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A Phase I Safety and Pharmacokinetic Study of OGT 719 in Patients with Liver Cancer

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OGT 719 (Oxford GlycoSciences, Abingdon, UK) is a novel nucleoside analogue with a galactose molecule attached to a fluorinated pyrimidine. OGT 719 has the capacity selectively to bind to asialoglycoprotein receptors that are found exclusively on hepatocytes and hepatocellular carcinoma (HCC) cells. The aim of this study was to establish the safety and to examine the pharmacokinetics of this novel compound in patients with liver cancer. Fourteen patients received a total of 37 cycles of OGT 719 at four dose levels ([500 mg/m^2 first cycle, 1 000 mg/m^2 subsequent cycles], 1000 mg/m^2, 3 300 mg/m^2 and 7500mg/m^2). OGT 719 was administered as a 3-h intravenous infusion in a 250 ml saline solution, daily for 5 days every 4 weeks. Pharmacokinetic parameters were studied during the first cycle of dose levels 1 and 2 (500 mg/m^2, and 1 000 mg/m^2, respectively). The maximum plasma concentration was attained within 5 min of completing the infusion and almost doubled, dose dependently, with a doubling of the infused dose. The plasma level declined rapidly in a monophasic manner with an elimination half-life of 2.1 and 2.5 h for dose level 1 and 2, respectively. The mean area under the curve ($AUC_{o-t,}$ area under the curve to 24 h; $AUC_{o-\infty,}$ area under the curve to infinity) doubled at the higher dose level. None of the patients had a significant tumor response. Elimination half-life of OGT 719 by 3-h intravenous infusion is short and monophasic. Toxicity was minimal at the highest dose level.

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The hepatic asialoglycoprotein receptor (ASGPR) binds to, and internalizes, circulating glycoproteins that have an exposed N-acetyl galactosamine residue (1). These receptors are found exclusively on the plasma membrane and sinusoidal surface of hepatocytes. Aside from its physiological function, the ASGPR may act as a target for autoimmune disease of the liver (2), and may also be a useful method of achieving liver (hepatocyte) specific drug delivery if the agent in question is tagged with an appropriate residue that can be bound and internalized by the ASGPR.

OGT 719 (Oxford GlycoSciences, Abingdon, UK) is a novel nucleoside analogue rationally designed to allow selective uptake by hepatocytes using this general approach. The molecule achieves hepatic specificity by virtue of a galactose residue that has been incorporated into the cytotoxic agent 5-fluorouracil (5-FU) (Fig. 1). The results of animal studies suggest that selective binding to the ASGPR can enhance uptake and reduce systemic toxicity (3). Once OGT 719 enters hepatocytes, the galactose molecule is cleaved, and the remaining molecule should exert a cytotoxic action similar to that of 5-FU including thymidylate synthase inhibition and nucleoside precursor depletion. In vitro studies on ASGPR-bearing human hepatoma cell lines demonstrate dose-dependent OGT 719 cytotoxicity (4). OGT 719 suppresses tumor growth and improves survival in nude mice with peritoneally xenografted human hepatoma cells (5). In the same model, an oral formulation of OGT 719 inhibited growth of the

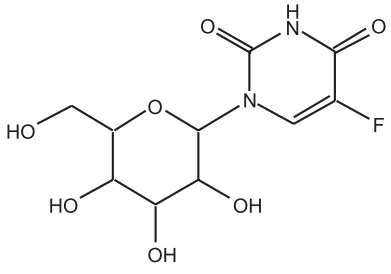

Fig. 1. Chemical structure OGT 719 (Oxford GlycoSciences, Abingdon, UK).

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human colorectal cancer cell line (C170HM2) and reduced development of metastases in the liver (6).

Following intravenous infusion in patients with normal liver function, OGT 719 is rapidly distributed in the extracellular space. Over 80% of the drug is then rapidly eliminated unchanged in the urine (7). Using radiolabelled drug high concentrations of OGT 719 was demonstrated in the liver, suggesting either specific hepatocyte uptake or hepatic catabolism (4). Metabolism of 5-FU also occurs in the liver, and over 80% of 5-FU is eliminated following intravenous administration with a plasma half-life of 6 to 20 min (8). 5-FU degradation is enzyme (dihydropyrimidine dehydrogenase) dependent, and such catabolism may also be inadequate in patients with liver tumors (9). However, despite these theoretical limitations, drug availability, plasma and tissue concentration of 5-FU in patients with hepatocellular carcinoma (HCC) or cirrhosis does not appear to be different from that in patients with normal liver function (10, 11). OGT 719 depends on selective uptake by normal hepatocyte, therefore, the pharmacokinetics of this drug could be different in patients with chronic liver disease.

