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European Journal of Cancer 40 (2004) 2748–2752

European Journal of Cancer

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Phase II study of OSI-211 (liposomal lurtotecan) in patients with metastatic or loco-regional recurrent squamous cell carcinoma of the head and neck
An EORTC New Drug Development Group Study

F. Duffaud [a,*], M. Borner [b], P. Chollet [c], J.B. Vermorken [d], J. Bloch [e], M. Degardin [f], F. Rolland [g], C. Dittrich [h], B. Baron [i], D. Lacombe [i], P. Fumoleau [g], for the EORTC-New Drug Development Group/New Drug Development Program

[a] *Department of Medical Oncology, La Timone University Hospital, Bld. J. Moulin, Marseilles cédex 5, 13385, France*
[b] *Inselspital, Berne, Switzerland*
[c] *Centre Jean Perrin, Clermont Ferrand, France*
[d] *Universitair Ziekenhuis, Edegem, Belgium*
[e] *CHU La Pitié Salpétrière, Paris, France*
[f] *Centre Oscar Lambret, Lille, France*
[g] *Centre René Gauduchau, Nantes, France*
[h] *Ludwig Boltzmann-Institute for Applied Cancer Research (LBI-ACR Vienna) Kaiser Franz Josef Hospital, Vienna, Austria*
[i] *EORTC New Drug Development Program, Brussels, Belgium*

Received 19 July 2004; received in revised form 25 August 2004; accepted 27 August 2004
Available online 1 October 2004

Abstract

The purpose of this study was to evaluate the activity and safety of OSI-211, the liposomal form of lurtotecan, in patients ineligible for curative surgery or radiotherapy and with metastatic/locoregional recurrent squamous cell carcinoma of the head and neck (SCCHN) and target lesions either within a previously irradiated field (''within'') or outside a previously irradiated field (''outside''). OSI-211 was given intravenously over 30 min on days 1 and 8 at 2.4 mg/m^2/day, repeated every 21 days (1 cycle). From July 2001 to March 2002, 32 patients from 14 institutions were enrolled in the ''within'' arm and 18 in the ''outside'' arm. In the ''within'' arm, two patients were ineligible because their tumour site was not allowed in the protocol (nasopharynx, skin) and two other patients never started treatment. Of the 46 eligible patients who started treatment, there was one objective response (response rate: 2.2% (95%Confidence Interval (CI): [0–11.5%]). Twelve patients in the ''within'' arm and 6 in the ''outside'' arm had stable disease, with a median duration of 18 weeks, 95% CI (12.7–25.7). The median time to progression was 6 weeks (95%CI: [5.9–12.7] weeks). Haematological toxicity was moderate in both arms. The most common haematological toxicity was grade 1–2 anaemia in 79% of patients. Non-haematological toxicity was mild in both arms. The most common grade 3–4 non-haematological toxicity was infection in 8.5% of patients. OSI-211 administered on d1 and d8, every 3 weeks, is well tolerated, but shows only minimal activity in locally advanced/metastatic SCCHN.

Keywords: Recurrent/metastatic squamous cell carcinoma of the head and neck; Liposomal lurtotecan; Topoisomerase I inhibitor

* Corresponding author. Tel.: +33 4 91 38 57 08; fax: +33 4 91 38 76 58.
E-mail address: fduffaud@mail.ap-hm.fr (F. Duffaud).

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doi:10.1016/j.ejca.2004.08.024

1. Introduction

The prognosis for patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) remains dismal, with a median of survival of 6–8 months [1]. For these patients, chemotherapy is usually only palliative, the main objective being to improve quality of life by reducing symptoms, but this produces considerable toxicity. Further investigation of new agents is therefore needed to try to improve survival in this patient population.

OSI-211, formerly known as NX211, is the liposome encapsulated form of lurtotecan which is a water-soluble analogue of camptothecin that inhibits mammalian DNA topoisomerase I with *in vivo* potency similar to topotecan [2–4]. Pharmacology/toxicology studies in tumour xenograft models show that encapsulation of lurtotecan results in a significant increase in therapeutic index (% tumour growth inhibition) and in plasma concentrations over free lurtotecan and topotecan [2–5]. During these studies, head and neck tumours (KB tumours) are among the most sensitive xenograft tumour types. Phase I study results show that liposome encapsulation results in a more marked increase in plasma concentrations than was observed for the free drug [6,7]. A phase I study with a day (d) 1 and 8 schedule of administration determined the recommended phase II dose of 2.4 mg/m^2/day given by 30 min intravenous infusion (i.v.) d1 and d8, every 21 days [7]. Based on the above results, and taking into account that new drugs are needed for head and neck patients with loco-regional recurrent or metastatic tumours, we thought it was worthwhile to test OSI-211 in order to assess its potential activity and tolerability in this patient population.

