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Chemoimmunotherapy for Metastatic Malignant Melanoma Using Vincristine (NSC-67574), DTIC (NSC-45388) and Bacillus Calmette-Guerin

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Abstract—*Forty-seven patients with stage* IV *malignant melanoma were treated with pulses of Vincristine and DTIC. Intercalated, monthly BCG was administered by multiple puncture gun. No patient exclusions were made. The response rate was* 38%; *all complete responders* (8.5%) *were metastatic to skin and nodes only. The median survival of the responder patient group was* 6.7 months (1–21) *and* 2 months (<1–47+) *for non-responders. No significant differences were found for response nor survival length between patients grouped according to sex, severity of haematological toxicity, intervals from initial diagnosis to appearance of metastases or to start of therapy. Patients with the higher Karnofsky scores survived longer. No side effects attributable to BCG were noted and no serious haematological toxicity was encountered. Despite a high response rate, survival was disappointing, and represented the presence of metastases in more than one organ system with only a minority* (13%) *of patients having metastases in 'favourable' (skin, node) sites. A full description of metastatic sites and other prognostic features is necessary for future treatment evaluation.*

INTRODUCTION

METASTATIC malignant melanoma is frequently unresponsive to current chemotherapy [1]. The use of DTIC (5-3, 3, dimethyl-1-triazeno imidazole 4 carboxamide), one of the more effective agents in this disease, is associated with 20–25% objective response rates [1]. A small number of other agents, including the vinca alkaloids, possess some antimelanoma activity [1–3]. Attempts at tumour control by immunological manipulation have met with limited success [4–6], but few reports are available describing combination chemoimmunotherapy regimes [4, 7].

The incorporation into combined chemoimmunotherapy regimes of DTIC and Vincristine, agents with antimelanoma activity and associated with only minimal immunosuppression in man [6], is worthy of consideration. The small number of reports describing these combinations are suggestive of an increased response rate, about 55%, of longer duration and improved survival than those obtained using chemotherapy alone [7, 8].

The present study was proposed to investigate whether a chemoimmunotherapy regime using DTIC, Vincristine and BCG without inoculation of allogeneic melanoma cells produced similar results. The BCG was administered by multiple puncture gun instead of by scarification or by intradermal injection. This simplified regime would avoid the collection, storage and other problems associated with tumour cell immunisation and would not involve the morbidity of intradermal inoculations and scarifications described by other investigators [4, 7, 8].

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MATERIALS AND METHODS

Patient population

Forty-seven consecutive patients with progressing histologically proven malignant melanoma were studied. All patients had distant metastases involving more than one organ system. There were twenty-one men and twenty-six women with a median age of 46

(range 20–72 years). Extent of disease was defined by routine examination, haematology, biochemistry and radiology including isotope scans and other investigations as appropriate.

The primary skin tumour occurred on the limbs of thirty-one patients, on the trunk of nine patients and over the head and neck area of seven patients. A proportion (11 patients) of the total 47 with distant metastatic disease also exhibited local recurrence at the start of chemoimmunotherapy. The distribution of metastases is displayed in Table 1.

Table 1. Distribution of metastases within patient population

Site		Patient No.	Site		Patient No.
Nodal	(N)	37	Hepatic	(H)	14
Cutaneous	(D)	31	Cerebral	(B)	10
Pulmonary	(P)	29	Osseous	(O)	9

All patients had metastases involving more than one organ system.
Six patients had metastases involving N + D sites.
Ten patients had metastases involving N and/or D, and P sites.
Five patients had metastases of P, H, B, O sites (in various combinations).
Twenty-six patients had metastases of N and/or D sites and in various combinations of P, H, B, O sites.

No patient had previous chemotherapy. Five patients had received radiotherapy to regional (unresectable) nodal or cutaneous metastases; at least four weeks had elapsed from the end of any irradiation treatment.

There were no exclusions from the study analyses due to 'incomplete' treatment caused by early deaths, toxicity etc. Tumour measurements were recorded monthly before each course of chemotherapy.

Chemoimmunotherapy regime

The regime was prescribed as follows: 5(3, 3 dimethyl-triazeno)-imidazole-4 carboxamide (DTIC) was administered i.v. at a dose of 250 mg/m^2 for five consecutive days. On the first day, a single i.v. injection of Vincristine 1.4 mg/m^2 was given. The courses were repeated every 28 days. BCG was given between courses of chemotherapy, 10 days from the start of the preceeding course. Dried BCG vaccine, percutaneous (Glaxo), was reconstituted in 0.3 ml sterile water (average number of organisms 1.5×10^8) and administered by multiple puncture gun. Two applications of vaccine (40 needles punctures, 2 mm depth) were given to each limb. If disease progression was observed, chemotherapy was discontinued, otherwise a maximum of eight courses was administered.