To verify the above hypothesis we undertook a study of the pharmacokinetics of OGT 719 in patients with both chronic liver disease and liver cancer. We chose patients with HCC because chronic hepatitis B virus infection and cirrhosis are prevalent in this population (12, 13). Unresectable HCC is a fatal illness associated with poor treatment response and short survival. Current systemic therapy including 5-FU, doxorubicin and/or cisplatin can not prolong survival and is associated with significant toxicity (14–16). OGT 719, with its specific target organ uptake, might represent a less toxic alternative. In this study we studied the pharmacokinetics and safety of OGT 719 in patients cirrhosis and HCC.

MATERIAL AND METHODS

Patient selection

Patients with unresectable or metastatic HCC, confirmed by either histology or radiological evidence of a hepatic mass with a serum alpha-fetoprotein (AFP) of 500 ng/ml or more, were recruited. The protocol was approved by the Ethics Committee of the Chinese University of Hong Kong and conducted in accordance with the standards of the International Conference on Harmonization—Good Clinical Practice (ICH-GCP) guidelines, and in accordance with the Declaration of Helsinki. All patients provided informed consent before enrolment in the study. Eligible patients had bi-dimensionally measurable lesions with clearly defined margins with both diameters greater than the distance between cuts of the imaging study; neutrophil count $> 1.5 \times 10^9$/l; platelet count $> 75 \times 10^9$/l; adequate renal (serum creatinine $< 1.5 \times$ the upper limit of normal) and liver function (serum bilirubin $< 2 \times$ the upper limit of normal; albumin > 2.5 g/dl; International Normalized Ratio for Prothrombin Time [INR] < 1.5) and an ECOG performance score of 0, 1 or 2.

Patients were ineligible if they had received any treatment for HCC or experienced abdominal surgery within 4 weeks of the anticipated first study drug administration; if they had ascites that were not manageable using medication alone; if they had unstable or severe concurrent medical conditions or active, uncontrolled infection or were HIV positive. Pregnant or breastfeeding women, or fertile women not willing to exercise adequate contraceptive practice for the duration of the study were also excluded, in keeping with standard clinical trial practice.

Treatment

OGT 719 was administered as a 3-h intravenous infusion in 250 ml saline solution daily for 5 days every 4 weeks (constituting one treatment cycle). The first cohort of 3 patients received OGT 719 at 500 mg/m^2 per day for one cycle and 1 000 mg/m^2 per day for subsequent cycles (dose level 1). The second cohort received OGT 719 at 1 000 mg/m^2 per day (dose level 2) for all cycles. Doses were thereafter escalated to a 3 300 mg/m^2 per day and 7 500 mg/m^2 per day in the third and fourth cohorts. Maximum treatment duration for each patient was up to 6 cycles. Our dose level and escalation scheme is atypical because the pharmacokinetic profile of OGT 719 in patients with hepatic dysfunction was unknown and we were concerned about unforeseen toxicity. The first dose level was set at only 10% of the maximum tolerated dose (MTD) in animal studies. We have conservatively maintained the first two levels at relatively low doses for the pharmacokinetic study and noticed minimal toxicity. Then we increased the dosage closer to the MTD level in animal studies in the third and fourth cohorts and increased the cohort size to 4 patients for better assessment of toxicity.

Sample collection and pharmacokinetic analysis

We collected blood samples (5 ml whole blood in a lithium heparin tube) for pharmacokinetic study from 3 patients at dose level 1 and from 3 patients at dose level 2 on day 1 of the first cycle. Each sample was immediately centrifuged at 4°C for 5 min at 2 000–3 000 r.p.m. Plasma from each tube was transferred into 3 sterile cryotubes and frozen for storage at -20°C. Blood samples were collected in cycle 1 at the following points: 5-min pre-infusion, beginning of infusion, 2 and 1 h during infusion, end of infusion (0 min) 5, 15, 30 min and 1, 2.5, 5, 8 and 24 h after infusion. For all other patients and cycles we collected the trough and peak plasma levels at 5 min before infusion and at the end of infusion on day 1 and day 5, respectively. The samples were sent to Quintiles England Ltd. (Ledbury, UK) for pharmacokinetic analysis.

