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Phase II Study of Vindesine and Dacarbazine with or without Non-specific Stimulation of the Immune System in Patients with Metastatic Melanoma

Claire F. Verschraegen, Sewa S. Legha, Evan M. Hersh, Carl Plager, Nicholas Papadopoulos and Michael A. Burgess

A single dose of dacarbazine (DTIC), followed by a 5-day intravenous infusion of vindesine (VDS) was administered every 3 weeks to 103 patients with metastatic melanoma. One half of the patients were randomised to receive intravenous methanol extraction residue (MER) of bacillus Calmette-Guarin (BCG) in addition to chemotherapy, on days 7 and 14 of each course. 98 patients were evaluable. The response rates in treatment groups were 16 and 17%, respectively (confidence interval 9–24%). Neither the response rate nor the survival improved when MER was added to chemotherapy. Toxicity was moderate except for a significant granulocytopenia. The combination of DTIC and VDS is not more effective than DTIC alone and has added neurotoxicity.
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INTRODUCTION

DESACETYL VINBLASTINE amide sulphate or vindesine (VDS) is a synthetic vinca alkaloid derived from vinblastine sulphate, with a spectrum of experimental antitumour activity similar to vincristine [1]. Phase II studies of this agent for stage IV malignant melanoma have shown response rates varying from 0 to 35% [2–8]. The continuous 5-day infusion has been shown to be significantly superior to the single weekly administration schedule with less overall toxicities [9–11]. Dimethyl triazeno imidazole carboxamide (DTIC) or dacarbazine is the single most effective agent against melanoma with a response rate of 20 to 25% and a median survival of 4 months [12]. So far, combinations of DTIC with various antitumour agents have not yielded better therapeutic results than treatment with DTIC alone [13–14]. The most commonly used schedule of DTIC has been 250 mg/m^2/day × 5 every 3–4 weeks. However, studies with high-dose DTIC once a month have given similar response rates with less toxicity, particularly gastrointestinal side-effects [15–16]. In this phase II study we evaluated the efficacy and safety of a combination of high-dose DTIC followed by continuous 5-day infusion of VDS in 103 patients with metastatic malignant melanoma.

Methanol extraction residue (MER) of bacillus Calmette-Guerin (BCG) which has an acceptable toxicity consisting of fever, chills and rare pulmonary infiltrates when administered intravenously [17], has been shown to have significant antitumour activity against murine tumour models [18]. Some evidence of antitumour activity was also observed in phase I studies [19–21] and with intra-lesional treatments [22–24]. Its biological effects can be monitored by *in vitro* assays including antibody-dependent cytotoxicity (ADCC) [25]. Since the use of BCG in patients with melanoma has been associated with some beneficial effects, there was hope that intravenous administration of MER may have superior therapeutic effects. In order to further evaluate the role of non-specific stimulation of the immune system, the patients were randomised to receive either chemotherapy alone or additional therapy with MER intravenously on days 7 and 14 of each cycle of chemotherapy.

PATIENTS AND METHODS

Patients of both sexes, aged 15 or more, with histologically confirmed diagnosis of metastatic melanoma not amenable to surgery, were eligible to enter this study, provided they fulfilled the following conditions. Informed consent was required from each patient. The lesions evaluated for response to therapy had to be measurable (measures of two perpendicular diameters) or evaluable (measure of the biggest diameter). They had to be appropriately documented and surveyed by diagnostic procedures when necessary. Patients were expected to have a life expectancy of at least 12 weeks. They had to be put off all

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previous chemotherapy, immunotherapy or radiotherapy for 4 weeks prior to entry with no signs of residual toxicity from such treatments. Haematological parameters (absolute granulocyte count of over 2000/mm^3 and a platelet count over 100 000/mm^3), bilirubin (<2 mg/dl) and creatinine (<2 mg/dl) also had to be satisfactory.

