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Phase II Trial of Procarbazine, Vincristine and Lomustine (POC) Chemotherapy in Metastatic Cutaneous Malignant Melanoma

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40 patients with symptomatic metastatic melanoma were treated with procarbazine, vincristine and lomustine (POC). 4 patients had received chemotherapy previously. Responses were seen in 8 patients (20%), 4 of whom had a complete remission. All responding patients had some tumour shrinkage after one cycle. The median duration of response was 27 weeks, with 2 patients remaining in complete remission at 6 and 6.5 years. The median survival for the whole group was 22 weeks, whilst that of the responding patients was 35 weeks. Using conventional anti-emetics, the principal toxicities were nausea and vomiting, severe in 15% of cycles. Other non-haematological toxicity was uncommon. Neutropenia (WHO grade 3 or 4) occurred in 11% of cycles and thrombocytopenia in 8%. The response rate of metastatic melanoma to POC chemotherapy was similar to other cytotoxic regimens though toxicity, other than nausea and vomiting, was minimal. The rapid response allows patients with unresponsive disease to be identified early, avoiding continuing toxicity.

Key words: melanoma, chemotherapy, procarbazine, vincristine, lomustine
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INTRODUCTION

THE PROGNOSIS of patients with metastatic malignant melanoma is poor, with a median survival of only 7 months from the diagnosis of metastases [1].

Generally, the impact of chemotherapy in this condition has been disappointing. Such agents as dacarbazine and the nitrosoureas have been widely reported as producing responses in 10–20% of patients [1, 2], but these are usually of short duration and often with significant toxicity. Furthermore, treatment with such agents has produced little survival advantage.

In contrast, Carmo-Pereira and co-workers [3, 4] found a response rate of 48% using a combination of procarbazine, vincristine and lomustine (CCNU; POC) in 44 patients. Furthermore, the POC regimen appeared to be well tolerated with minimal toxicity. However, a multicentre study [5] failed to reproduce the high response rate found by Carmo-Pereira. This phase II study using POC was initiated to produce further data on both the activity and toxicity of this regimen in metastatic melanoma.

PATIENTS AND METHODS

Entry criteria

The principal protocol requirements were that patients should have symptomatic metastatic melanoma from a cutaneous primary lesion with measurable disease either clinically or radiologically. At least two cycles of chemotherapy were planned unless there was clear evidence of progression earlier.

Pretreatment evaluation included clinical examination, full blood count, biochemistry screen and chest X-ray. Bone scintigrams, skeletal X-rays and CT scans were performed if indicated.

Patients' characteristics

Pretreatment characteristics of the 40 patients are shown in Table 1. The median age was 42 years (range 27–73 years) and the median number of metastatic sites was three (range one to five). Some sites, such as skin, lung or lymph nodes are known

Table 1. Pretreatment characteristics of patients

	Number of patients (n = 40)
Sex	
Male	22
Female	18
Previous therapy	
Hormone therapy	6
Chemotherapy	4
Radiotherapy	13
Primary site	
Head and neck	4
Trunk	12
Extremity	18
Primary unknown	6

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to respond favourably to chemotherapy [3–5] and 13 patients (33%) had disease confined to these sites. Performance status at the start of chemotherapy was 0 in 15 patients, 1 in 14 patients, 2 in 7 patients, 3 in 1 patient and not recorded in 3 patients.

6 patients had received hormone therapy with tamoxifen or megestrol acetate with no response and 4 patients had received prior chemotherapy. Of these, 2 received dibromodulcitol, 1 carboplatin and 1 CI-921, an investigational drug with no response noted. 13 patients had received radiotherapy to symptomatic sites of disease, 6 for bone metastases, 4 for nodal disease and 3 had received cranial irradiation for cerebral disease. In no instance was a previously irradiated site used as the only site to assess response.

Drug regimen

The regimen followed that originally reported by Carmo-Pereira and colleagues [3, 4]: procarbazine 100 mg/m^2 (maximum 150 mg) orally days 1–10, vincristine 1.4 mg/m^2 (maximum 2 mg) intravenously days 1 and 8, and CCNU 150 mg/m^2 (maximum 200 mg) orally day 1, the cycle was repeated every 4–6 weeks, depending upon bone marrow recovery.

Dose modifications

Haematological parameters were monitored weekly. The dose of CCNU was decreased by 25–50% if grade 4 haematological toxicity or significant infection occurred. If myelosuppression persisted at the time of the next cycle, chemotherapy was withheld until the neutrophil count recovered to at least 2 × 10^9/l and platelets to 100 × 10^9/l.

Assessment of response

Patients were assessed for disease response every 4 weeks by clinical examination and radiology of disease sites. Bone scintigrams and CT scans were repeated as necessary to ascertain response status. Response and toxicity categories were based on WHO criteria [6], except for nausea and vomiting which was graded as follows. Grade 1: mild nausea (< 24 h) or one to three vomits, grade 2: moderate nausea (< 48 h) or four to 10 vomits, and grade 3: severe nausea (> 48 h) or > 10 vomits. The response duration and survival were measured from the commencement of treatment with POC. The median time to progression and median survival were determined by the method of Kaplan–Meier [7].

RESULTS

Response

Patients received a median of two cycles of POC (range one to six). 8 patients (20%) achieved a response, 4 with a complete response (CR) (duration 5 months, 8 months, 6+ years, and 6.5+ years) and 4 with a partial response (PR) (duration 1.5, 2, 3.5 and 11 months). A further 6 patients (15%) had static disease for 4–8 months.

