Phase II trial of vinorelbine tartrate in patients with treatment-naïve metastatic melanoma

Antonio Jimeno[a], Ricardo Hitt[a], Miguel Quintela-Fandino[a] and Hernán Cortés-Funes[a]

Metastatic melanoma carries a dismal prognosis and there is a need to develop new treatment strategies. Vinca alkaloids have shown consistent activity in melanoma patients, as monotherapy and as part of combination regimens. The current study evaluates the clinical activity and tolerability of vinorelbine as first-line monotherapy in patients with metastatic melanoma. Patients were eligible if they presented metastatic melanoma not amenable to curative resection, had received no prior systemic therapy for advanced disease and had an adequate performance status (ECOG 0–1). Patients received vinorelbine at a dose of 30 mg/m^2 on days 1 and 8 of a 21-day cycle, on an outpatient basis. Thirteen patients were accrued into the study and received 64 cycles. All patients were assessable for response, toxicity and survival. No objective responses were documented, for an overall response rate of 0% [95% confidence interval (CI) 0–19%] and the trial was terminated in accordance to the predetermined early discontinuation rule. The median progression-free survival was 3.3 months (95% CI 2.3–4.3 months) and the estimated median overall survival was 8.1 months (95% CI 6.0–10.2 months). No life-threatening toxicities occurred. Neutropenia was the main hematologic toxicity, but none of the three episodes of grade 3–4 neutropenia were complicated by infection. The most common non-hematologic toxicities were asthenia, nausea, neuropathy and myalgia. We conclude that vinorelbine as a single agent on days 1 and 8 of a 21-day cycle has a favorable toxicity profile, but appears to have no relevant clinical activity in patients with metastatic melanoma. ***Anti-Cancer Drugs*** **16:53–57 © 2005 Lippincott Williams & Wilkins.**

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[a]Medical Oncology Department, University Hospital 12 de Octubre, Madrid, Spain.

The first two authors contributed equally to this work.

Correspondence to A. Jimeno, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, 1650 Orleans Street, Room 162 A, Baltimore, MD 21231, USA.
Tel: +1 410 502-5835; fax: +1 410 614-9006;
e-mail: ajimeno1@jhmi.edu

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Introduction

Melanoma is considered the most aggressive cutaneous malignancy, with 50 000 new cases and 8000 attributable deaths per year in the US [1]. After systemic recurrence, median survival with standard treatment is 6–9 months [2–4]. This dismal prognosis highlights the need to develop new treatment strategies. The most active agent in the treatment of melanoma is dacarbazine, with a single-agent response rate of 20% [5]. A number of combination chemotherapy regimens have been developed, such as the CVD regimen (cisplatin/vinblastine/DTIC), the CVDT regimen (cisplatin/vinblastine/DTIC/tamoxifen), or the Dartmouth regimen or CDBT (cisplatin/dacarbazine/carmustine/tamoxifen). Although these regimens showed a superior response rate in a phase II setting, phase III studies have not confirmed that superior efficacy and have evidenced a lack of survival benefit along with a more pronounced toxicity of combination chemotherapy compared with monotherapy [6–8].

Several vinca alkaloids (such as vincristine, vinblastine or vindesine) have been evaluated as monotherapy or as part of combination therapy regimens in metastatic melanoma patients, with monotherapy response rates between 10 and 15% [8–12]. Vinorelbine is a novel vinca alkaloid that has shown preclinical activity as monotherapy [13] and in combination with paclitaxel [14] in human melanoma cancer cell lines. These promising preclinical results prompted the evaluation of vinorelbine in patients with advanced melanoma. A phase II trial of paclitaxel and vinorelbine in two alternative sequences as first-line therapy in 15 patients documented a 20% response rate [15]. Feun *et al.* evaluated weekly vinorelbine plus tamoxifen as second-line therapy in 31 patients with metastatic melanoma, evidencing a 20% response rate [16]. The present study was designed to evaluate the clinical activity and tolerability of vinorelbine as a single agent in patients with treatment-naïve, metastatic melanoma.

