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Multicentre phase II and pharmacokinetic study of RFS2000 (9-nitro-camptothecin) administered orally 5 days a week in patients with glioblastoma multiforme

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Abstract

A phase II trial was instigated to investigate the antitumour activity, the safety and the pharmacokinetic parameters of RFS2000, a recently identified oral topoisomerase I inhibitor, given once daily (1.5 mg/m^2/day) as first-line chemotherapy treatment for patients with advanced glioblastoma multiforme (GBM). Between 9 March and 15 September 2000, 17 patients were entered onto the trial. 15 patients were considered eligible. A total of 49 cycles (range 1–8) were administered. Grade 3-4 toxicity was observed in 5 patients. Neutropenia and thrombocytopenia were common toxicities. Pharmacokinetic analysis showed that 9-nitro camptothecin (9-NC) could be detected in the plasma and is progressively converted into 9-amino-camptothecin (9-AC). The response rate was poor, with 5 patients experiencing tumour stabilisation and 10 progressing. Thus, the results do not support the further evaluation of RFS2000 as a single agent in patients with recurrent GBM.

Keywords: 9-Nitro-camptothecin; 9-Amino-camptothecin; Camptothecin; Glioblastoma

1. Introduction

Nitrosoureas and temozolomide are standard chemotherapies for patients with glioblastoma multiforme (GBM), but have a limited impact on the overall survival [1]). Therefore, several new agents such as topoisomerase I inhibitors were recently investigated [2]. Animal studies indicated that camptothecins penetrate into tumours in which the blood–brain barrier is disrupted [2]. In glioma xenograft models in nude mice, several camptothecin derivatives displayed marked antitumour activity. More recently, clinical trials with irinotecan in patients with malignant gliomas including GBM showed promising response rates [2]. 9-Nitrocamptothecin (RFS2000), a novel oral topoisomerase I inhibitor, showed dose-limiting haematological toxicity and cystitis in phase I clinical trials [3] with evidence of activity in several tumor types including pancreatic and ovarian carcinoma [4,5]. In this phase II trial, we investigated the antitumour activity, the safety, and the pharmacokinetic parameters of RFS2000, a recently identified oral topoisomerase I inhibitor, in first-line chemotherapy treatment of patients with advanced GBM.

2. Patients and methods

Patients eligible for this study had to meet the following inclusion criteria: age $\geqslant$18 years old, histologically-confirmed diagnosis of GBM, evidence of recurrent disease documented by computed tomography (CT) scans or magnetic resonance imaging (MRI), contrast enhancing lesion of at least 2 cm, no brain irradiation within the last 3 months, stable or decreasing corticosteroids intake, surgery for primary lesion completed at least 3 months before, no surgery for recurrent disease, and written informed consent according to European and Institutional guidelines had to be provided.

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RFS2000 was given in the morning once daily as an oral intake of 1.5 mg/m^2/day with a 5 days on 2/days off schedule. A cycle was arbitrarily defined as a 3-week treatment period.

The principal objective of the trial was to assess the therapeutic activity of RFS2000 in patients with GBM. The main end point was the objective response to treatment as defined by the MacDonald's criteria [6]. The secondary objectives were to characterise the acute side-effects of RFS2000 in patients with GBM and to study the pharmacokinetic profile of the compound. In addition, for patients presenting with an objective response, the duration of response was to be assessed. According to Gehan's rule, 14 eligible patients were required to be included at the first step of this phase II trial. The trial was designed so that if the treatment is active in 20% or more of the patients, the chance of erroneously rejecting the drug after the first 14 patients is 0.044.

Pharmacokinetic blood samplings were drawn at the first infusion at the following time points: 30 min before intake, 30 min, 1 h, 5 h after first intake, 24 h (before the second intake) and on day 5 and day 21 before intakes.

3. Results

Between 9 March and 15 September 2000, 17 patients (13 males and 4 females with a median age of 52 years, range 19–75 years and a median Eastern Co-operative Oncology Group (ECOG) performance status of 1 were entered from six European Organization for Research and Treatment of Cancer (EORTC) institutions. Surgery of the primary tumour consisted of partial resection in 14 patients and stereotaxic biopsy in 3 patients. All but 1 patient had previous brain radiotherapy and 11 patients had been previously exposed to adjuvant chemotherapy with fotemustine (8 patients), temozolomide (3 patients) or belustine (1 patient). Patients were concomitantly treated with various anticonvulsant therapies and 14 patients had corticosteroids at study entry. 15 patients were considered eligible, while 1 patient was considered ineligible due to an absence of measurable lesions at baseline and another due to surgery 2 months before study entry.

