EUROPEAN JOURNAL OF CANCER 45 (2009) 732–735

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Short Communication

Phase II study of weekly Kahalalide F in patients with advanced malignant melanoma

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ARTICLE INFO

Article history:
Received 23 October 2008
Received in revised form
1 December 2008
Accepted 4 December 2008
Available online 29 January 2009

Keywords:
Chemotherapy
Kahalalide F (KF)
Metastatic
Melanoma

ABSTRACT

This phase II clinical trial evaluated the antitumour response of Kahalalide F (KF) 650 μg/m^2 given as a 1-h weekly infusion in advanced malignant melanoma patients, both untreated and those who relapsed or progressed after one line of systemic therapy. Of 24 enrolled patients (median age, 55 years; range, 28–89), 14 patients had been previously treated with chemotherapy or biological therapy. No RECIST responses occurred; five chemotherapy-naïve patients with cutaneous melanoma had disease stabilisation for ⩾3 months; median progression-free survival was 1.7 months (95% CI, 1.2–1.9 months); and median overall survival was 10.8 months (95% CI, 5.0-upper limit not reached). The most common laboratory toxicities were non-cumulative increase of transaminases (ALT/AST) and gamma-glutamyltransferase (GGT). No patients experienced leukopenia and thrombocytopenia during the study. KF was a well-tolerated and safe chemotherapy regimen. Despite a favourable safety profile, this trial was closed after the first stage because of the lack of objective response in patients with malignant melanoma.

1. Introduction

Kahalalide F (KF) is a cyclic depsipeptide isolated from the herbivorous marine molusk *Elysia rufescens* and its algae diet *Bryopsis pennata*.[1,2] One unconfirmed partial response and one pathological complete response were found during phase I studies in two patients with malignant melanoma.[3,4] This multicentre, two-stage, single-arm, exploratory phase II trial assessed the antitumour activity, pharmacokinetics (PK) and safety profile of KF given as a weekly 1-h 650 μg/m^2 intravenous (i.v.) infusion to patients with advanced cutaneous malignant melanoma.

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doi:10.1016/j.ejca.2008.12.005

2. Patients and methods

The study protocol was approved by the institutional review board of each participating centre and written informed consent was obtained from each patient. Patients had unresectable, advanced and histologically-confirmed malignant melanoma with progressive disease (PD) and at least one measurable lesion. Both systemic therapy-naïve patients and patients who had relapsed or progressed after first-line of systemic therapy (up to one previous line) were included. Patients were ⩾18-years-old, had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score ⩽2 and a life expectancy of ⩾3 months, and had an adequate organ function.

KF (Pharma Mar, Colmenar Viejo, Spain) was infused at a dose of 650 μg/m^2 as a weekly 1-h i.v. infusion, with no resting weeks (one weekly infusion = one cycle), until disease progression, unacceptable toxicity or patient refusal. A maximum of two dose reductions (from 650 to 530 μg/m^2 and then to 400 μg/m^2) were permitted in case of toxic events: febrile neutropenia; grade 4 neutropenia for >5 days; platelets <25,000 × 10^9/l; ALT or AST > 20 × baseline value; grade 2 neurological, grade ⩾ 2 renal or grade 2 cardiac toxicity; or any other grade 3/4 toxicity excluding alopecia or hypersensitivity. If toxicity recurred, the patient was to be withdrawn from the study. Premedication included histamine antagonists 30 min before. Erythropoietin use was acceptable only among patients with transfusion-dependent anaemia. Prophylactic antiemetic treatment was allowed since KF is a moderately emetogenic compound.[5] Therapeutic use of haematopoietic growth colony stimulating factors was allowed according to ASCO guidelines.[6]

The primary efficacy endpoint objective was tumour response rate according to the Response Evaluation Criteria in Solid Tumours (RECIST).[7] Tumour assessments were done every 8 weeks while on therapy (minimum of eight cycles to be evaluable) and every 3 months in follow-up. Response has to be confirmed 4 weeks later. Secondary efficacy endpoints were time to response, duration of response, progression-free survival (PFS) and overall survival (OS). Time-to-event efficacy endpoints and their fixed time point rates were analysed according to the Kaplan–Meier method. PK (after first and second infusion) and toxicity profile of KF (graded according to the National Institute of Health Common Toxicity Criteria (NCI-CTC), version 3.0[8]) were also evaluated.

