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ORIGINAL ARTICLE

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Bioavailability study of oral and intravenous OGT 719, a novel nucleoside analogue with preferential activity in the liver

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Abstract *Purpose*: Although oral fluoropyrimidine prodrugs are increasingly being administered in preference to intravenous nucleoside analogues in cancer chemotherapy, their activation in malignant liver tissue may be insufficient. OGT 719 (1-galactopyranosyl-5-fluorouracil) is a novel nucleoside analogue, preferentially localized in hepatocytes and hepatoma cells via the asialoglycoprotein receptor. The aim of this study was to assess the systemic bioavailability of this rationally designed drug in 16 patients with advanced solid cancers. *Method*: Crossover pharmacokinetic study of oral (400 or 800 mg) and intravenous (250 mg/m^2) OGT 719. *Results*: Linear pharmacokinetics and oral bioavailability of approximately 25% were observed at the dose levels used in this study. Like other 5-FU prodrugs, considerable interpatient variability was observed in bioavailability following oral dosing. The mean half-life for oral doses was 4 h. OGT 719 was well tolerated. No objective tumour responses were demonstrated. *Conclusion*: The systemic bioavailability and half-life of oral OGT 719 are sufficient to merit dose escalation studies with frequent daily dosing. Subsequent efficacy studies should be performed in patients with primary and secondary liver malignancies.

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Introduction

Nucleoside analogues have been used as chemotherapeutic agents against a variety of cancers for several decades. Their mechanism of action is related to their structural similarity to naturally occurring substrates. These agents replace nucleosides in DNA and RNA synthesis, and inhibit enzymes essential to cell metabolism [1]. Current dosing regimens of nucleoside analogues, particularly intravenous (i.v.) regimens of 5-fluorouracil (5-FU), are often limited by systemic toxicities, most notably nausea, mucositis, diarrhoea, neutropenia, and palmar-plantar erythrodysesthesia [1]. Similarly, orally active prodrugs of 5-FU exhibit dose-limiting toxicities, e.g. palmar-plantar erythrodysesthesia with capecitabine and diarrhoea with tegafur (UFT) [2, 3]. There exists a need for orally active nucleoside analogues with lower toxicity.

OGT 719 (1-galactopyranosyl-5-fluorouracil) is a novel nucleoside analogue. It is structurally related to 5-FU, with galactose incorporated onto the fluoropyrimidine moiety of the cytotoxic agent (Fig. 1). OGT 719 was rationally designed to target the asialoglycoprotein (ASGP) receptor found almost exclusively on hepatocytes and hepatoma cells [4], with the intention that its localized activity would reduce the systemic toxicity normally associated with fluoropyrimidines such as 5-FU. The target indications for OGT 719 are therefore primary hepatocellular carcinoma and liver metastases from primary tumours such as colorectal cancer.

Initial in vivo studies have shown intraperitoneal administration of OGT 719 to slow tumour growth and increase survival time in nude mice implanted with human hepatoma xenografts [5]. In a rat sarcoma model, 150 mg/kg per day and 300 mg/kg per day OGT 719 given by continuous infusion into the mesenteric vein proved as effective as 5-FU at 15 mg/kg per day in

reducing tumour burden [6]. In mice, an oral dose of 1500 mg/kg per day inhibited metastatic colorectal cancer growth in the liver by 95% compared with vehicle control, without any observable signs of toxicity [7].

Metabolism studies in the rat and the dog using whole-body autoradiography have shown that OGT 719 given i.v. is rapidly distributed into a volume approximately equal to the extracellular compartment, and is rapidly cleared in the urine [8]. Examination of qualitative distribution following a single i.v. administration of radiolabelled OGT 719 and 5-FU to rats resulted in a relatively higher concentration of radioactivity in the liver following OGT 719 administration, compared to a more generalized distribution after 5-FU administration [8]. OGT 719 has been administered intravenously in mouse and rat species at doses up to 2 g/kg body weight without any toxic effects. In the dog, 250 mg/kg per day for 14 days is the maximum tolerated dose, as determined by the development of liquid faeces. Initial metabolism studies of OGT 719 in the rat suggest that the compound is approximately 20% orally bioavailable [8].