Median duration of response was 27 weeks and the median survival of patients with a response was 35 weeks. For all 40 patients receiving POC, the median time to progression was 8 weeks and the median survival was 20 weeks. There was no apparent difference in response rate according to age, performance status, disease-free interval and the delay from first metastases to commencement of POC, although numbers were small (Table 2).

Table 2. Response to POC chemotherapy

	Number of patients	
	n	CR + PR
Overall	40	8
Age		
< 50 years	27	6
50+ years	13	2
Performance status		
0–1	29	3
2–3	8	2
Unknown	3	3
Disease-free interval		
> 1 year	17	2
1–5 years	11	3
> 5 years	12	3
Interval first metastases to POC		
0–3 months	10	3
4–12 months	15	3
> 12 months	15	2

The response at individual metastatic sites is shown in Table 3. Responses were seen predominantly in skin, lymph node or lung disease, but other metastatic sites showing response included bone, adrenal gland and stomach and kidney (1 patient each). No response was seen in a previously irradiated site. All patients who achieved CR or PR had clear evidence of some tumour shrinkage before the second cycle. In 2 patients, who eventually achieved CR, this did not become complete until 15 and 19 months after finishing therapy. During this time, there was gradual resolution of residual masses in the breast and skin, respectively. Both remain free of disease at over 6 years. One of 8 patients who received further chemotherapy on relapse after POC achieved a PR with dacarbazine in combination with interferon-α.

Toxicity

Toxicity data are summarised in Table 4. Despite standard dose anti-emetics, some nausea and vomiting occurred in 89% of treatment cycles and was severe in 15%. 4 patients stopped treatment due to intolerable nausea or vomiting. 5-Hydroxytryptamine ($5HT_3$) antagonists were not available at the time of the study.

Haematological toxicity was generally not severe with the neutrophil count falling below 1.0 × 10^9/l in 11% of cycles and the platelet count falling below 50 × 10^9/l in 8% of cycles. 13 patients (33%) had treatment delays due to slow recovery of the

Table 3. Response rate at individual metastatic sites

Site	Involved	Number of patients	
		Evaluable	CR + PR*
Skin	24	22	6 (27%)
Nodes	21	19	4 (21%)
Lung	22	16	5 (31%)
Bone	8	6	1 (17%)
Liver	6	2	0 (0%)
Other intra-abdominal	11	6	3 (50%)

*Percentage is of patients evaluable at site. CR, complete response; PR, partial response.

neutrophil and/or platelet count. 8 patients required red blood cell transfusion and 1 patient required a platelet transfusion.

Table 4. Toxicity of 97 cycles of POC

Toxicity	WHO grade (% of cycles)		
	0	1–2	3–4
Nausea/vomiting*	11	74	15
Alopecia	86	14†	–
Mucositis	92	7	1
Neuropathy	80	20‡	–
Infection	91	8	1
Neutropenia	71	18	11
Thrombocytopenia	81	10	8

*Nausea and vomiting toxicity grading defined in text. †7 patients ‡8 patients.

DISCUSSION

Metastatic melanoma has a poor prognosis and is relatively resistant to chemotherapy, with single-agent dacarbazine generally showing response rates of less than 20%. The response rate from combination chemotherapy has been disappointing [8–10] and often associated with considerable toxicity. The use of immune modulating agents, such as interferon-α or levamisole, either alone or together with cytotoxic chemotherapy failed to improve the response rate at least in early studies [11–13]. Therefore, there was considerable interest when Carmo-Pereira and co-workers [3, 4] suggested the POC regimen could produce high response rates with modest toxicity. Subsequently, Shelley and associates [5] published results from a multicentre trial of 64 patients using the POC regimen, reporting only a 13% response rate.

The distribution of disease sites in the patients included in these different trials varied, and has been used to explain the discrepancy in the response rates. Higher response rates are commonly found in disease confined to the skin, lymph nodes or lungs. In the study by Carmo-Pereira, 84% of patients had disease confined to soft tissues, lymph nodes or lungs compared with 58% in Shelley's study and 33% in the current study. Most responses occurred in these sites, though in contrast to the earlier studies responses were seen in the current study in non-pulmonary visceral sites, but not in the liver. It should be noted that although patients were only treated for symptomatic disease in the current study, the majority had good peformance status and only 1 patient had a performance status of 3.

Toxicity to the POC regimen in the current study was generally not severe except for nausea and vomiting, which appeared related to the lomustine. Low-dose conventional anti-emetics were used in the study, which was conducted before the general availability of $5HT_3$ antagonists. Almost all patients experienced nausea and vomiting, but fortunately this was only severe in 15% of cycles. It is likely that this toxicity would be greatly reduced using the $5HT_3$ anti-emetics.

The regimen is easy to administer with only two brief outpatient visits required per cycle for the injection of vincristine. A major advantage of the regimen was that all patients who had useful control of their disease in the current study showed a response after one cycle of treatment. It is, therefore, possible to avoid continuing toxicity for those who fail to respond.

Subsequent to this study only patients with evidence of a response after the first cycle have been encouraged to continue on therapy.

The current study has confirmed the activity of the POC regimen in metastatic melanoma at least in ambulant patients. Although the overall response rate was similar to other chemotherapy combinations, it does have useful features: modest toxicity and early identifiable improvement in responding patients. In common with other regimens there is potential to enhance efficacy by combining it with tamoxifen [15], interferon [16] or other biological response modifiers. Whether the advantages of the POC regimen seen in the present study would be maintained in these circumstances awaits further study.

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