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RFS2000 (9-nitrocamptothecin) in advanced small cell lung cancer, a phase II study of the EORTC New Drug Development Group

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Abstract

Camptothecins have shown efficacy in terms of response rate in patients with small cell lung cancer (SCLC). RFS2000 is a new camptothecin derivative, which has shown objective responses in various tumour types. The aim of this phase II study was to determine the objective response rate of RFS2000 in patients with sensitive and refractory SCLC. RFS2000 was given orally at 1.5 mg/m^2 per day for five consecutive days (five days on – two days off) on a continuous basis. Patients were evaluated weekly for toxicity and every six weeks for response. Thirty seven patients were included, 36 patients (14 with sensitive and 22 with refractory SCLC) were evaluable for toxicity, and 35 patients were evaluable for response. No objective responses were observed. Toxicity was acceptable, with myelosuppression, nausea/vomiting, and diarrhoea as the main toxicities. RFS2000 therefore has an acceptable toxicity profile but is not active as a single agent in SCLC.

Keywords: Small cell lung cancer; Chemotherapy; RFS2000; Rubitecan; Phase II study; EORTC

1. Introduction

The prognosis for patients with small cell lung cancer (SCLC) upon progression after first-line systemic treatment remains poor. Among new active agents, the camptothecin analogues irinotecan and topotecan have shown promising response rates in this setting [1,2]. However a small, randomised study failed to demonstrate a benefit for topotecan when given as consolidation treatment after cisplatin plus etoposide [3]. RFS2000 (9-nitro-20(*S*)-camptothecin; rubitecan) is a new camptothecin derivative that inhibits topoisomerase I [4]. The identification of topoisomerase I as the cellular target was confirmed by the observation that single point mutations in topoisomerase I confer resistance to RFS2000 [5,6]. In experimental models RFS2000 has demonstrated high cytotoxic activity *in vitro* and *in vivo* [reviewed in 7]. In a phase I study, RFS2000 was given orally for five consecutive days every week for four weeks at doses up to 2 mg/m^2 per day [8]. The dose-limiting toxicity was myelosuppression; other toxicities included nausea, vomiting, diarrhoea and chemical cystitis. The recommended dose with this schedule for phase II studies was determined at 1.5 mg/m^2 per day. The bioavailability of RFS2000 was shown to be strongly dependent on the timing of food intake in relation to its oral intake [9]. We here report on a phase II study in patients with advanced SCLC. Phase II studies in colorectal cancer [9], pancreatic cancer [10],

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glioblastoma multiforme [11], soft tissue sarcoma [12], melanoma [13] and gynaecological cancers [14] have been reported, with objective responses being observed in several tumour types in a minority of patients.

2. Patients and methods

The primary endpoint of this study was to determine the objective response rate. Main eligibility criteria included histologically proven SCLC, advanced extensive disease, measurable disease with at least one target lesion of $\geqslant 10$ mm on spiral computed tomographic scan or $\geqslant 20$ mm with conventional techniques, ECOG performance status 0–2, age $\geqslant 18$ years, adequate use of contraceptives, adequate bone marrow, liver, renal and cardiac function, no chemo- or radiotherapy during the past four weeks, not more than one previous line of chemotherapy, no symptoms of central nervous metastases, and written informed consent.

Patients were divided into two groups: *sensitive patients*, defined as having had a response to previous chemotherapy lasting for at least three months from the end of all previous treatments, including radiotherapy, until time of progression; and *refractory patients*, defined as having had no response to previous chemotherapy or having had a response but progressing within three months of completing all previous treatments. The sample size calculation was based on the two-stage Gehan design. If, in the first stage, in 14 sensitive and 19 refractory patients, no responses were observed, the respective group would be closed to patient entry. If in the first stage, there were $\geqslant 1$ objective responses, additional patients were to be included in the respective group to a total of 25 sensitive patients and 24 refractory patients. This ensured that, if the drug was active in 20% or more of the sensitive patients and 15% or more in the refractory patients, the chance of erroneously rejecting the drug after the initial stage was 0.044 and 0.046, respectively.

RFS2000 (Supergen, San Ramon CA, USA) was provided as capsules of 0.5 and 1.25 mg, which were to be stored at a refrigerated place, and given orally weekly for five consecutive days at a dose of 1.5 mg/m^2 per day, rounding to the nearest total dose. One cycle was defined as three weeks of 'five days on–two days off' treatment. RFS2000 was given in the morning with an acidic pH beverage, $\approx$1 h after a light meal. Daily oral hydration of at least 3 l was recommended to reduce the incidence of chemical cystitis. Treatment was continued until disease progression, unacceptable toxicity, patient refusal, or any condition that was not considered to be in the interest of the patient.