Patients with other previous or current malignancies were excluded, except cured carcinoma of the cervix or squamous or basal cell carcinoma of the skin. Immunological evaluation consisted of an intermediate purified protein derivative (PPD) skin test prior to treatment and a measurement of mononuclear ADCC done on entry and prior to the second course of treatment.

MER treatment or no immunological therapy was chosen randomly for each patient prior to the start of chemotherapy. DTIC at a starting dose of 800 mg/m^2 was administered intravenously in 250 ml of 5% glucose on day 1 followed by a continuous infusion of VDS 1 mg/m^2 in 1000 ml of 5% glucose over 24 h, daily for 5 days. Patients were free to choose ambulatory outpatient treatment or hospitalisation. Treatment was repeated every 3 weeks. Treatment was modified according to the toxicity of the previous course. If the absolute granulocytopenia was below 500/mm^3 or the platelet count below 50 000/mm^3, DTIC and VDS doses were decreased by 20%. On the contrary, if the absolute granulocytopenia was over 1000/mm^3 and below or equal to 2000/mm^3 and the platelet count was between 75 000 and 100 000/mm^3, the dose was increased by 12.5% for DTIC and 20% for VDS. Counts over 2000 granulocytes and 100 000 platelets/mm^3, prompted an increase of the DTIC dose by 25% and of the VDS dose by 40%. Immunotherapy with MER was given on day 7 and day 14 of each cycle of chemotherapy to the appropriately randomised patients. A suspension of 0.5 mg/m^2 of MER in 150 ml of 5% glucose was infused over a 1-h period. Patients with a prior history of BCG vaccination, tuberculosis or patients with a positive intermediate PPD skin test received a tenth of the MER dose. The dose was reduced by 50% if there was a reduction in performance status from MER toxicity. If pulmonary infiltrates appeared secondary to MER treatment, the immunotherapy was discontinued. At least 2 courses of treatment were required for the patients to be considered evaluable.

Treatment was discontinued if progression was objectively demonstrated after two courses. Otherwise, patients were kept on the same drug regimen until progression occurred or unacceptable toxicity developed.

All measured or evaluated lesions were assessed for response to treatment after every other course of therapy. Complete remission (CR), partial remission (PR), no change (NC) and progression (PD) were evaluated according to the WHO classification [26]. Minor responses, i.e. shrinkage of the lesions of more than 25% but less than 50%, were classified as NC. Mixed responses, i.e. response at one site and progression at another were considered as progression.

RESULTS

103 patients were entered in this study. 98 were evaluable for response to therapy and 5 were excluded—2 lost to follow-up and early death in 3. Patient characteristics are described in Table 1.

All documented responses were reassessed at the end of the study by two independent observers. All pertinent diagnostic procedures were reviewed for response when indicated. The global response rate was 16% [95% confidence interval (CI) = 9–24%] (Table 2). For both arms, the median survival was 34 weeks (range 7–400+) (Fig. 1).

Table 1. Evaluable patients' characteristics

	VDS–DTIC (n = 51)	VDS–DTIC-MER (n = 47)
Sex		
Female	15	25
Male	36	22
Age		
Median	49	39
Range	16–75	17–73
Dominant site		
Visceral	36	34
Soft tissue	15	13
Prior chemotherapy (no/yes)	47/4	40/7
Prior radiotherapy (no/yes)	45/6	38/9
Prior BCG (no/yes)	47/4	41/6
Performance status at entry		
0	28	19
1	18	18
2	3	9
3	1	1
4	1	0

In the chemotherapy arm, two CR were observed, one at 6 weeks and the other at 26 weeks. The former one was seen in a 46-year-old man with soft tissue metastases and lasted 39 weeks. This patient relapsed with brain metastases. The latter response occurred in a 74-year-old man who presented with biopsy-proven lung metastases. This patient is still alive and free of disease 9 years later. 6 patients had a PR which was observed 3 to 17 weeks after onset of therapy. They lasted 16 to 39 weeks (median 34 weeks). All patients but 1 had visceral metastases. Only 1 patient had been previously treated with radiotherapy and chemotherapy. 7 patients had a NC status lasting up to 47 weeks (median 18 weeks). 36 patients had obvious PD despite treatment.