2. Patients and method

2.1. Eligibility

Patients with metastatic or loco-regional recurrent histologically proven squamous cell carcinoma of the head and neck (SCCHN), who were considered ineligible for curative surgery or radiotherapy were enrolled into this study. Patients were stratified according to the presence of a target lesion present either ''within'' or ''outside'' of a previously irradiated field. Eligible ''within'' patients were those presenting with head and neck target lesions in the irradiated field, with or without other target lesions (any organ) outside of the irradiated field. Eligible ''outside'' patients were those presenting with relapsed head and neck target lesions exclusively outside the irradiated field or patients with metastatic disease at first presentation.

The main inclusion criteria were: measurable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST), Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, normal blood cell count, normal renal and hepatic function, no clinical symptomatic evidence of brain leptomeningeal metastatic disease, and signed informed consent.

Exclusion criteria included: undifferentiated and non-keratinising carcinomas including lymphoepitheliomas of all locations, tumours of the nasal and paranasal cavities and of the nasopharynx. The extent of the disease was evaluated by cervical and chest computed tomography (CT) scans, within the 14 days prior to starting the treatment.

2.2. Treatment plan and dose modifications

OSI-211 was given to all patients i.v. over 30 min on d1 and d8 at a starting dose of 2.4 mg/m^2/day, repeated every 21 days (1 cycle). The cumulative dose was 4.8 mg/m^2/cycle. Toxicity was graded using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 2.0. A dose escalation to 2.8 mg/m^2/day as of cycle 2 for patients experiencing toxicities $\leqslant$ grade 2 during cycle 1 and haematological recovery on day 21 was recommended. Any grade 3 or 4 toxicity required a delay of therapy until resolution to grade 1 or less. Re-institution of treatment, if medically appropriate, was applied with a dose-reduction. OSI-211 dose was adjusted by nadir counts and by worst major organ toxicity grade. No re-escalation was permitted for subsequent cycles. Patients whose toxicity did not resolve after a 2-week delay (i.e. by day 35) were withdrawn from the study.

2.3. Response assessment

Patients were evaluated clinically at least every 3 weeks and responses were assessed radiographically every 2 cycles to measure the antitumour activity of the treatment. The same evaluation modality was used throughout the study. Response guidelines, as defined by RECIST, were used [8], defining all responses after at least 8 weeks of therapy as either a complete response (CR), a partial response (PR), progressive disease (PD), or stable disease (SD). Confirmation of all responses was required after 4 weeks. We defined disease control as the sum of patients achieving a CR, PR, or SD.

2.4. Statistical considerations

Considering that patients were stratified according to the target lesions ''within'' or ''outside'' of the previous irradiated field, the Simon 2 stage minimax design was applied to each stratum separately. In the first stage of the design, 19 patients (per stratum) were needed to assure with a 90% power and a type I error of 10% that if the true response rate is 20% the investigations were stopped as early as possible, i.e. 3 or less responses out

of the first 19 patients. If 4 responses or more were observed then 17 more patients could be registered to establish if the true response rate was 40%, the regimen can then be recommended for further investigation in phase III studies. The expected maximum number of patients was 36 per stratum.

The primary end-point of the study was the response rate and its 95%Confidence Interval (CI) was calculated by pooling the CR and PR. Secondary end-points included the protocol treatment toxicity, the estimation of time to progression (TTP), overall survival (OS) and the duration of response. Survival was measured from the date of starting treatment until the date of death or last follow-up. TTP was defined as the time interval between the date of starting treatment to the date of objective progression. If progression was not observed, the patient was censored at the date last seen, alive or dead. Duration of response was measured for the complete and partial responders from the date the response was observed until the first sign of radiological progression of disease.

OS, TTP and duration of response were estimated by use of the Kaplan–Meier method. Only the patients who met eligibility criteria and who were assessable for response were included in the response analysis. All patients who were registered and started the treatment (received the drug) were included in the toxicity analysis.

2.5. Pharmacokinetic sampling

All patients were asked to participate in a population pharmacokinetic and pharmacodynamic study with blood sampling procedures on day 1 of cycle 1. This pharmacokinetic evaluation was conducted to confirm the plasma PK profile of total lurtotecan following OSI-211 administration observed in phase I. The sampling times were as follows: before start of the infusion, at the end of OSI-211 dose administration and 4 and 24 h after the OSI-211 administration. At each sampling time, 4 ml of blood were taken from the arm opposite to the infusion using heparin vacutainers. Blood samples were cooled immediately on wet ice (approximately 4–8 °C) and centrifuged at 1500–2000*g* to obtain plasma within 45 min. Plasma samples were stored at −20 °C until shipment. The first amendment in the protocol (July 11, 2001) added sampling of urine to evaluate the possible correlation between the fraction of dose excreted in urine × dose and the percentage decrease in haematological parameters using 24-h urine excretion collected on day 1 of cycle 1. Urine was collected from each patient on day 1 of cycle 1 for each time period using the following schedule: prior to infusion, 0–12 h, 12–24 h. Samples were analysed using a validated high-performance liquid chromatography (HPLC) assay with fluorescence detection. The limit of quantitation was 1 ng/ml of lurtotecan [9].