Pharmacokinetic analysis

The plasma concentration of OGT 719 was determined by high-pressure liquid chromatography. The chromatographic conditions were as follows: Waters Spherisorb column 250×4.6 mm, buffered acetonitrile (0.05 M) mobile phase, flow-rate of 1.0 ml/min, injection volume of 50 l and internal standard 5-FU. Run time was 30 min and the approximate retention times of OGT 719 and the internal standard were 5 and 12 min, respectively. Ultraviolet detection at 266 nm was performed following protein precipitation, solid-phase extraction and sample concentration. The method was validated to determine OGT 719 in human plasma over the concentration range of 1.0 to 100 g/ml. Samples above this concentration range were diluted to the range of the method with water. All results were calculated from peak height ratios that were within the calibration line.

We plotted the data on a concentration-time curve and assessed the following pharmacokinetic parameters: maximum concentration (C_{max}), time after dosing at C_{max} (T_{max}), elimination rate constant (k_e), area under the concentration curve between 0 and last quantifiable time-point (AUC_{0-t}), area under the concentration curve to infinity ($AUC_{0-\infty}$) and elimination half-life ($t_{1/2}$). The elimination half-life was estimated from natural log 2/k and AUC_{0-t} was calculated using the trapezoid rule. The peak and trough values (C_{min} and C_{max}) on days 1 and 5 of each cycle of all patients were also measured. Calculation was based on a single compartment model.

Safety and evaluation

Adverse events were graded according to the NCI Common Toxicity Criteria Version II (CTC). Patients were assessed weekly for documentation of toxicity during chemotherapy. Dose-limiting toxicity (DLT) was defined as CTC grade 3 or above. Patients who experienced DLT had administration of the drug delayed for one week and/or a 25% dose reduction in the subsequent cycle. A serious adverse event (SAE) was defined as one that was life threatening, required prolonged hospitalization, resulted in disability, involved congenital anomaly or resulted in death. All SAEs directly related to OGT 719 were reported to the regulatory authorities and to the ethics committee.

Assessment of tumor response was based on the WHO criteria (17). The alternative efficacy evaluation was serologic tumor marker response including serum AFP and ferritin. Provided serum AFP is > 500 ng/ml at baseline, a reduction of serum AFP or ferritin to less than 50% of the baseline value for at least 4 weeks is considered to represent a partial serological response. Normalization of either tumor marker to less than the upper limit of the reference range lasting for 4 weeks or more was considered a complete serological response.

RESULTS

Between July 1998 and March 2000 we enrolled 14 patients (11 males and 3 females) with a mean age of 62.6 years (range 45–77). Patient characteristics and baseline liver function are summarized in Table 1. All patients were treatment-naïve at enrolment. Three patients were treated at the 500 mg/m^2 level for cycle 1 and 1 000 mg/m^2 OGT 719 for subsequent cycles dose group (level 1), 3 were treated in the 1 000 mg/m^2 OGT 719 for all cycles dose group (level 2), 4 were treated in the 3 300 mg/m^2 OGT 719 for all cycles dose group (level 3) and 4 were treated in the 7 500 mg/m^2 OGT 719 for all cycles dose group (level 4). The mean

Table 1

Patient characteristics and baseline liver function

Patient No.	Sex	Age	Bodyweight (kg)	Body surface area (m^2)	Serum creatinine	Total bilirubin (μmol/L)	Albumin (g/L)	ALT (iu/L)	ALP (iu/L)	INR
1*	M	66	73.5	1.8	111	6	31	41	163	1.03
2*	M	52	51.0	1.53	75	28	36	65	462	1.22
3*	F	46	40.5	1.37	60	10	36	37	200	1.02
4*	M	68	55.5	1.61	112	24	30	49	156	1.22
5*	F	56	46.0	1.42	83	10	35	63	133	1.01
6*	M	45	57.0	1.60	84	23	35	108	201	1.09
7	F	68	41.0	1.26	103	13	39	< 10	121	1.02
8	M	60	62.0	1.74	75	9	30	69	193	1.22
9	M	73	50.3	1.49	103	19	30	35	158	1.13
10	M	61	56.0	1.63	96	16	37	102	166	1.11
11	M	68	58.0	1.66	103	13	41	28	216	1.06
12	M	63	57.0	1.59	81	24	32	383	206	1.24
13	M	73	45.5	1.50	54	20	35	149	300	1.15
14	M	77	64.0	1.64	103	7	33	61	276	1.03