Methods

Patient eligibility

For inclusion in the study, patients were required to be 18 years of age or older with histologically documented melanoma that was metastatic or deemed unresectable

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and have measurable disease. All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, life expectancy of 12 weeks or longer, and adequate bone marrow, hepatic and renal function [absolute neutrophil count (ANC) $\geq 2.0 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, hemoglobin level ≥ 10.0 g/dl, AST or ALT levels of < 1.5 times the upper limit of normal, alkaline phosphatase level < 5 times the upper limit of normal, normal bilirubin level, creatinine clearance > 50 ml/min and a normal serum calcium level]. Patients who had undergone previous chemotherapy or immunotherapy for recurrent disease, systemic adjuvant therapy in the previous 6 months or radiation to major bone marrow areas were excluded from the study. Patients with central nervous system (CNS) metastases were excluded from the study. Patients with grade 2 or higher peripheral neuropathy or other serious medical or psychiatric condition were also excluded. Patients with prior malignancies were eligible if they had been treated curatively and had been disease-free for longer than 5 years. The scientific review board and the ethics committee of our institution granted protocol approval. Patients were required to provide written informed consent prior to enrollment into the study.

Within 1 week of study entry, all patients had a complete clinical history and physical examination, complete blood counts, serum biochemistry tests (liver and renal function tests and electrolytes), urinalysis and electrocardiogram. A chest radiograph and a computed tomography (CT) scan documenting measurable disease were performed within 3 weeks before study entry. A brain CT scan was routinely performed to assess CNS disease.

Treatment plan

Vinorelbine was administered at a dose of 30 mg/ mg/m^2 as a 10-min i.v. infusion on days 1 and 8 of a 21-day cycle. Treatment was administered on an outpatient basis. Re-treatment on day 8 required an ANC count $\geq 1.5 \times 10^9$/l, a platelet count $\geq 100 \times 10^9$/l, a creatinine clearance rate > 50 ml/min and resolution of all non-hematological toxicities (except alopecia and fatigue) to baseline or less than grade 1. In case of a delay longer than 14 days, the patient was removed from the study. Predetermined dose adjustments (dose reduction or delay in administration) were permitted after occurrence of specific toxic effects. The dose of vinorelbine was reduced by 25% following any episode of febrile neutropenia, grade 4 neutropenia lasting more than 5 days, grade 4 thrombocytopenia or in the event of grade 3 non-hematologic toxicity (excepting except inadequately managed nausea and vomiting, and alopecia). Doses were not re-escalated except in the case of neutropenia, provided that granulocyte colony stimulating factor was used. Toxic events were recorded on a continuous basis and followed until they were resolved to baseline or less than grade 1. Follow-up history and physical examination, complete blood cell counts, and serum biochemistry tests were performed at weekly intervals during treatment. Chest radiographs and re-staging CT scans were performed every 3 cycles (9 weeks) or when disease progression was clinically suspected.

Study end points

The primary end point of the study was tumor response. The criteria used to define response [complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD)] were based on standard RECIST definitions [17]. Patients were considered evaluable for response once therapy was initiated. Secondary efficacy parameters were progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from diagnosis of recurrent or advanced disease to the last contact or progression, either clinical or radiological. OS was defined as the time from diagnosis of recurrent or advanced disease to the last contact or death. Adverse events were classified and graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. Patients were considered evaluable for toxicity once therapy was initiated.

Statistical analysis

The trial followed a two-stage Simon Minimax design [18], allowing early closure in case of treatment failure. The null hypothesis of a true response rate of 5% or lower was evaluated against the alternative hypothesis of a true response rate of 20% or higher (α error 0.05, β error 0.20). At least one response was required in the first 13 patients to initiate the second stage; globally, four responses out of 27 evaluable patients were required to consider the drug promising enough to warrant a comparative trial. The 95% confidence intervals (CIs) were calculated with the exact method. Survival was estimated by the Kaplan–Meier product limit method [19]. All tests were two-sided at the 0.05 level of significance. The SPSS (version 10.0) statistical package was used for all statistical analyses.

Results

Patients

Between December 2002 and August 2003, 13 patients with metastatic melanoma were accrued into the study. All patients were assessable for response, toxicity and survival. Demographic and clinical characteristics of the subjects are summarized in Table 1. Ten patients presented a relapse from a previously diagnosed and treated melanoma, and three patients presented with metastatic disease at diagnosis. All but one patient presented visceral disease. The interval between initial diagnosis and relapse ranged between 4.7 and 72 months (median 24.3 months). Three patients had previously received adjuvant interferon and none of the patients had received any therapy for advanced disease.