A total of 49 cycles were administered (four cycles to the ineligible patients) with a median of two per patient (range 1–8). The median relative dose intensity was 98% (range 58–106%) of the theoretical dose. Neutropenia and thrombocytopenia were common toxicities of RFS2000. Grade 3–4 toxicity was reported in 5 patients and 16 cycles, among which half occurred at cycle 1. This corresponded to 33% of all 49 administered cycles. Febrile neutropenia that required hospitalisation was observed in 3 patients. Grades 1–2 diarrhoea was reported in 9 patients. Grades 1–2 and 3 fatigue was observed in 7 and 2 patients, respectively. Grades 1–2 nausea and vomiting were observed in 5 and 4 patients, respectively. Grade 2 arthralgia and myalgia were reported in 2 patients. Other toxicities consisted of evidence of grades 1–2 stomatitis and grade 3 urinary infection in 3 and 1 patient, respectively. No evidence of cystitis was reported in this study.

Pharmacokinetic analysis showed that, as previously reported [7,8], after an oral intake of RFS2000, 9-nitro-camptothecin (9-NC) can be detected in plasma and is progressively converted into 9-amino-camptothecin (9-AC) (Fig. 1). High interpatient variability was observed for both 9-NC and its metabolite 9-AC (AUC_{0-24h}: 231 +/−137 and 36.9 +/−28.5 ng h/ml, respectively). Peak plasma concentrations of 9-NC (18.0 +/−10.4 ng/ml) were found 3.5 +/−1.8 h after the first drug intake, and the disappearance was shorter than that of 9-AC with a $t_{1/2}$ of 7.1 +/−3.3 h. Peak plasma concentrations of 9-AC (2.5 +/− 3.1 ng/ml) were found 5 h or 24 h after the first drug intake, and the disappearance was longer than that of 9-NC with a $t_{1/2}$ of 9.0 +/−4.1 h. No drug accumulation was observed during the 21 days of the 5 days on 2 days off schedule. Residual levels of 9-NC at 24 h, 5 days and 21 days were 3.2 +/−2.5, 2.6 +/−2.6, and 1.3 +/−2.6 ng/ml, respectively. Residual levels of 9-AC were 1.9 +/−1.4 ng/ml at 24 h, 2.4 +/−1.7 ng/ml at day 5 and 1.1 +/−1.8 ng/ml at day 21.

Among the 15 eligible patients, no objective responses were observed. 5 patients experienced tumour stabilisation and 10 tumour progression. The median time to progression was 44 days (95% confidence interval (CI) 41–76 days). According to the study design, as no clinical response (partial response (PR) or complete response (CR)) has been observed, the study was definitely closed at first step on 21 September 2000.

In summary, despite a good safety profile using this dose and regimen, these preliminary results do not

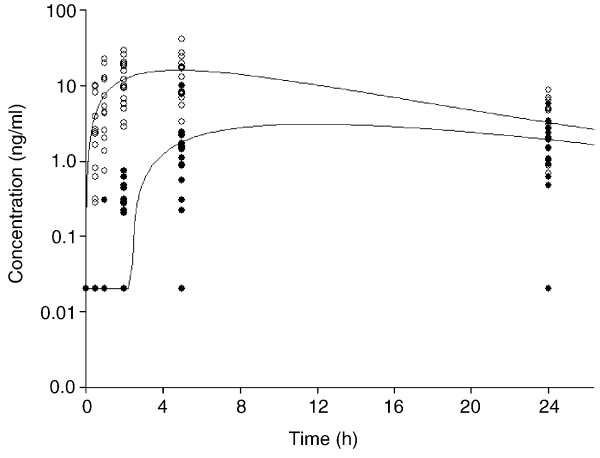

Fig. 1. Pharmacokinetic profiles of 9-nitro-camptothecin (9-NC) and 9-amino-camptothecin (9-AC) after oral intake of RFS2000 in patients with recurrent glioblastoma multiformes. Individual plasma concentrations of 9-NC (○) and 9-AC (●).

support the further evaluation of RFS2000 as a single agent in patients with recurrent GBM.

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