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Phase II study of IV vinflunine in patients with chemotherapy naive metastatic malignant melanoma

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ABSTRACT

This phase II study evaluated vinflunine in chemotherapy naive patients with metastatic melanoma. Vinflunine was administered at 350 mg/m^2 every 3 weeks, but after 9 patients this was reduced to 320 mg/m^2 based on interim analyses of all phase II trials. A partial response was observed in 1 of the first 9 patients (11.1%) treated at 350 mg/m^2, which gives a 3.0% [95% confidence interval (CI): 0.08–15.8] response rate in 33 patients. No change was the best response in 13 patients (39.4%) with progressive disease in 16 (48.5%) and 3 were not evaluable for response. The time to response was 1.4 months and duration was 6 months. At 350 mg/m^2 grade 4 neutropaenia occurred in 3 patients (33.3%) and grade 3 in 2 patients (22.2%) while at 320 mg/m^2 grade 4 neutropaenia occurred in 6 patients (25%) and grade 3 in 3 patients (12.5%) with 2 episodes of grade 3 febrile neutropaenia. Two patients (8.3%) had grade 3 anaemia. These results do not show activity at this dose and schedule for vinflunine in patients with chemotherapy naive metastatic melanoma.

1. Introduction

Almost 30% of patients with melanoma develop metastatic disease and survival is short when metastases are detected in multiple visceral sites.[1] Systemic chemotherapy is palliative. There is no randomised trial which demonstrates that the most frequently used cytotoxic drug, dacarbazine, as a single agent is better than supportive care. Systematic reviews have demonstrated that dacarbazine has reported response rate of between 5.3% and 28.6%.[2] In a meta-analysis the addition of alpha interferon to dacarbazine, but no other combination therapy, increased disease free survival but not overall survival.[3] Therefore, patients with metastatic disease should be considered for enrolment in investigational studies.

The vinca alkaloids, vindesine, vincristine, and vinblastine, have antitumour activity against metastatic melanoma but less than 20%.[4] More encouraging results have been reported when used in combinations.[5]

Vinflunine ditartrate is a novel microtubule inhibitor of the vinca alkaloid class obtained by a semi-synthetic process

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using superacidic chemistry. Vinflunine (VFL) inhibits tubulin assembly, blocks cells at G2/M phase and induces cell death *via* apoptosis. Tumour cells *in vitro* readily accumulate vinflunine and its transport appears to be P-glycoprotein mediated.[6] Vinflunine disrupts the functions of endothelial cells of already formed vasculature and is anti-angiogenic.[7] Vinflunine has a tri-exponential model of elimination with a rapid decrease in blood levels during the first hour and a long terminal half-life close to 40 h. Metabolism is a major method of elimination with 4-O-deacetyl-vinflunine being the main metabolite.[8] Based on clinical and pharmacokinetic data from the three dose regimens evaluated in phase I trials, 350 mg/m^2 VFL every 3 weeks was chosen for further development.

In phase II trials vinflunine has published activity in non-small cell lung cancer, bladder cancer and renal cancer.[9–11] This study evaluates its efficacy in metastatic melanoma.

2. Patients and methods

This study was a multicentre, open-label, non-randomised, phase II study designed to evaluate vinflunine given intravenously to chemotherapy naive patients with metastatic malignant melanoma of the skin. The primary endpoint was response rate with the secondary endpoints being response duration, progression free survival and overall survival. The safety of vinflunine was also recorded.