In view of these findings, OGT 719 was selected for clinical studies as a cytotoxic agent potentially similar in antitumour activity to 5-FU but with different patterns of distribution, toxicity and oral bioavailability. The primary aim of this study was to assess the oral bioavailability of OGT 719 in patients with advanced cancer. Secondary objectives included assessments of this novel drug's tolerability and antitumour efficacy.

Patients and methods

Patient selection

Patients were recruited in three UK oncology centres: Glasgow, Leicester and Nottingham. Local ethics committee approval was obtained at each site. Eligibility criteria included: histologically or cytologically confirmed advanced solid tumour for which there was no available established form of therapy; age at least 18 years; ECOG performance score 0, 1 or 2; absolute neutrophil count more than 1.5×10^9/l and platelet count more than 100×10^9/l at screening; adequate renal and liver function; and minimum life expectancy of 8–12 weeks. Major exclusion criteria included patients who had received radiotherapy or chemotherapy within 4 weeks of the screening visit and patients who had previously suffered severe toxicity with a fluoropyrimidine. Written, informed consent was obtained from each patient. Physical examination, vital signs, body surface area calculation, biochemistry, haematology and adverse event assessments were performed prior to each dose and up to 4 weeks after the final study visit.

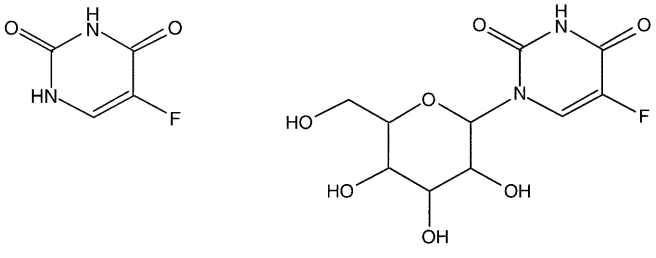

Fig. 1 Chemical Structures of 5-FU and OGT 719 (Oxford GlycoSciences, Abingdon, UK)

Study design

The study was divided into two parts. Part 1 (Table 1) was a crossover pharmacokinetic study of oral and i.v. OGT 719. The time interval between i.v. and oral administration was 2–14 days. The i.v. dose was based on the lowest dosage that gave reproducible pharmacokinetic results in an ongoing dose-escalation trial (Carmichael et al., submitted for publication). The oral doses were calculated from bioavailability data in rodents [6, 7, 8], based on the minimum oral dose that gave reproducible plasma concentrations of OGT 719, and double that dose on the basis of preliminary pharmacokinetic data from the first two patients in this study. Part 2 (Table 2) was a voluntary extension of OGT 719 to offer patients a continuing treatment option. In this part of the study, OGT 719 was administered i.v. weekly until significant adverse events were experienced or disease progression was established. The i.v. dose was based on the highest dose reached safely, at the time of planning the current trial, in a parallel dose-escalation trial which was ongoing (Carmichael et al., submitted).

Administration

The oral preparation was supplied as clear gelatin capsules containing 200 mg OGT 719 as a white powder. Patients fasted for 2 h after a standard hospital breakfast, and the capsules were swallowed with water under medical supervision. OGT 719 was administered i.v. in 250 ml 0.9% w/v sodium chloride solution over 3 h via a peripheral venous cannula, immediately followed by a 25 ml saline flush over 5 min.