The primary endpoint was the objective response according to RECIST criteria. Patients were evaluable for response when at least two cycles were completed. All responses were to be reviewed by an independent panel. Secondary endpoints were the duration of response, overall survival and progression-free survival, and toxicities upon treatment with RFS2000. Duration of response was measured for the complete and partial responders from the first date the response was observed until the first sign of radiological or clinical progression of disease. Overall survival was measured from the date of starting treatment until the date of death or last follow up. Progression-free survival was defined as the time interval between the date of starting treatment to the date of progression or death, whichever occurs first. If neither progression nor death was observed, the patient was censored at the date last seen alive. Toxicity was assessed by use of the CTC criteria version 2. Patients were evaluated weekly for toxicity and every two cycles for response. In case of toxicities, strict criteria for dose modifications were provided as per protocol. No standard prophylactic medication was administered. All analyses were to be restricted to patients who started treatment per arm separately and for all patients pooled. This population was further restricted to eligible patients for the response and efficacy analyses. The associated 95% confidence intervals (CI) were estimated for the study endpoints.

3. Results

Between May 2000 and March 2002, 37 patients from 10 institutions were entered in the trial. Patient characteristics are presented in Table 1. One patient did not start the study treatment and was therefore not included in the analysis. This patient as well as one other patient was also ineligible because of grade 3 hyponatraemia before the start of treatment. Patients received a median number of two cycles (range 1–11). Thirty five patients were therefore evaluable for response, 14 patients with sensitive and 21 patients with refractory disease. No objective responses were observed; the 95% CI for response rate in the 14 sensitive patients was (0–23%) and in the 21 refractory patients (0–16%). Two partial responses reported by the local investigator were not confirmed and were therefore classified as stable disease. Stable disease was achieved in both groups together in 11 (31%) patients. Progression-free and overall survival was 1.4 months (95% CI: 1.2–1.8 months) and 5.5 months (95% CI: 5.0–8.3 months), respectively.

Thirty six patients were evaluable for toxicity (Table 2). Grade 3–4 haematological toxicity occurred in nine patients (25%). Febrile neutropenia occurred in three (9%) patients, grade 3 in one and grade 4 in two patients. One patient was considered a toxic death due to febrile neutropenia and pulmonary infection. The most frequently occurring grade 3–4 non-haematological toxicities were diarrhoea (grade 3:4 (11%) patients), and nausea/vomiting (grade 3:2 (6%) patients). The incidence of other grade 3–4 non-haematological toxicities

Table 1
Patient characteristics

	Sensitive	Refractory	Total
N	14	22	36
Age (years; median, range)	59 (50–76)	59 (48–75)	59 (48–76)
ECOG PS (median, range)	1 (0–2)	1 (0–2)	1 (0–2)
Prior radiotherapy	4 (29%)	9 (41%)	13 (36%)
Prior surgery	1 (7%)	2 (9%)	3 (8%)
Prior chemotherapy:	14 (100%)	22 (100%)	36 (100%)
Adjuvant only	0	1	1
Advanced disease	14	20	34
Both	0	1	1
Months (median, range) between last chemotherapy and study start	7 (4.2–20.8)	3 (0.9–15.4)	4.7 (0.9–20.8)

Table 2
Most frequently occurring RFS2000-related grade 3–4 toxicities

	Sensitive	Refractory	Total
Neutropenia	1 (7%)	3 (14%)	4 (11%)
Thrombocytopenia	1 (7%)	4 (18%)	5 (14%)
Anaemia	1 (7%)	4 (19%)	5 (14%)
$\geqslant 1$ Haematological toxicity	3 (21%)	6 (28%)	9 (25%)
Febrile neutropenia	1 (7%)	2 (10%)	3 (9%)
Diarrhoea	3 (21%)	1 (5%)	4 (11%)[a]
Nausea	0	2 (9%)	2 (6%)[a]
Vomiting	1 (7%)	1 (5%)	2 (6%)[a]

[a] All events grade 3 toxicity.

was $\leqslant 3\%$. Clinically relevant symptoms of chemical cystitis were not observed. Two patients (5%) discontinued treatment for reasons of toxicity.

4. Discussion

We conclude that RFS2000 is not active in patients with sensitive or refractory SCLC. These results are disappointing given the promising response rates for irinotecan and topotecan in this setting as well as the fact that RFS2000 has resulted in objective responses in pancreas carcinoma [10], soft tissue sarcoma [12], gynaecological tumours [14], and breast, ovarian, and haematological tumours [8]. RFS2000 has an acceptable toxicity profile, with myelosuppression, nausea/vomiting and diarrhoea as the most frequently occurring toxicities in a minority of patients. These results do not support further evaluation of RFS2000 as a single agent in SCLC.

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