Evaluation

Patients were evaluated for response according to the following criteria:

(1) Complete response (CR)—disappearance of all clinical, radiological and laboratory evidence of tumour, persisting for at least one month.

(2) Partial response (PR)—>50% decrease in the product of perpendicular diameters of a lesion without the appearance of new lesions or tumour progression elsewhere, lasting at least one month.

(3) No response (NR)—no change or less than 50% reduction in a measured lesion, or evidence of disease progression.

Haematological toxicity criteria were as in the COG studies [9].

RESULTS

The overall objective response rate (complete and partial responses) was 38.3% (CR = 8.5% and PR = 29.8%). The majority of responses (14/18) were recorded four weeks after the first two courses of chemoimmunotherapy. The response rate was not statistically significantly different ($P > 0.05$) between patients grouped accordingly to the intervals taken from initial diagnosis to appearance of metastases or the intervals from appearances of metastases to the start of chemotherapy.

All the patients achieving complete response were female and of the partial responders eight were female and six male. There was, however, no statistically significant difference ($P > 0.05$) between response for females and males. The Karnofsky status assessed before chemotherapy was 50 or less for six of the responders. There was no significant difference between the Karnofsky status for the responding and non-responding patient groups.

The change in the grading of the severity of side effects following chemotherapy courses was assessed for toxicity. There was no statistically significant difference in toxicity between the responding and non-responding patient groups.

The sites of metastases which responded to treatment are displayed (Table 2); ten patients responded in both visceral and non-visceral sites, seven of these patients exhibited response of lung metastases and three liver regression as well as in cutaneous and/or

Table 2. Response distribution within the metastatic site pattern

	CR	PR	NR
Metastatic pattern			
Visceral	—	4	1
Non visceral	4	—	2
Visceral + Non visceral	—	10	26

nodal deposits. All four of the complete responders were metastatic to non-visceral (cutaneous/nodal) sites alone. The remaining four patients who achieved responses had a visceral metastatic pattern; the response occurred in the lung deposits of three patients and in the liver of the fourth patient.

The survival of the patients who responded and who failed to respond to chemoimmunotherapy is given in Fig. 1 (Log rank chi

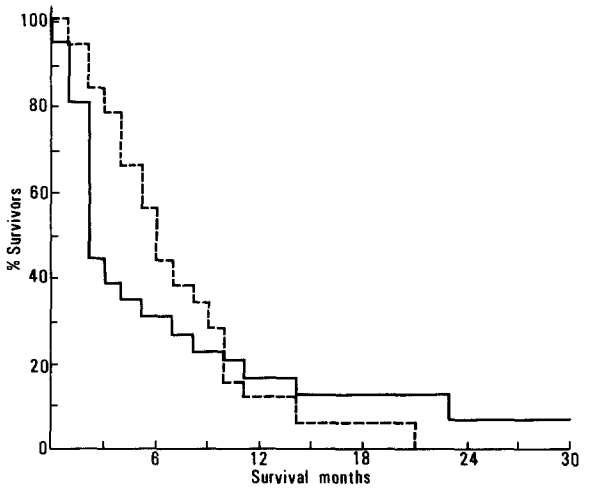

Fig. 1. Survival times for responding and non-responding patient groups. ———Non-responding patients (29); --- *responding patients* (18). $P=0.59$.

squared analysis). The median value for the responder group was 6.7 months (range 1–21) and for the non-responder group 2 months (range <1–47+). There were no statistically significant differences in survival of male (median 2 months, range <1–47+) and female (median 5.5 months, range <1–21) patients, nor between patients grouped according to change in toxicity. The interval from initial diagnosis to appearance of metastases and the interval from appearance of metastases to start of chemotherapy were also investigated; patients grouped within different intervals exhibited no statistically significant difference in length of survival ($P=0.36$ and $P=0.21$, respectively). There was, however, a statistically significant difference ($P=0.037$) in survival of patients with different Karnofsky performances scored before treatment. However, when the survival was examined for the responder patients group's performance scores there was no statistically significant difference ($P=0.96$) but the difference was still significant ($P=0.003$) for the non-responder patient group.

The total number of chemotherapy courses administered was 185; 6 patients received only a single course, 25 patients 2–4 courses, 16 patients five courses or more. Vomiting occurred with 160 chemotherapy courses and lasted two days or more with 26 of these treatment pulses. There were no statistically significant differences ($P>0.05$) between severity of side effects and the intervals between initial diagnosis, or diagnosis of metastases and start of chemotherapy.