Pharmacokinetics

Plasma sampling was performed predose, at 30 min, and at 1, 2, 3, 4, 6, 8, 10, 12, 20 and 24 h after oral dosing. For i.v. dosing, plasma sampling was performed predose, at 1, 2 and 3 h into the i.v. infusion, and at 5, 15 and 30 min, and 1, 2.5, 5, 9, 20 to 24 h after the end of the infusion. Urine was collected predose and from 0 to 4 h, 4 to 12 h, and 12 to 24 h. OGT 719 and 5-FU levels (retention times 18 and 37 min, respectively) were determined by high-pressure liquid chromatography (Rezex monosaccharide column 300×7.8 mm, water mobile phase 0.4 ml/min, injecting volume 0.05 ml) with 220 nm ultraviolet detection, following protein precipitation and solid-phase extraction (Inveresk Research, Tranent, UK). Linearity of the detector response was demonstrated for a concentration range of OGT 719 equivalent to 18–911 μg plasma. Maximum plasma concentration (C_{max}) and time to maximum

Table 1 Study design – part 1: pharmacokinetic assessment

Treatment course	OGT 719 dose 1	OGT 719 dose 2
A	400 mg oral	250 mg/m^2 i.v.
B	250 mg/m^2 i.v.	400 mg oral
C	800 mg oral	250 mg/m^2 i.v.
D	250 mg/m^2 i.v.	800 mg oral

Table 2 Study design – part 2: extension study

	Cohort 1	Cohort 2
Weekly cycles	1000 mg/m^2 OGT 719 i.v.	1750 mg/m^2 OGT 719 i.v.

plasma concentration (t_{max}) were determined for each dose and route of administration. Apparent elimination half-life ($t_{1/2}$) was estimated from natural log2/k, where k is the apparent rate constant of elimination estimated from the slope of the concentration versus time data plotted on a logarithmic scale. AUC from time 0 to infinity ($AUC_{0-\infty}$) was estimated from the sum of the AUC_{0-t} and $C_{t\ last}/k$. AUC_{0-t} was calculated using the trapezoidal rule. Bioavailability was calculated two ways, from the AUC results and from the renal excretion on the assumption that OGT 719 is excreted entirely in the urine.

Results

Patients

Of 16 patients who completed part 1 of the study, 14 continued into part 2. Clinical characteristics are shown in Table 3. A total of 32 evaluable doses were administered in part 1 of the study, and 105 cycles were administered in part 2 (84 at 1000 mg/m^2 and 21 at 1750 mg/m^2).

Pharmacokinetics

All 16 patients received an i.v. dose of 250 mg/m^2, 8 patients received the oral dose of 400 mg and the other 8 patients received the oral dose of 800 mg. The mean plasma concentrations of OGT 719 are shown in Fig. 2. The C_{max} and $AUC_{0-\infty}$ for oral OGT were approximately dose-proportional, showing slightly less than doubling between the 400 mg and 800 mg doses (1.88 and 3.35 μg/ml for 400 and 800 mg, respectively). The C_{max} for the i.v. dose was much higher (16.61 μg/ml), suggesting that the absorption from the oral dose was not high. The mean dose-grouped C_{max}, t_{max}, $AUC_{0-\infty}$ and mean renal clearance values are shown in Table 4. Like other nucleoside analogues [2, 3], the $AUC_{0-\infty}$ values for OGT 719 showed considerable interpatient variability. No significant differences were found in the bioavailability results calculated by the two methods (AUC and urinary excretion), although there was considerable variation between patients. Overall, the bioavailability of oral OGT 719 was around 25%.

Following i.v. administration, peak plasma concentrations were reached approximately 3.3 h after the start of the infusion, and the half-life appeared biphasic. The first phase appeared to be a rapid elimination/redistribution phase, with a half-life of approximately 1.3 h, and the second phase had a half-life of 3.5 h. The majority of the elimination was determined by the shorter half-life. Following oral administration of OGT 719, peak plasma concentrations were lower and were reached later: At approximately 6.0 h for the 400 mg dose and 5.6 h for the 800 mg dose. Elimination was