A Simon's two-stage MiniMax design was used to test the null hypothesis that the probability of objective response was $p \leqslant 0.05\%$ *versus* the alternative hypothesis that it was $p \geqslant 0.2\%$.[9] After testing the drug on 18 patients in a first stage, the trial was to be terminated in case of no responses. Otherwise, the trial was to go onto a second stage and another 14 patients were to be evaluated (a total of 32 evaluable patients). The schedule was not warranted for further evaluation if objective tumour responses ⩽3.

3. Results

3.1. Patient and disease characteristics

The median age was 55 years (range, 28–89) and ECOG PS score was 0 (70.8%) or 1 (29.2%). The most common primary tumour site was cutaneous melanoma (83.3%), mostly located in the trunk (60.0%). All patients had documented metastatic lesions [median = 2 (range, 1–8)], with the lung (50.0%), liver (50.0%) and lymph nodes (41.7%) as the most frequent. Patient and disease characteristics at baseline of the 24 enrolled patients are shown in Table 1.

Fourteen patients (58.3%) had received previous systemic therapy for advanced disease. Most patients were exposed to one (40.0%) or two (40.0%) agents of systemic therapy (range, 1–3), and all of them had previously received alkylating compounds.

3.2. Adherence to treatment schedule

A total of 231 cycles (median, seven per patient; range, 1–35) were administered, with a median relative dose intensity of 98.2% (range, 43.5–102.4%). Two patients received concomitantly erythropoiesis-stimulating agents (ESAs; epoetin alfa during one cycle and darbepoetin alfa during five cycles). A total of 13 cycles were delayed in seven patients (median duration of 7 days). Four delays were due to transient KF-related transaminase increases, and nine were unrelated to treatment. No dose reductions were required. The most common cause of KF discontinuation was disease progression (87.5%).

3.3. Efficacy

No objective tumour responses were achieved with this KF treatment in 21 evaluable patients. Stable disease lasting for ⩾3 months according to RECIST was observed in five patients with chemotherapy-naïve, cutaneous melanoma (23.8%) (Table 1). The median PFS for all 21 evaluable patients was 1.7 months (95% CI, 1.2–1.9 months). The median OS was 10.8 months (95% CI, 5.0-upper limit not reached). PFS rates at 3 and 6 months were 23.8% (95% CI, 5.6–42.0%) and 4.8% (95% CI, 0.0–13.9%), respectively. The percentage of patients alive at 6 and 12 months was 63.4% (95% CI, 38.8–88.0%) and 31.7% (95% CI, 0.0–77.3%), respectively.

3.4. Pharmacokinetics

PK was assessed in 23 and 22 patients during the first and second cycle respectively. The PK profile of KF in this study was characterised by a narrow distribution (median distribution at steady-state [V_{ss}] at first cycle 7.0 l, range: 4.7–10.3 l) and a short body residence (median terminal half-time [$t_{\frac{1}{2}}$] at first cycle 0.46 h, range, 0.27–1.07 h). Intrapatient and interpatient variabilities were low for total body clearance (CL) and V_{ss}, and moderate for $t_{\frac{1}{2}}$. Correlations between PK variables (V_{ss}, CL or $t_{\frac{1}{2}}$) and demographic variables (age, weight or body surface area [BSA]) showed that body size was a predictor of KF clearance and V_{ss}, with CL increasing with BSA ($p = 0.0083$) and height ($p = 0.0349$), and V_{ss} increasing with height ($p = 0.0039$). Furthermore, an inverse relationship was detected between total plasma proteins at baseline and V_{ss} ($p = 0.0271$).

3.5. Toxicity

All 24 treated patients were assessed for toxicity. All KF-related adverse events (AEs) were grade 1/2 and involved a

Table 1 – Patient and disease characteristics, prior anticancer therapy and response to treatment (n = 24 patients).

Parameters		No. of patients (*n*)[a]	%
Age (years)	Median (range)	55 (28–89)	
ECOG PS	0	17	70.8
	1	7	29.2
Primary tumour site	Cutaneous	20	83.3
	Trunk	12	60.0
	Head and neck	4	20.0
	Limb	4	20.0
	Ocular	2	8.3
	Unknown primary site	2	8.3
Tumour extension	Metastatic	23	95.8
	Locally advanced/advanced	1	4.2
Number of sites involved	Median (range)	2 (1–8)	
Sites of disease observed in ⩾8% of patients	Lung	18	75.0
	Liver	12	50.0
	Lymph node	10	41.7
	Other[b]	16	66.7
Previous treatment	Chemotherapy	10	41.4
	Biological therapy	4	28.6
	Surgery	23	95.8
	Radiotherapy	3	12.5
No. of lines of chemotherapy (*n* = 10; 41.4%)	Median (range)	1 (1–2[c])	
No. of agents of chemotherapy	Median (range)	2 (1–3)	

