the present one is that they employed lower doses of cisplatin. Whether the increased dose is important or whether our and Wussow *et al.*'s (1987) better response rate was a chance occurrence cannot be determined. The sites most likely to respond to chemotherapy remain skin, lymph nodes and lungs and no responses were observed in hepatic and skeletal metastases.

The DVP combination as first line chemotherapy in disseminated malignant melanoma seems to yield a useful response rate with moderate toxicity, but the mean duration of response remains disappointing.

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