*Subjected to pharmacokinetics profiling.
Normal range: Total bilirubin 1–15 umol/L, albumin 36–48 g/L, ALT 10–58 iu/L, ALP 30–145 (females), 35–105 (males) iu/L, INR 1.0–1.2.

number of cycles administered at each dose level was 2, 3, 2.5 and 3, respectively and the mean cumulative dose for each patient group (levels 1–4) was 7 500 mg/m^2, 15 000 mg/m^2, 41 250 mg/m^2 and 112 500 mg/m^2, respectively. Eight patients discontinued treatment because of unacceptable disease progression; one patient withdrew at the investigator's request (owing to poor compliance) and one withdrew at the patient's own request. The other 4 patients were excluded from the study because of severe adverse events: 1 hepatic rupture, 1 committed suicide and 2 had rapid deterioration of liver function and uncontrolled ascites. All patients were evaluable for safety and response.

Pharmacokinetics

All pharmacokinetic parameters were calculated using actual sampling times as opposed to protocol sampling times. The concentration-time curves of OGT 719 on day 1 following a 3-h infusion to the 6 patients are shown in Fig. 2. The pharmacokinetic parameters of 3 patients receiving OGT 719 at 500 mg/m^2 and the 3 patients receiving 1 000 mg/m^2 are summarized in Table 2. The time taken to attain maximum concentrations in plasma was within 5 min of completion of the infusion at both dose levels. The maximum concentration was dose dependent and almost doubled with a doubling of the infused dose. After the maximum concentration had been reached, the plasma level declined rapidly with a monophasic descending portion. The elimination half-life of OGT 719 was similar at both drug levels investigated, with values of 2.1 and 2.5 h, respectively. The drug was barely detectable in plasma after 24 h. The mean area under the curve (AUC_{o-t}, area under curve to 24 h; $AUC_{o-\infty}$, area under curve to infinity) increased linearly and doubled with doubling of the infused dose. The average distribution volumes were 36.4 and 44.2l for dose levels 1 and 2, respectively The pharmacokinetic profiles of the three patients at dose level 1 were similar. However, the maximum concentration and the mean AUC of one patient at dose level 2 were significant lower than those of the other two patients. As there was no difference in the renal and hepatic function of this patient compared with that of the others, the observation may suggest inter-patient variability.

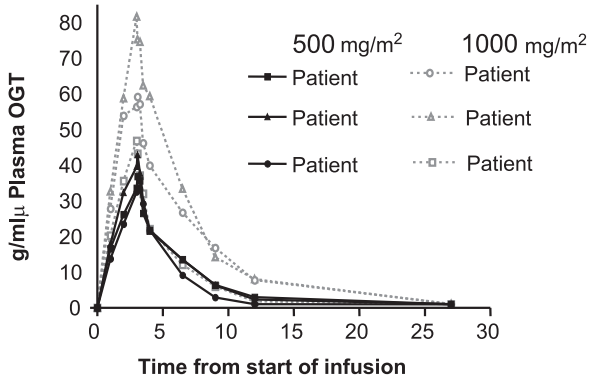

Fig. 2. Concentration time curves of OGT 719 (Oxford GlycoSciences, Abingdon, UK) of patients 1–6.

The trough and peak plasma concentrations were collected on days 1 and 5 of each cycle (Table 3). The mean peak plasma concentrations showed an approximately linear correlation with increasing dose level. Trough plasma concentrations were negligible on days 1 and 5. These findings are compatible with the short elimination half-life of OGT 719. The trough and peak profiles were similar following repeated dosing for up to six cycles of treatment. Peak plasma levels measured on the 1st and 5th days of each treatment cycle showed some variability, but there was no consistent trend indicative of any accumulation. Overall, peak values following the first and last infusion were similar and trough values remained very low throughout treatment.