Gender	Age (years)	ECOG PS	Melanoma cutaneous tumour site	Cycles received	PFS (months)	OS (months)	Off-study reason
Characteristics of patients with stable disease lasting for ⩾3 months[d]							
Male	58	0	Cutaneous (limb)	15	3.7	+3.9	PD
Male	79	0	Cutaneous (head and neck)	35	8.9	+10.1	PD
Female	58	0	Cutaneous (trunk + abdomen + pelvis)	16	4.0	+6.0	PD
Male	73	0	Cutaneous (trunk + abdomen + pelvis)	18	3.8	+7.4	PD
Female	71	1	Cutaneous (trunk + abdomen + pelvis)	15	3.6	+3.6	PD

Three of 24 patients were not evaluable due to treatment refusal, drug-related hypersensitivity reaction or persisting paraesthesia. These three patients discontinued before undergoing any disease assessments.
ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PD, progressive disease; and PFS, progression-free survival.
a Data shown are *n* of patients except for median and range.
b Skin (*n* = 5), soft tissue (*n* = 5), abdominal wall (*n* = 2), bone (*n* = 2) and right paratracheal mass (*n* = 2).
c Protocol deviation. Two patients received two lines but remained in the study.
d All patients were chemotherapy-naïve.

low number of patients. Pruritus (41.7% of patients/13.8% of cycles), paresthesia (20.8% of patients and 4.8% of cycles), and fatigue (16.7% of patients and 10.4% of cycles) were the most common KF-related AEs.

The most frequent laboratory abnormality was asymptomatic and transient increases in the blood transaminases levels (ALT: 83.3% and AST: 70.8% of patients) and GGT (66.7% of patients). Grade 3/4 ALT and AST levels occurred in 14 patients (58.3%) each and grade 3/4 GGT levels were observed in two patients (8.3%). Of note, all grade 3/4 transaminase increases were noticed after the first KF infusion and returned to grade ⩽2 before cycle 2. The most common haematological abnormalities were anaemia (62.5% of patients) and lymphopenia (37.5% of patients). Lymphopenia reached grade 3 and grade 4 in one patient (2.7%) each during one cycle (0.4%). No patients experienced leukopenia and thrombocytopenia.

4. Discussion

The best response observed was SD lasting for more than 3 months in five of 21 evaluable patients (23.8%). The lack of complete or partial responses prompted the early study closure after the first stage. The level of response found here was unlikely affected by ESAs effects on tumour growth and proliferation,[10,11] as only two patients (non-responders) received these agents. Studies on the genetic expression profile of the melanocyte–melanoma transformation indicate that melanoma is a heterogeneous group of diseases with distinct genetic pathways.[12] Gene expression, associated with metastatic dissemination of cutaneous melanomas, may play an important role in the molecular mechanisms underlying poor prognosis in melanoma patients.[13] Considering that one pathological complete response was found in one patient with amelanotic melanoma of the nasal cavity during the

phase I programme[3] and taking into account that all patients treated in this study had cutaneous melanoma from sun-exposed skin, further studies with KF in the patient subset of mucosal melanoma could be considered.

This weekly KF regimen had a favourable safety profile in this patient population. Toxicity consisted of mild/moderate AEs that agreed with toxicities previously observed with KF in other malignancies.[14,15] In contrast to many other chemotherapeutic agents, KF did not induce alopecia, mucositis, diarrhoea, or cardiac, renal and severe bone marrow toxicity. The most common toxicities were transient, reversible and asymptomatic increases of transaminases and GGT, which were also in accordance with the most common DLTs in the phase I programme.[14,15]

The PK profile of this 1-h weekly KF schedule in melanoma patients agrees with that reported for other schedules, with only slight differences compared to phase I results at the same dose: CL and V_{ss} were higher and the area under the plasma concentration–time curve (AUC) and maximum plasma concentration (C_{max}) were lower in patients with melanoma.[14,15] Nevertheless, a narrow volume of distribution and a short terminal half-life were also found here.

In conclusion, the lack of significant antitumour activity despite a favourable safety profile does not warrant further clinical trials with KF as a single agent in cutaneous malignant melanoma.

Conflict of interest statement

Adnan Tanovic is currently an employee of Pharma Mar. There are no other conflicts of interest.

Acknowledgements

The authors would like to acknowledge the work done by Antonio Nieto (statistician, Pharma Mar) in the preparation of this manuscript. This study was also supported by funding from Pharma Mar.

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