Table 1 Patient characteristics

Characteristic	Patients ($n=13$)	
	N	%
Sex		
male	0	77
female	3	23
Age (years)		
median	71	
range	56–76	
ECOG performance status		
0	7	54
1	6	46
Initial staging at diagnosis		
I	1	8
II	7	54
III	2	15
IV	3	23
Prior adjuvant therapy		
interferon	3	23
none	10	77
Metastatic organ involvement		
lymph node, skin, soft tissue	11	85
lung/pleura	8	62
adrenal gland	2	15
liver	2	15
bone	1	8
Extent of metastatic disease		
single metastatic site	3	23
multiple metastatic sites	10	77

Table 2 Summary of hematologic and non-hematologic toxicity ($n=13$)

	All grades		Grade 3–4	
	No. patients	%	No. patients	%
Hematologic				
neutropenia	6	46	3	23
anemia	4	31	0	0
thrombocytopenia	2	15	0	0
Non-hematologic				
asthenia	7	54	0	0
nausea	5	38	0	0
neuropathy	5	38	0	0
myalgia	4	31	0	0
anorexia	3	23	0	0
vomiting	3	23	0	0
mucositis	2	15	0	0
alopecia	2	15	0	0
diarrhea	1	8	0	0

Table 3 Response to treatment

	Patients ($n=13$)	
	N	%
Overall response rate	0	0
95% CI	0–19	
CR	0	0
PR	0	0
SD	6	46
PD	7	54

Treatment administered

A total of 64 cycles of the study regimen were delivered (median 5 cycles; range 3–8). Most chemotherapy cycles (98%) were delivered at the planned doses. The dose was reduced in one patient due to persistent grade 2 neutropenia. Three treatment administrations were delayed for 1 week (due to two episodes of grade 2 neutropenia and one episode of grade 2 mucositis).

Toxicity

Hematologic and non-hematologic toxicities are shown in Table 2. Neutropenia was evidenced in six patients (46%) and represented the only grade 3 ($n=2$) or grade 4 ($n=1$) toxicity documented in the present study. These three episodes were detected at scheduled nadir blood evaluations and none of them was associated with infectious complications. Median nadir ANC count was 6.7×10^9/l (range $0.36–13.9 \times 10^9$/l). Anemia was documented in four patients (31%) and was predominantly grade 1; grade 2 anemia was evidenced in one subject (8%). Grade 1 thrombocytopenia was documented in two patients (15%). Median nadir platelet count was 132×10^9/l (range $89–396 \times 10^9$/l). There were no grade 3 or 4 non-hematologic adverse events. Among them, the most frequent were asthenia (seven patients), nausea (five patients), neuropathy (five patients) and myalgia (four patients). The most severe was an episode of grade 2 mucositis that lasted 10 days and was responsible for a treatment delay.