2.1. Patient selection

Patients required histologically proven melanoma which was metastatic, progressive and previously untreated, except that adjuvant alpha interferon and prior biological therapy were allowed. Patients required at least one bidimensionally measurable lesion of $\geqslant$15 mm in lung, $\geqslant$20 mm in liver or $\geqslant$10 mm $\times$ 10 mm on skin, subcutaneous nodules or lymph nodes. Eligible patients were $\geqslant$18 years, with a Karnofsky performance status (KPS) $\geqslant$80, and had a life expectancy of at least 12 weeks. Evidence of adequate haematological function (absolute neutrophil count $\geqslant 2.0 \times 10^9$/L, platelets $\geqslant 100 \times 10^9$/L), hepatic function (bilirubin $\leqslant 1.5 \times$ upper normal limit (UNL), transaminases $\leqslant 2.5 \times$ UNL, unless due to liver involvement), renal function and a normal electrocardiogram (ECG) was required. Patients were excluded if they had cerebral, meningeal or intraocular melanoma or only unmeasurable disease such as effusions or cysts. Patients with serious concomitant illnesses or cancers, those pregnant or lactating, or who required other anticancer medication or long term steroids or otherwise could not comply with the protocol were also excluded. All patients were required to give written informed consent before any study procedure and the study was approved by the institutional ethics committees at each centre.

2.2. Treatment schedule

Vinflunine was initially administered at the dose of 350 mg/m^2 every 3 weeks, based on the recommended dose schedule established in the previous vinflunine phase I studies. However, after 9 patients had been treated on this trial, an interim toxicity analysis across the phase II trials resulted in the dose of vinflunine being reduced to 320 mg/m^2 on day 1 every 21 days.

A cycle was defined as the 3-week period between 2 administrations of intravenous vinflunine (Day 1 of cycle). At least 2 cycles of treatment were to be administered unless there was unacceptable toxicity. The patients were to be treated until documented disease progression or stable disease was observed in 2 successive cycles or until patient refusal to participate further. The treatment was modified on the basis of haematological and/or non-haematological toxicities.

Efficacy was assessed on an intention to treat basis, and evaluations occurred after every 2 cycles of treatment according to criteria for the evaluation of response defined by the World Health Organisation (WHO) criteria as modified by the South West Oncology Group (SWOG). The duration of response, progression free survival and survival were assessed by the Kaplan Meier method. Decision rules were based on the one-sample multiple testing procedures designed by Fleming.[12]

Tolerance was assessed throughout the treatment period and before each administration according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 2.0. All patients having started at least one cycle of treatment were considered to be evaluable for safety.

3. Results

Thirty-three patients with metastatic malignant melanoma of the skin were recruited from 6 active centres over 16 months (Table 1). Five out of 33 patients registered and treated were non-evaluable for tumour response, including 2 patients at 350 mg/m^2 and 3 patients at 320 mg/m^2. The reasons for non-evaluability were that 2 patients received only cycle 1, 1 patient experienced unacceptable toxicity and the other patient refused to continue, one patient was not evaluated after cycle 2 and the other 2 were ineligible for the trial, one because of psychosis and the other because there was no bidimensionally measurable disease.

Eight patients had received prior immunotherapy, 3 in the adjuvant setting, 3 for metastatic disease and 1 for both. The median time between diagnosis and study entry was 3.1 years (range 0.5–20.3 years). The extent of disease is evidenced by 14 patients having 3 or more organs involved and 10 patients having 2 organs involved (Table 1).

The overall response of patients was defined as the best confirmed response recorded from the date of registration. Patients progressing before the first assessment were considered as early progressive.

The first step of Fleming's procedure was to be performed according to the investigator assessment on the first 20 evaluable patients but initially the trial was stopped at 9 patients for safety reasons and the dose decreased to 320 mg/m^2 where a further 20 patients were planned to be recruited, but 24 were entered due to the delay between inclusion time and evaluability.

A partial response (PR) was observed in 1 out of the first 9 patients (11.1%) treated at 350 mg/m^2, which gives a 3.0% [95% CI: 0.08–15.8] response rate in the 33 patients of the overall population. No change was the best response in 13 patients