Table 3 Patient characteristics

	Part 1					Part 2
	Treatment course				Overall	
	A	B	C	D		
Sex						
Male	3	0	1	3	7	6
Female	2	3	2	2	9	8
Age (years)						
Mean ± SD	62.0 ± 5.43	64.3 ± 10.6	64.7 ± 9.0	56.4 ± 11.8	61.2 ± 9.1	60.6 ± 9.6
Range	56–69	53–74	59–75	37–68	37–75	37–75
Race						
White	5	3	3	4	15	13
Mixed race	0	0	0	1	1	1
ECOG at screening						
0	4	2	0	2	8	7
1	1	1	0	2	4	3
2	0	0	3	1	4	4
Primary tumour type						
Colorectal	2	2	0	2	6	5
Pancreatic	1	0	2	2	5	4
Other	1	1	1	1	4	4
Unknown	1	0	0	0	1	1
Metastases						
Liver	3	3	3	4	13	11
Lung	0	1	0	1	2	1
Nodes	0	1	0	2	3	2
Other	0	2	2	1	5	4
Previous chemotherapy						
5-FU	2	1	0	1	4	4
Other	2	1	1	3	7	5
None	1	1	2	1	5	5
Previous radiotherapy	1	0	1	1	3	3
Previous surgery	3	2	2	2	9	8

uniphasic, with half-lives of around 4.2 and 5.4 h for the 400 mg dose and 800 mg dose, respectively. No sequence effects were observed.

Further evidence for two mechanisms of elimination, dependent on plasma concentration of the drug, were provided by the urinary excretion results. Approximately 85% of the administered dose of OGT 719 was eliminated unchanged in the urine after i.v. dosing, but only 2–31% after oral dosing. No quantifiable amount of 5-FU was detected in plasma or urine.

Toxicity and response

OGT 719 was well tolerated at the doses given in this study. There were no drug-related deaths. Although all the patients experienced adverse events during the study, there was no evidence to suggest that their incidence was related to dose or increased with repeated dosing.

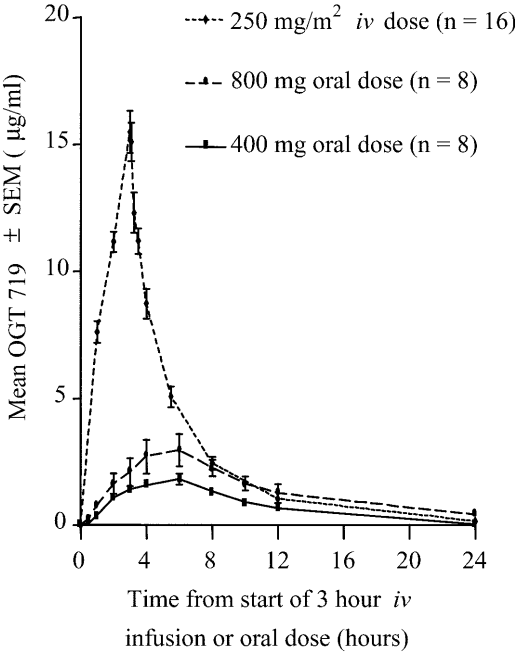

Fig. 2 Mean plasma concentrations of OGT 719 after i.v. and oral administrations

The most frequently occurring adverse event was nausea and the most common adverse events in general were gastrointestinal symptoms (e.g. abdominal pain, vomiting, constipation) and malaise (e.g. lethargy, tiredness, somnolence). Dose-limiting toxicity was observed in only one patient who suffered diarrhoea (NCI CTC grade 3) after an i.v. dose of 1750 mg/m^2.

Of the 16 patients treated with OGT 719 in this study, 8 experienced at least one serious adverse event (SAE). Eight SAEs were attributed to disease progression and one was due to a pneumonia that was unlikely to have been related to treatment. One patient experienced vasculitis of both feet, which resolved on discontinuing OGT 719 and may have been drug-related. One report of anaemia was possibly related to the trial drug, and there were no reports of neutropenia or thrombocytopenia.

No objective tumour responses were demonstrated in this study according to the WHO criteria, although one patient exhibited stable disease at cycle 12 according to definitions in the study protocol (between a 50% decrease and a 25% increase in cross-sectional area of index lesions). This patient received a further four cycles of treatment before withdrawing from the study due to disease progression.