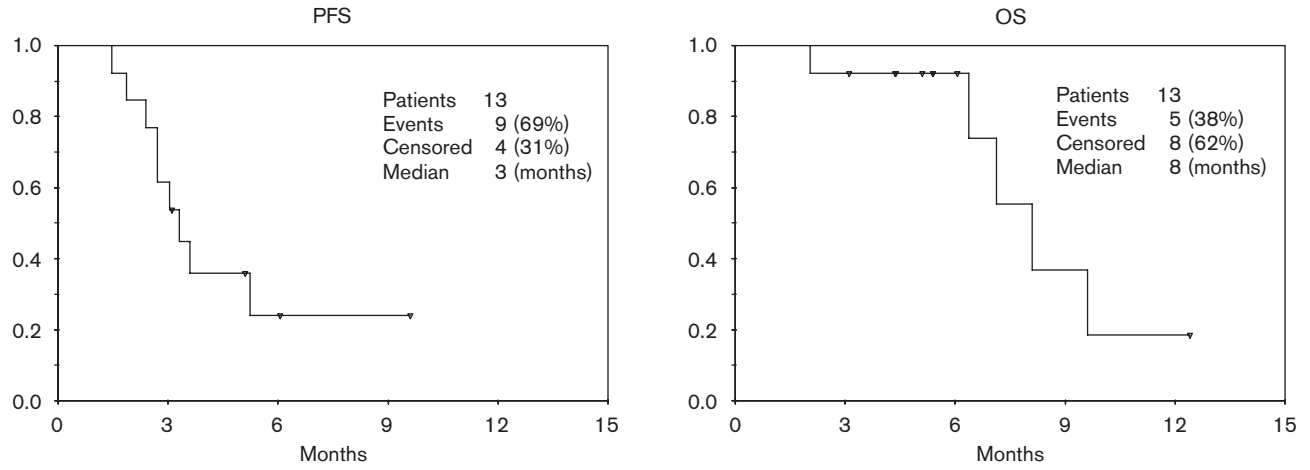
Response and survival

No responses were documented in the first 13 patients (response rate 0%; 95% CI 0–19%) and thus the trial was terminated (Table 3). There were six disease stabilizations (46%) and seven disease progressions (54%) as best response to therapy at the time of the first scheduled assessment (after 4 cycles). An additional two patients presented disease progression after 6 and 7 cycles, respectively. No CNS disease progressions occurred after vinorelbine treatment. Four patients were stable after 6, 6, 7 and 8 cycles, respectively; one declined further therapy and the other three were removed from the study at the discretion of the treating physician. The estimated median PFS was 3.3 months (95% CI 2.3–4.3 months) and the median OS was 8.1 months (95% CI 6.0–10.2 months) (Fig. 1).

Discussion

Despite the preclinical indications that vinorelbine possessed antimelanoma activity and the relative success of combination trials of vinorelbine plus either paclitaxel or tamoxifen, in the small study currently presented no clinical activity was demonstrated. The patient population showed a significant burden of disease and the majority presented with more than one site of metastases. Nonetheless, performance status was remarkably good and it can be stated that the treated cohort is representative of the general metastatic melanoma

Fig. 1



PFS and OS.

population. Toxicity was moderate and was consistent with the usual toxicity profile of this drug; no life-threatening toxicities occurred. Neutropenia was the main hematologic toxicity, but the median nadir ANC count was well above normal limits and none of the episodes of neutropenia were complicated by infection. The most common non-hematologic toxicities were asthenia, nausea, neuropathy and myalgia.

A phase II study evaluating the activity of vinorelbine as second-line therapy in 21 patients with disseminated melanoma has been recently communicated [20]. This regimen delivered vinorelbine on a weekly, continuous schedule and this may explain the apparently higher hematologic toxicity observed, particularly neutropenia (seven and six episodes of grades 3 and 4, respectively) and febrile neutropenia (one episode each of grades 3 and 5, respectively). Unfortunately, details regarding treatment characteristics such as duration, number of cycles or dose intensity achieved are not specified and, therefore, no further comparisons can be reasonably made. Notwithstanding, no clinical responses were documented and after 21 patients the trial was terminated. PFS and OS figures are equivalent when compared with those of the current study.

It is intriguing that the addition of tamoxifen to vinorelbine improved the clinical activity of the latter drug to such an extent [16]. From a biological perspective, the mechanism behind this synergism is not clearly understood, although preclinical data supports a potential role of tamoxifen in the inhibition of protein kinase C, as well as angiogenesis inhibition (partially mediated by transforming growth factor-β stimulation) [21]. These findings are even more compelling when considering a recent meta-analysis that addressed the role of tamoxifen in metastatic melanoma; the analysis encompassed 912 patients from six randomized trials and evidenced that tamoxifen does not improve the overall response rate, complete response rate or survival rate when administered along with combined chemotherapy regimens [22].

A potential criticism of the current study could be that the number of patients treated is small. However, the trial was intentionally designed in a conservative, two-stage fashion following a Minimax design in order to avoid exposing an unnecessary number of treatment-naïve patients to a relatively novel drug with an unknown level of efficacy. The evaluation of new drugs in untreated, incurable patients is gaining increasing acceptance; this approach is safe provided that the necessary level of caution is applied in the designing (and conduction) of the trials and minimizes potential biases such as acquired resistance or toxicity evaluation issues. Also, it permits the closest possible correlation with existing preclinical data. Altogether, both monotherapy trials have shown a lack of activity of this agent in this patient population and it seems unreasonable to encourage any further appraisals of this strategy in this patient population.

In summary, the administration of vinorelbine as a single agent on days 1 and 8 of a 21-day cycle has a favorable toxicity profile, but appears to have no relevant clinical activity in patients with metastatic melanoma.

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