Table 1 – Demographic data and melanoma characteristics

Demographic data	Initial dose level of vinflunine	
	350 mg/m^2	320 mg/m^2
Number of patients	9	24
Age (years)		
Median	59.4	54.5
Range	[28.4–67.8]	[22.6–73.2]
Sex	*N* (%)	*N* (%)
Males	6 (66.7%)	18 (75.0%)
Females	3 (33.3%)	6 (25.0%)
Body surface area (m^2)		
Median	2.0	1.9
Range	[1.7–2.4]	[1.5–2.4]
Karnofsky performance status (%)	*N* (%)	*N* (%)
100	5 (55.6%)	6 (25.0%)
90	2 (22.2%)	8 (33.3%)
80	2 (22.2%)	10 (41.7%)
Histological type of melanoma	*N* (%)	*N* (%)
Superficial spreading	4 (44.4)	5 (20.8)
Lentigo malignant	1 (11.1)	1 (4.2)
Acral lentiginous	–	1 (4.2)
Nodular	3 (33.3)	7 (29.2)
Unclassified	–	8 (33.3)
Unknown	1 (11.1)	2 (8.3)
Number of organs involved	*N* (%)	*N* (%)
1 organ	3 (33.3)	6 (25.0)
2 organs	2 (22.2)	8 (33.3)
$\geqslant$3 organs	4 (44.4)	10 (41.7)
Types of organs involved	*N* (%)	*N* (%)
Lung only	5 (55.6)	9 (37.5)
Liver only	–	3 (12.5)
Bone only	–	1 (4.2)
Lung + liver	2 (22.2)	3 (12.5)
Lung + bone	–	1 (4.2)
Lung + liver + bone	–	1 (4.2)
Lymph nodes	6 (66.7)	14 (58.3)
Skin	1 (11.1)	5 (20.8)
Soft tissues	1 (11.1)	6 (25.0)
Breast	1 (11.1)	–
Other organs	3 (33.3)	10 (41.7)

(39.4%) with progressive disease in 16 (48.5%) and 3 were not evaluable for response. The responder had lymph node and pleural disease and received 12 cycles of treatment.

The time to response was 1.4 months and the duration was 6 months. The median time of progression-free survival (overall population) was 1.4 months, 95% CI [1.4–2.8]. The median survival time for the overall population was 7.0 months [95% CI 4.8–10.8]. To assess clinical benefit, the Karnofsky performance status was recorded at baseline and prior to each cycle of treatment. During treatment, KPS was maintained or improved in 4 out of 9 patients (44.4%) treated at 350 mg/m^2, and in 15 out of 24 patients (62.5%) treated at 320 mg.

The most frequent drug-related adverse events were haematological. In the 9 patients treated at 350 mg/m^2, grade 4 neutropaenia occurred in 3 patients and grade 3 in 2 patients but there was no febrile neutropaenia. At 320 mg/m^2 grade 4 neutropaenia occurred in 6 patients and grade 3 in 3 patients with 2 episodes of grade 3 febrile neutropaenia. Two patients had grade 3 anaemia at 320 mg/m^2.

The most frequent non-haematological toxicity was fatigue but it did not reach grade 3 or 4 in any patient. At 350 mg/m^2 2 patients experienced stomatitis, one grade 4 and the other grade 3. At 320 mg/m^2 2 patients had grade 3 constipation.

There were 4 deaths within 30 days of receiving vinflunine. One was as a result of drug-related neutropenic sepsis, one a concomitant cerebrovascular accident and the other 2 were due to progressive disease.

4. Discussion

These results do not show that vinflunine given once every 3 weeks has any clinically relevant activity in the management of patients with chemotherapy naive metastatic melanoma.

This result is consistent with other current first-line or second-line chemotherapy options in metastatic melanoma, including dacarbazine, temozolomide, cisplatin, the taxanes, fotemustine and other vinca alkaloids which result in disappointing response rates and have not had a meaningful impact on survival.[13–16]

Combinations of cytotoxic drugs or chemotherapy with biological agents have not improved this outcome and novel approaches for first line therapy are warranted in metastatic melanoma.[17,18]

Conflict of interest statement

None of the clinical trial investigators and authors of this study have any conflict of interest to declare. Two of the authors who are from the sponsoring pharmaceutical company have a potential conflict of interest. The investigators had input into the initial design of the study and the manuscript was written by the investigators.

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