In the MER-treated group two CR were observed at 15 and 31 weeks from the beginning of therapy. They lasted 92 and 68 weeks, respectively. The first patient was a 24-year-old man who presented with visceral metastases. He died 3 years later of brain metastases. The second patient was a 38-year-old woman with skin metastases only. She relapsed with recurrence of skin disease while still on chemotherapy. 6 patients had a PR which occurred 3–15 weeks after the start of therapy. These responses lasted at least 21 weeks (median 25 weeks) and 1 patient is still alive and free of disease 8 years later with the help of surgery. These patients had visceral metastases and two of them had been

Table 2. Response to therapy

	VDS–DTIC	VDS–DTIC-MER
Complete response	2	2
Partial response	6	6
No change	7	7
Progression	36	32
Total	51	47

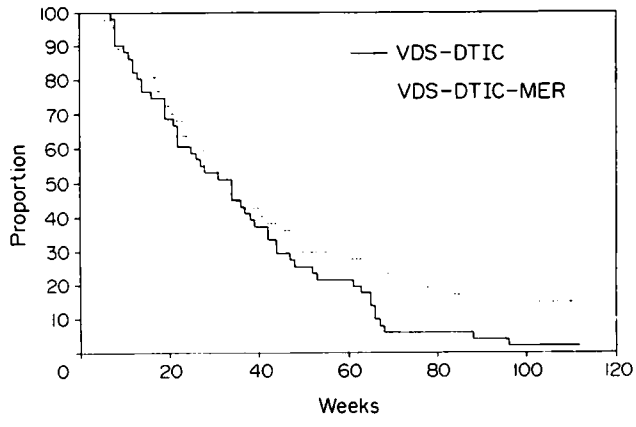

Fig. 1. Survival of patients treated with the two regimens. The difference noted in the right-hand curve is probably due to additional curative surgery.

treated with irradiation prior to entry. 7 patients had a NC status lasting up to 53 weeks or longer when the tumour was surgically removed (median 28 weeks). 32 patients failed to respond.

Evaluated patients received two to 17 courses of VDS–DTIC (median, three courses) for a total of 191 courses, and one to 18 courses of VDS–DTIC with MER (median, three courses) for a total of 228 courses. Nausea and vomiting of grade 2 or over (WHO scale) [26] were observed during 50 and 52 courses without and with MER, respectively. Neutropenic fever was seen in 22 patients, requiring hospitalisation in most of the cases. Nevertheless, no toxicity-related deaths were recorded. Drug fever was recorded 37 times for VDS and twice for DTIC, but was never long lasting. Neurological toxicity of grade 2 or over occurred in 18 patients. 6 cases of grade 2 diarrhoea were seen in each treatment arm. Other grade 2 toxicities included mucositis and alopecia. Rash and constipation were occasional complaints. No significant difference was found between the two treatment groups regarding leucopenia. Haematological toxicity was described for 160 courses of VDS–DTIC and 176 of VDS–DTIC-MER. The median nadir of white blood cells was 2500/mm^3 (range: 400–9200/mm^3) with a granulocytes nadir of 400/mm^3 (range: 0–6800/mm^3). 50% of patients had a granulocyte count below 1000/mm^3 after the first course, 63% after the second and 70% after the third course of treatment. Thrombopenia and anaemia were not significant. Fever and chills related to MER therapy were recorded in 46 patients. 4 patients developed pulmonary infiltrates which were attributable to MER toxicity. They appeared after the third to fifth course of therapy. As soon as this toxicity was noted, administration of MER was stopped. Only 1 patient refused treatment because of toxicity. He developed granulomatous lesions in the liver from MER infusions after the 13th course. MER-related immunological parameters have been reported elsewhere [27–28].

