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European Journal of Cancer 41 (2005) 1547–1550

European Journal of Cancer

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A phase II trial with RFS2000 (rubitecan) in patients with advanced non-small cell lung cancer

S. Baka [a,*], M. Ranson [a], P. Lorigan [b], S. Danson [a], K. Linton [a], I. Hoogendam [c], K. Mettinger [d], N. Thatcher [a]

[a] *Department of Medical Oncology, Christie Hospital NHS Trust, Wilmslow Road, Manchester M20 4BX, UK*
[b] *Department of Medical Oncology, Weston Park Hospital, Sheffield, UK*
[c] *NDDO Representative, UK*
[d] *Supergen Representative, UK*

Received 10 November 2004; received in revised form 23 February 2005; accepted 1 March 2005
Available online 27 April 2005

Abstract

Rubitecan (RFS2000, 9 nitrocamptothecin,) is a new oral topoisomerase I inhibitor. We report a phase II, single-arm, open-label study of RFS2000 as first line treatment for non-small cell lung cancer (NSCLC). Seventeen treatment-naïve patients with stage IIIB (9/17) and IV (8/17) NSCLC (11 male and 6 female) were treated, the median age was 62 years (range 52–86), and the majority of patients (14/17) were of performance status 1. RFS2000 was given orally, daily for 5 days, repeated every week. The starting dose was 1.5 mg/m^2/day, and dose adjustment was permitted based upon toxicity. Fifteen patients had a dose escalation to 1.75 mg/m^2/day and 7 had a second dose escalation to the protocol maximum level of 2.0 mg/m^2/day. RFS2000 was tolerated well. Almost all adverse events were grade 1 and 2. The most frequently encountered adverse events were diarrhoea, nausea, anorexia, and lethargy. Neutropenia and thrombocytopenia were not observed in any patient. There were no responders to RFS2000 treatment, 10 patients had stable disease as their best response, whilst five had tumour progression. Two patients were not assessable for tumour response. The median survival time was 257 days (95% CI = 222–352). RFS2000 appears to be inactive at dose levels of 1.5–2.0 mg/m^2/day in advanced NSCLC patients. Since only mild toxicity and no myelosuppression were encountered, these dose level are too low for this treatment-naïve patient population with NSCLC. Further studies at an increased dose would be required to identify whether this agent has merit in the treatment of NSCLC.

Keywords: Rubitecan; RFS2000; Non-small cell lung cancer; Topoisomerase I inhibitor

1. Introduction

The development of more effective systemic therapy is required if overall treatment results are to be improved in advanced non-small cell lung cancer (NSCLC). A number of single agents have been tested in advanced NSCLC and active agents have yielded single agent response rate of 10–20% [1–3]. Several derivatives of the plant alkaloid camptothecin have also been evaluated clinically in NSCLC (irinotecan, topotecan, exetecan (DX-8951F) [4–6] and these agents have been reported to be synergistic with platinum agents in pre-clinical models. RFS2000 or rubitecan (9-nitro-20 (S)-camptothecin, 9-NC) an orally available topoisomerase I inhibitor has been selected for clinical development [7–9] and in experimental models demonstrated promising cytotoxic activity *in vitro* and *in vivo* [10]. In phase I evaluation, RFS2000 was administered orally for five

* Corresponding author. Tel.: +44 161 446 3126; fax: +44 161 446 3299.
E-mail address: sofia.baka@christie-tr.nwest.nhs.uk (S. Baka).

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doi:10.1016/j.ejca.2005.03.009

consecutive days each week for four weeks at doses up to 2.0 mg/m^2/day [11], and was found to be well tolerated. At 2.0 mg/m^2/day myelosuppression was dose-limiting. Other toxicities included nausea, vomiting, diarrhoea and chemical cystitis. Phase II studies in colorectal cancer [12], pancreatic cancer [13], glioblastoma multiforme [14], soft tissue sarcoma [15], melanoma [16] and gynaecological cancers [17] have been reported, demonstrating preliminary evidence of activity.

The primary aim of this Phase II trial was to determine the objective response rate to RFS2000 in previously untreated patients with advanced or metastatic NSCLC. The selection of the 5-day schedule every week was based upon preclinical data indicating greater efficacy for prolonged schedules and on the tolerability of this regimen in a Phase I setting. The trial was conducted as a two centre open-label study and represents the first evaluation of RFS2000 in advanced NSCLC.

2. Patients and methods

Patients with histological proven stage IIIB/IV NSCLC were treated at two UK centres. Eligibility criteria included: no previous chemotherapy or radiotherapy, ECOG performance status $\leqslant 2$, age $\geqslant 18$ years, predicted survival $\geqslant 12$ weeks, adequate bone marrow, liver, renal and cardiac function, no known brain metastases, no previous malignancy, no serious concurrent medical illness and, where applicable, approved methods of birth control. All patients gave written informed consent and the trial was conducted to ICH–GCP and in accordance with the Declaration of Helsinki and with the approval of the local research ethics committee at each participating institution.

Patients commenced RFS2000 at a dose of 1.5/m^2/day for 5 days per week (dose level 0) [1]. A period of 4 weeks was defined as 1 cycle of treatment. The treatment dose level could be increased in subsequent cycles in steps of 0.25 mg/m^2, providing there was no grade II/IV toxicity in the preceding cycle. The maximum protocol dose level was 2.0 mg/m^2/day. The dose level was reduced by 0.25 mg/m^2 if substantial toxicity was experienced.