3. Results

3.1. Patient characteristics

Between July 2001 and May 2002, 50 patients from 14 institutions were entered in this trial, 32 in the "within" arm and 18 in the "outside" arm. Two patients in the "within" arm were ineligible because their tumour site was not allowed per protocol (one patient had a nasopharyngeal cancer and the other a skin tumour). Two other patients never started treatment. All analyses were therefore done on the 48 patients except response to treatment analysis, which was calculated on the basis of 46 eligible patients. In addition, the haematology and toxicity forms were not received for one patient, thus the toxicity tables were calculated based on 47 patients.

Forty-five males and 3 females were treated. The median age was 57 years (range, 41–83 years) and the performance status was 0, 1, 2 in 27%, 56% and 17% of patients, respectively. Ninety-two percent of the patients ($n = 44$) received prior radiotherapy, 48% ($n = 23$) received a prior chemotherapy, and 71% of patients ($n = 34$) had undergone a prior surgical procedure. Prior chemotherapy was administered as a part of an initial curative intent concomitant with radiotherapy ($n = 15$), or as a neoadjuvant/adjuvant treatment ($n = 8$). Of the 23 patients who had received chemotherapy at any time during their treatment, 22 (96%) had had a prior platinum-containing regimen.

3.2. Toxicity

Safety analyses were done on the 47 patients who started treatment since for one patient no toxicity information was received because he died shortly after the first infusion (17 patients in the "outside" arm and 30 patients in the "within" arm). Table 1 shows the haematological and non-haematological drug-related toxic effects. A total of 55 cycles (median 2 cycles, range 1–12 cycles) of OSI-211 were administered in the "outside" arm and 86 cycles (median 2 cycles, range 1–8 cycles) in the "within" arm. Sixty-eight percent of patients completed 2 cycles or more of the protocol treatment.

The median relative dose intensity of OSI-211 was 92% (48–115.5%) in the "outside" arm and 99.7% (78–112%) in the "within" arm. So, 35 patients (73%) received a relative dose intensity of > 90%. Twenty patients (42%) had dose escalation at cycle 2, as allowed in the protocol, 6 (33%) in the "outside" arm and 14 (47%) in the "within" arm. For 12 (25%) patients, the dose of OSI-211 was reduced. These dose reductions were due to drug-related toxicity for 4 patients, but were non-drug-related for 8 patients. The day 8 dose was omitted in 12 patients (25%) for one cycle only due to haematological toxicity. Eleven patients (23%) had cycle-delays, 7 patients for 1 cycle and 4 for 2 cycles.

Table 1
Grade of drug-related toxicity per patient in the two treatment arms (%)

CTC grade events	"Outside" group ($n = 17$)				"Within" group ($n = 30$)			
	1	2	3	4	1	2	3	4
Leucocytes	2 (12%)	1 (6%)	6 (*35%*)		4 (13%)	4 (13%)	5 (17%)	3 (10%)
Neutrophils		2 (12%)	3 (*18%*)	2 (*12%*)	1 (3%)	4 (13%)	2 (7%)	6 (20%)
Platelets			2 (*12%*)		3 (10%)	1 (3%)	3 (10%)	
Haemoglobin	4 (24%)	11 (65%)	2 (*12%*)		12 (40%)	10 (33%)	5 (17%)	
Fatigue	3 (18%)	4 (24%)			5 (17%)	10 (33%)	1 (3%)	
Nausea	5 (29%)	1 (6%)	1 (*6%*)		6 (20%)	2 (7%)		
Vomiting	4 (24%)		1 (*6%*)		5 (17%)			
Anorexia		1 (6%)			3 (10%)	2 (7%)	1 (3%)	
Dysphagia	1 (6%)				4 (13%)	1 (3%)	1 (3%)	
Fever without Neutropenia					1 (3%)			
Haemorrhage/bleeding	0/1 (6%)				1 (3%)		1 (3%)/1 (3%)	
Febrile neutropenia			2 (12%)				1 (3%)	
Infection[a]		2 (12%)	2 (12%)			1 (3%)	2 (7%)	
Dyspnoea		0			0	2 (7%)	0	1 (3%)
Stomatitis	1 (6%)	1 (6%)	1 (6%)		2 (7%)	1 (3%)		
Pain other than cancer pain		1 (6%)			7 (23%)		1 (3%)	
Constipation	2 (12%)				4 (13%)	2 (7%)		

CTC, common toxicity criteria.
[a] Bronchitis, pneumonia.