Safety

OGT 719 was well tolerated up to a dose of 7 500 mg/m^2. The adverse events profile is summarized in Table 4. The drug has minimal bone marrow toxicity. Lymphopenia was noticed at all dose levels but none of the patients required dose adjustment and none of them suffered from infection. The most common non-hematologic adverse event was hepatic dysfunction. Nine patients had raised levels of bilirubin, which was most likely related to disease progression, although we cannot rule out a possible association with the study drug in 5 cases. Other toxicities including malaise, nausea and vomiting were mild and transient. Four patients representing 3 of the 4 dose groups died during the study period. One patient committed suicide and 3 patients died of disease progression (1 ruptured HCC and 2 liver failures); none was related to the study drug.

Tumor response

None of the patients had complete or partial tumor responses. The tumors of 2 patients showed no change, one patient could not be assessed and all the others had tumor progression. For the 5 patients with serum AFP above 500 ng/ml at baseline, no partial or complete serological tumor response was evident. The overall time to disease progression for all dose levels was 92 days.

DISCUSSION

The current study represents the first pharmacokinetic analysis of OGT 719 in patients with cirrhosis and liver cancer. The pharmacokinetic profile of OGT 719 in patients with HCC appears to be similar to that described by Sharma et al. (8), who used a lower dosage of OGT 719 (250 mg/m^2) in patients with other advanced solid tumors and without liver disease. In both studies, plasma levels peaked within minutes of a 3-h intravenous infusion of OGT 719, and thereafter. There was a linear relation between peak

Table 2

Pharmacokinetics parameters

Patient No.	Dosage	C_{max} (μg/ml)	T_{max}	$t_{1/2}$ (hr)	$Vol_{(d)}$	k_e (1/hr)	AUC_{o-t}	$AUC_{o-\infty}$
Patient 1	500 mg/m^2	37	0.08	2.45	35.8	0.283	113.7	105
Patient 2	500 mg/m^2	40	0.08	2.39	36.8	0.291	107.6	100
Patient 3	500 mg/m^2	31	0.08	1.51	36.7	0.460	68.2	70
Mean ± SD	500 mg/m^2	35.8 ± 4.4	0.08	2.11 ± 0.53	36.4 ± 0.6	0.34 ± 0.1	96.5 ± 24.7	91.7 ± 18.74
Patient 4	1000 mg/m^2	59	0.08	3.03	41.0	0.229	245.5	250
Patient 5	1000 mg/m^2	75	0.08	2.43	29.0	0.286	278.3	257
Patient 6	1000 mg/m^2	43	0.08	1.97	62.7	0.351	104.6	98
Mean ± SD	1000 mg/m^2	59.3 ± 16.02	0.08	2.48 ± 0.53	44.21 ± 17.1	0.291 ± 0.06	209.5 ± 92.3	201.8 ± 90.06

Abbreviations: C_{max} = maximum plasma concentration; AUC_{o-t} = area under curve to 24 h; $AUC_{o-\infty}$, area under curve to infinity; $t_{1/2,}$ elimination half life; $k_{e,}$ elimination rate constant.

concentration and infused dose. By 24 h from the end of infusion, almost all OGT 719 disappeared from the plasma. It thus appears that the pharmacokinetic profile of OGT 719 is not significantly altered in patients with cirrhotic liver. The catabolic pathway for elimination of 5-FU, the fluorinated pyrimidine that is structurally related to OGT 719, occurs in the liver but also, particularly after intravenous injection, in the lungs and kidney (11). The inactive metabolite, dihydrofluorouracil, appears in plasma within minutes of an intravenous bolus injection of 5-FU. Thus approximately 60–90% of the administered drug is excreted as metabolites in the urine and less than 10% is excreted as the parent compound. In marked contrast, over 80% of OGT 719, when given as an intravenous infusion, was excreted unchanged in the urine (8) suggesting that the addition of the galactose residue inhibited catabolism at all sites and that hepatic drug uptake was not extensive.