Discussion

The study reported here was the first clinical trial of oral administration of the novel fluoropyrimidine, OGT 719, rationally designed for the treatment of primary or secondary liver malignancies.

Oral administration of 5-FU results in unpredictable and low systemic bioavailability [9], which has been attributed to catabolism of the drug by dihydropyrimidine dehydrogenase [10]. Inactivators of this enzyme have been coadministered with 5-FU, but the occurrence of severe toxicity has limited the clinical utility of this approach [10]. A more successful strategy has been the development of inactive prodrugs of 5-FU, such as the fluoropyrimidine carbamate, capecitabine. Oral administration of this drug results in high levels of 5-FU in colorectal tumour tissue compared to normal surrounding healthy tissue [11]. Unfortunately, such

Table 4 Mean C_{max}, t_{max}, $AUC_{0-\infty}$ and renal clearance values for each treatment group

	Treatment group		
	400 mg oral ($n=8$)	800 mg oral ($n=8$)	250 mg/m^2 i.v. ($n=16$)
C_{max} (µg/ml)			
Mean	1.88	3.35	16.61
Range	0.92–2.68	0.99–5.96	10.40–20.50
t_{max} (h)			
Median	6.04	5.63	3.27
Range	2.62–6.57	4.08–23.50	2.50–4.22
$AUC_{0-\infty}$ (µg·h/ml)			
Mean	18.3	37.9	71.7
Range	6.8–26.4	16.9–58.9	43.8–92.8
Renal clearance (ml/min)			
Mean	69.3	104.4	319.3
Range	30–168	15–173	162–1074

preferential activation does not occur in liver metastasis tissue compared to normal liver [11]. Targeted delivery of OGT 719 via the ASGP receptor, found almost exclusively on hepatocytes and hepatoma cells [4], offers the potential for localized chemotherapeutic activity as an alternative or perhaps a complement to other 5-FU prodrugs.

The bioavailability of oral OGT 719 in this study was approximately 25%. Although low, this is higher than therapeutic doses of 5-FU [9] and capecitabine [2]. However, it remains to be established whether the dose range of OGT 719 used in this study is of chemotherapeutic benefit. The interpatient variability in the pharmacokinetic parameters of capecitabine may be rationalized in terms of differences between individuals in the three metabolic steps required for its activation [11], but no clear explanation exists for such variability in OGT 719 levels observed in this study. The absence of 5-FU in plasma or urine would suggest that the low bioavailability of OGT 719 is more likely to be due to low absorption than first-pass metabolism into 5-FU.

The principal aim of this study was to determine whether OGT 719 represents an attractive candidate for protracted oral administration. In particular, such administration may be of value in patients for whom palliation is the management objective, avoiding hospital visits, pain, and the infectious and thrombotic complications related to indwelling intravenous catheters. Unlike the 5-FU prodrug UFT which can exhibit the onset of toxicity in relatively small dose increments [3], the pharmacokinetics of OGT 719 were not saturable at the dose levels assessed in this study. Whereas the $t_{1/2\alpha}$ for i.v. administration was short (1.3 h), the half-lives for the oral doses averaged approximately 4 h. This is significantly longer than those of 5-FU and capecitabine, and makes OGT 719 a suitable candidate for prolonged three- or four-times daily oral dosage rather than intermittent i.v. bolus administration. Its systemic availability provides the opportunity for prolonged tissue exposure, which may be a more attractive therapeutic option and may reduce the emergence of resistance to 5-FU seen with intermittent exposure [12].

OGT 719 offers the potential for lower toxicity and more selective tumour targeting than existing regimens of i.v. 5-FU and oral prodrugs for primary and secondary liver malignancies. We have shown that its systemic bioavailability following oral dosing in patients is sufficient to consider protracted three- or four-times daily oral dosing. Dose-escalation studies of the tolerability of oral OGT 719 are indicated, including assessments of pharmacokinetics and antitumour efficacy as secondary objectives.

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