Treatment omission on day 8 and treatment delays were mainly due to haematogical toxicity.

Overall, haematological toxicity was moderate in the two arms. The most common haematological toxicity was grade 1–2 anaemia in 79% of patients. Neutropenia was severe in 28% of patients, but admission for febrile neutropenia was required in 3 patients only. Non-haematological grade 3–4 toxicity was rare in both arms. The most common severe non-haematological toxicity was infection (bronchitis and pneumonia) observed in 4 patients (8.5%). The major reasons for stopping treatment were: disease progression in 29 patients (58%), toxicity in 3 patients (6%), patient's refusal in 5 (10%), completion of protocol treatment in 2 patients (4%), and intercurrent death in 5 patients (10%).

3.3. Pharmacokinetic analysis

Plasma lurtotecan concentrations were available in 42 patients (see Fig. 1). The area under the concentration–time curve (AUC) of the plasma lurtotecan concentration–time curve ranged from 204.4 to 23199 h ng/ml (mean 7891.1 ± 6278.1 h ng/ml), and the C_{max} ranged from 173 to 1518 ng/ml (mean 846.5 ± 364.5 ng/ml). The pharmacokinetic data show a high interpatient variability in AUC, as seen with other liposomal products, and a less variable effect on C_{max}.

3.4. Response and survival results

Two patients were not eligible to enter the study and were therefore excluded from the efficacy analysis. Out of the 46 eligible patients, only one patient had an objective response (in the "within" arm). The response rate was 2.2% (95%CI: [0–11.5%]). Stable disease was observed in 18 (39%) patients after 2 cycles of OSI-211, 12 in the "within" arm and 8 in the "outside" arm, with a median duration of 18 weeks, 95% CI (12.7–25.7). Nine patients died prior to response assessment and 14 patients (30%) had progressive disease. At the time of analysis, 15 (33%) of the 46 eligible patients were alive (8 in the "outside" arm and 7 in the "within" arm), with a median survival time of 4 months. Most of the patients died by 6 months. Median time to progression was 6 weeks (95% CI: [5.9–12.7] weeks). The RECIST response rate observed was much lower than the response rate expected for the first step of the Simon design. With a response rate of a maximum of 3.6% in the "within" arm and the number of patients registered, the 95%CI did not cover the planned minimum rate of 20% based on all eligible patients who started the treatment. The study was therefore stopped for both arms. However,

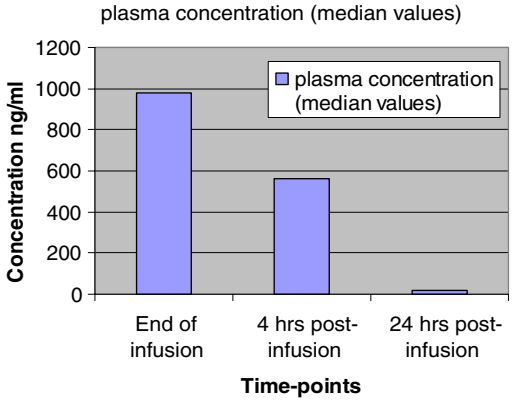

Fig. 1. Plasma concentration of lurtotecan.

12 more patients were recruited during the 15 days notification of study closure.

4. Discussion

This report presents the results of a phase II study with OSI-211, the liposomal encapsulated form of lurtotecan, administered as a single agent given as an i.v. infusion over 30 min on d1 and d8, every 3 weeks, in patients with loco-regionally recurrent or metastatic SCCHN who were not suitable for loco-regional treatment. Patients were stratified according to the presence of target lesions present ''within'' or ''outside'' of the previously irradiated fields. OSI-211 was administered as first-line chemotherapy. In this study, only one patient had an objective response, 39% of patients had disease stabilisation with a median duration of 18 weeks, and the median time to progression was 6 weeks (range, 6–13 weeks). Overall, OSI-211 did not demonstrate a clinically significant activity in patients with recurrent or metastatic SCCHN. The drug was well tolerated. The most common haematological toxicity was grade 1–2 anaemia in 79% of patients. Even if haematological toxicities were the main reason for dose reduction and cycle delay, only 28% of patients developed grade 3–4 neutropenia and there were only 3 episodes of admission for febrile neutropenia. Severe non-haematological toxicities were rare.

In conclusion, OSI-211 administered i.v. on d1 and d8, every 3 weeks, has a very acceptable toxicity profile, but has only limited activity in patients with loco-regionally recurrent or metastatic SCCHN. Therefore, OSI-211 with this particular schedule of administration, is not recommended for use as a single agent in such patients. These results stress the urgent need to discover new active agents to be used in the treatment of this disease.

Conflict of Interest Statement

None declared.

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