OGT 719 is minimally toxic at the fourth dose level. However, the study was terminated owing to lack of cytotoxic activity and slow accrual. Despite the lymphopenia that occurred at all dose levels none of the patient has suffered from sepsis. Bone marrow suppression and mucositis are the most common toxicities associated with 5-FU. We observed only mild myleosuppression from OGT 719. Cytotoxicity with respect to both normal and malignant cells was thus minimal. This finding may be explained by inadequate dosage, an inappropriate method of administration that results in a subtherapeutic serum drug level or true, targeted tumor selectivity. Our initial dosage of OGT 719 at 500 and 1 000 mg/m^2 was probably too low for

Table 3

Peak and trough plasma concentration (g/ml) of OGT 719 at repeat cyclical dosing

Dose level	Sample	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6	
		D 1	D 5	D 1	D 5	D 1	D 5	D 1	D 5	D 1	D 5	D 1	D 5
Level 1													
	Trough	0.0	0.0	0.0	2.0	0.0	1.3	0.0	3.9				
	Peak	32.1 (n = 3)	35.6	56.0 (n = 1)	66.6	64.7 (n = 1)	57.0	67.2 (n = 1)	54.1				
Level 2													
	Trough	0.0	1.2	0.0	0.8	0.0	1.9	0.0	1.7	0.0	1.8	0.0	2.2
	Peak	61.6 (n = 3)	62.5	52.7 (n = 2)	56.3	64.8 (n = 1)	78.0	82.3 (n = 1)	81.3	70.1 (n = 1)	69.3	62.9 (n = 1)	74.0
Level 3													
	Trough	0.0	7.1	0.0	5.1	0.0	7.7						
	Peak	240.1* (n = 4) (*n = 3)	717	221.9 (n = 3) (*n = 2)	208.8*	227.6 (n = 3)	231.1						
Level 4													
	Trough	0.0	6.8	0.0	7.5	0.0	11.7	0.0	17.2	0.0	13.0	0.0	22.8
	Peak	527 (n = 4)	457.7	431.1 (n = 3)	376.7	517.7 (n = 2)	424.5	511.2 (n = 1)	470.6	533.1 (n = 1)	522.9	482.3 (n = 1)	432.4

Abbreviation: D = day.
*Quality of one of the serum samples was inadequate for analysis.

Table 4

Adverse event profile

Grade	Dose level 1 (n = 3)		Dose level 2 (n = 3)		Dose level 3 (n = 4)		Dose level 4 (n = 4)	
	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4
Anemia	0	1	0	1	0	0	0	0
Lymphopenia	3	1	3	3	4	2	2	4
Thrombocytopenia	1	0	0	0	0	0	2	0
Nausea	0	0	0	0	2	0	1	0
Vomiting	0	0	1	0	1	0	1	0
Diarrhea	1	0	0	0	0	0	1	0
Stomatitis	1	0	0	0	0	0	0	0
Elevated Bilirubin	1	0	0	2	0	3	0	3
Elevated AST/ALT	0	1	0	1	0	1	0	0
Elevated ALP	0	0	0	1	0	0	0	0
Edema	1	0	2	0	0	0	0	0
Malaise	0	0	2	0	1	0	1	0

induction of tumor response. Even at a higher dosage the 3-h daily infusion may have failed to achieve a drug level that allows for hepatocyte uptake. The negligible trough level observed on day 5 of infusion and short elimination half-life suggested that the 3-h infusion might not be the best mode of administration. We speculate that continuous intravenous infusion may result in a more stable serum drug level that allows maximum duration of drug exposure to hepatocytes. True tumor selectivity may be possible and the lack of tumor response could be explained by insensitivity of hepatocellular cancinoma cells to 5-FU.

Other possible explanations for lack of clinical efficacy relate to the expression of ASGPR in HCC. Trere et al. performed immunohistochemical staining with anti-ASGPR monoclonal antibody on needle biopsies of 60 patients with HCC and reported only 33 cases with clear presence of ASGPR on the plasma membranes of cancer cells (18). Expression also varied with the degree of tumor differentiation and tumor size, an observation also made by Hyodo et al. (19). Eighty percent of well-differentiated HCCs had clear expression of ASGPR while only 20% of the poorly differentiated HCCs had a similar expression. Furthermore, the detection of receptors on plasma membranes does not necessarily imply that they are functional.

In conclusion, we found that there was no difference between the pharmacokinetics of OGT 719 in patients with HCC and that in patients without liver disease. Although anti-tumor activity against HCC is minimal, this could partly be due to the method of administration.

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