DISCUSSION

Analyses were performed on 98 patients entered in this phase II study, testing the efficacy and toxicity of a combination of DTIC and VDS and the randomised use of MER, a non-specific immunostimulant. Most of the patients were previously untreated and had a good performance status. A response rate of 16% was observed after DTIC–VDS treatment (95% CI = 9–24%). These results are similar to the ones observed in another study using a combination of DTIC and VDS with a different schedule [29]. The addition of MER did not improve the response rate or the survival but resulted in significant toxicity consisting of fever, chills, aching and sometimes visceral granulomatous disease seen mostly in the lungs and once in the liver, prompting termination of therapy. The toxicity related to DTIC and VDS was moderate, but affected the quality of life of the patients, especially the neurotoxicity of VDS. When comparing results obtained with DTIC alone in the treatment of disseminated melanoma, VDS did not add any benefit [30]. This lack of additive effect in the treatment of melanoma has also been seen with two-drug combinations of nitrosoureas and DTIC, despite their independent activity [31]. Consequently, we cannot recommend this combination regimen in the therapeutic choices against metastatic melanoma. On the other hand, several three-drug regimens, including the various active single agents such as vinca alkaloids, DTIC and nitrosoureas have produced higher response rates ranging from 30 to 40% [13]. These results, however, require confirmation in prospective trials using the appropriate control.

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Activity and Unexpected Lung Toxicity of the Sequential Administration of Two Alkylating Agents—Dacarbazine and Fotemustine—in Patients with Melanoma

Béatrice Gerard, Steinar Aamdal, Siow-Ming Lee, Serge Leyvraz, Catherine Lucas, Maurizio D'Incalci and Jean-Pierre Bizzari

We report the results and discuss the toxicity of clinical trials based on a single concept: the decrease in O⁶alkyl DNA alkyltransferase (O⁶AT) resistance mechanism when a chloroethylating agent is used sequentially after a methylating agent. This decrease in O⁶AT being dose dependent, several increasing doses of dacarbazine (DTIC) have been tested (400 mg/m² to 1000 mg/m² every 4 weeks, 3–4 h before fotemustine (100 mg/m² intravenously every 4 weeks). These results (mean overall response rate 27%) compared with reference regimes, demonstrate that DTIC is able to increase the alkylating power of fotemustine: same range of response rate with only half of the two drug doses compared to an alternated combination, high activity rate especially in lung metastases (10/42 complete responses + 13/42 partial responses), different pattern for haematotoxicity, and occurrence of a new side-effect: acute lung toxicity as adult respiratory distress syndrome (ARDS). This lung toxicity was totally unexpected since several hundreds of patients had been so far treated with fotemustine as single agent or in other combinations with DTIC without any case of acute or delayed lung toxicity. Prophylactic administration of corticoids was not effective and monitoring of the respiratory function was of no predictive value. Due to the additional depleting effects of DTIC on at least two main defence mechanisms—the O⁶AT system and cytosolic and/or nuclear glutathione—we suppose that the sequence is able to increase the alkylating power of fotemustine to an excessive extent and/or that the detoxication capacity of the cell against DTIC and/or fotemustine metabolites is overwhelmed. Other depletors of the O⁶AT activity which do not generate metabolites that compete for the same detoxication pathway as the chloroethylnitrosurea (CENU) metabolites should be tested.
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INTRODUCTION

WE HAVE RECENTLY reported the results of the first phase II clinical trial based on the application of the abundant preclinical knowledge about resistance to nitrosoureas in relation to DNA repair [1]. In a further series of clinical trials, the same sequence of two alkylating agents has been used at different dosages in a total of 107 patients with disseminated melanoma.

The sequence is based on *in vivo* and *in vitro* demonstrations of the role of a DNA repair system termed O⁶ alkyl DNA alkyltransferase (O⁶AT) in the sensitivity of tumour cells to