Haematological toxicity was uncommon, moderate thrombocytopenia (75,000–99,999 cell/m^3 and severe thrombocytopenia (50,000–74,999 cells/mm^3) occurred after 9 and 3 courses of chemotherapy, respectively. Moderate leucopenia (2,000–2,999 cells/mm^3) and severe leucopenia (1,000–1,999 cells/mm^3) were observed after 7 and 1 course of chemotherapy, respectively. The next course of chemotherapy was delayed because of these side effects by 1–4 weeks in three patients.

DISCUSSION

Dimethyl triazeno imidazole carboxamide (DTIC) has become established as one of the more effective agents in the treatment of metastatic melanoma, with responses in 20–25% of patients [1, 10]. Various combinations of DTIC, nitrosoureas, vincristine, actinomycin D, etc., may produce some improvement in the response rate (to about 30%) [2, 11, 12] and an increased number of responses in visceral metastases with combination chemotherapy compared with single agent DTIC have been reported [2].

The addition of BCG to DTIC with or without melanoma cell immunisation was associated with a doubling of response rates [13, 14], and was considered to lengthen survival [14]. The present chemoimmunotherapy study gave a similar response rate (38%) and is higher than the 21% described for DTIC and vincristine combinations [15]. The complete response rate (9%) is also somewhat higher than the 6–7% taken from the larger chemotherapy alone reports [1, 9, 10, 11, 16–19].

Despite these encouraging partial and com-

plete response rates, the duration of response was still short (median 3.5 months) and compares with the 3–6 month median values of other studies [2, 3, 9, 11, 18, 20]. The median survival of non-responding patients lies within a narrow range of 2–4 months [2, 3, 10, 11, 12, 18] and includes our two-month value. Survival of responding patient groups exhibits a wider range, 6.5–11.3 months [2, 3, 10–12, 18], with the current value at 6.7 months. A statistically significant increase in survival of responding patients compared with non-responding patients has been noted previously [1, 9, 12, 16, 20], but this difference was not found in the present report. The discrepancy may be partly explained by the few long-term survivors in the non-responding patient group whose disease stabilised with chemoimmunotherapy but who failed to fulfil the criterion for a partial response.

The variations in response rate, survival and statistical differences that are described in the literature could reflect a variable mixture of prognostic features within the patient populations being treated. Responses are more frequent in patients with soft tissue, nodal or pulmonary deposits and survival is longer if the metastases are confined to such sites [1, 9, 12, 13, 17, 18]. No marked improvement in survival of patients with metastases elsewhere, e.g., liver or bone, was obvious in this or other studies [13]. Previous reports have included about 30–60% of the patient group with prognostically favourable sites of metastatic involvement [2, 14, 20] and the inclusion of patients with inoperable but not necessarily distantly metastatic melanoma [8, 11, 14, 18, 20]. This situation should be contrasted with the present study which included only patients with widely (Stage IV) disseminated disease with metastases in more than one organ system, in which only a minority (13%) had disease confined to non-visceral (skin, nodes) metastatic sites, and only 21% of patients with lung deposits had associated non-visceral metastases. Furthermore, patients were consecutively entered into the study and no exclusions were made, which would have improved the treatment results. Such exclusions can amount to a sizeable proportion (11–16% [9, 14]; 20–23% [2, 10, 18]) of previously reported series. There is also a relationship between ambulatory status and prognosis [9] and in our analysis patients with higher Karnofsky scores were shown to survive longer. This feature has been rarely described previously, but is of importance and should be considered in future investigations. A rigorous description of the patient population is therefore required to allow interpretation of different treatments and help explain the variations in the reported results.

The interval from primary diagnosis to the appearance of metastases and the interval from appearance of metastases to chemotherapy were not related to response or survival; these observations are similar to those of other authors [18, 19]; a longer disease-free interval might have been expected to be a good prognostic sign, indicative of a less aggressive tumour.

Haematological toxicity was very low; only 5% of all chemotherapy courses had to be modified and no serious side effects were encountered. Other chemotherapy schedules have been associated with moderate to severe toxicity in 30% or more patients [10, 12, 17, 19], which was life-threatening in 10–30% [10, 11, 19] and fatal in 3–13% of patients [2]. Unlike the COG study [9], no relationship was found between severity of haematological toxicity and response rate.

The low incidence of serious side effects could represent an effect of BCG, encouraging more rapid recovery from bone marrow depression. The complications of harvesting, storing and administering melanoma cells were avoided. The frequent BCG scarifications and intradermal injections used by other investigators have been associated with considerable morbidity [8, 13]; the tissue necrosis can be severe enough to require modification of the treatment protocol [13]. No such problems occurred with the monthly, multiple puncture gun method used in this study. The incidence of malignant melanoma is rising. Further attempts at controlling the disseminated disease, particularly in patients with viscerally dominant metastatic involvement, will become increasingly urgent.

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