Patients were assessed weekly for adverse events and full blood count. Physical examination, biochemistry and urine analysis, were also assessed at the commencement of each cycle. Tumour assessment was performed at baseline and every 8 weeks during treatment until progression. Objective tumour response was evaluated according to RECIST criteria with the definition of stable disease requiring duration of at least 6 weeks. Any investigator reported responses were to be subject to independent radiological review.

Toxicities were graded according to the revised common toxicity grading criteria version 2.0.

The primary aim of the study was the assessment of the response rate with RFS 2000. In a 2-stage design a sample size of 14 evaluable patients allows the true response rate to be predicted with a SE < 0.10. If there were no response in any patient at completion of stage 1, the trial would be closed. The chance at stage 1 of erroneously rejecting a drug with a true response rate of 20% is 0.044. Time to progression was taken from the date of the first treatment to the date of the progression. Survival was calculated from the date of the first treatment to death, and a survival curve was formed using Kaplan–Meier estimation.

3. Results

Seventeen chemo naïve patients with stage IIIB/IV NSCLC, 11 male patients and 6 female, median age 62 years (range 52–86 years) were entered in the study. The majority of patients (15/17) had a Performance Status of 1 (WHO–ECOG criteria).

The starting dose for all patients was 1.5 mg/m^2/day (dose level 0). Fifteen of the 17 patients had a dose escalation to 1.75 mg/m^2/day (dose level +1), 14 in their second course and one in the third course. Of these 15 patients, 7 patients had a second dose escalation to 2.0 mg/m^2/day (dose level +2) in the third course. Dose reduction from 2.0 to 1.75 mg/m^2/day was required in only one patient due to marked nausea, vomiting and diarrhoea. The 2 patients who did not have dose escalation were both withdrawn from the study for progression of disease or disease-related symptomatic deterioration within the first 8 weeks.

A total of 67 cycles (4 weeks) were administered in the 17 entered patients. Patients received a median of 2 cycles (range 1–11). Seven of the 17 patients received $\geqslant 4$ cycles. Forty-nine cycles were administered as full courses of treatment whilst 18 cycles were incomplete. In 10 of these 16 cycles, treatment was discontinued because of progressive disease or disease-related symptomatic deterioration rather than for toxicity reasons. In only two instances was drug omitted during a cycle because of drug-related adverse events.

Fifteen patients were evaluable for tumour response in accordance with the protocol and RECIST tumour response criteria. No objective tumour responses were observed. Ten patients had stable disease as their best response, and five patients had progressive disease. Of the 2 patients who were non-evaluable for response, 1 received only two weeks of study medication, and the other had no post treatment response evaluation. Twelve of the 17 patients had thoracic radiotherapy after RFS2000, and 3 patients received second line chemotherapy. Two patients had no further treatment. At the time of analysis 15 (88%) of 17 entered patients

had died. The median survival time was 257 days (95% CI = 222–352 days). The one-year survival was 19%.

The most frequently reported drug-related adverse events, were diarrhoea, nausea, anorexia, and lethargy. Although diarrhoea and nausea were common, treatment with RFS2000 was well tolerated and adverse events were typically mild to moderate (CTC grades 1 and 2) in severity. In keeping with this, 15 of 17 patients were dose escalated and dose reduction (from 2.0 to 1.75 mg/m^2/day) was required in only one patient. In the Phase I evaluation of RFS2000, myelosuppression was dose limiting. In this trial involving chemotherapy-naïve patients with advanced NSCLC, bone marrow suppression was not a significant feature. Grade 1 anaemia was reported in only 1 patient and drug-related leucopoenia, granulocytopenia and thrombocytopenia were not observed in any patient. No drug-related adverse events were seen in biochemistry assessments.

4. Discussion

No partial or complete responses were seen in this Phase II trial of RFS2000. Ten of 15 evaluable patients had stable disease as their best response, and 5 patients had progressive disease. The median survival for all patients treated in this study was 257 days (95% CI = 222–352 days). The median survival time in this trial was comparable to phase II studies in advanced NSCLC patients using other single agents (vinorelbine, gemcitabine and topotecan) [18–22]. However, the impact of additional radiotherapy and second line chemotherapy prevent detailed interpretation of the survival data from this trial.

Treatment with RFS2000 was well tolerated. Drug-related toxicity was usually mild.

Our results are in agreement with the toxicity results from previous papers [17]. The dose-limiting toxicity was myelosuppression. Other toxicities included nausea, vomiting, diarrhoea and chemical cystitis.

It is interesting to note that a phase II trial of oral topotecan similarly found that the starting dose of topotecan based on phase I experience was too conservative for a chemotherapy-naïve patient population [22]. This suggests that future trials with similar topoisomerase I inhibitors should include dose escalation schemes which allow for differences in patient population and tolerability. Toxicity in this study was not different.

RFS2000 has little or no activity in patients with advanced NSCLC at the dose levels of this protocol. Given the low toxicity and absence of bone marrow suppression, the current study does not preclude the possibility that RFS2000 has activity in advanced NSCLC at doses that are attended by myelosuppression.

Phase II and III studies are being conducted with RFS2000 in several tumour types and further results are awaited.

Conflict of interest statement

None declared.

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