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ORIGINAL ARTICLE

A phase I trial of lomeguatrib and irinotecan in metastatic colorectal cancer

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Abstract
Background Expression of the DNA repair protein O^6-methylguanine-DNA methyltransferase (MGMT) correlates with resistance to irinotecan in colorectal cancer cell lines. This phase I study evaluated the maximum tolerated dose (MTD) of lomeguatrib, an inactivating pseudosubstrate of MGMT, in combination with irinotecan in patients with metastatic colorectal cancer and assessed the safety, toxicity and clinical pharmacology of combination treatment.
Patients and methods Patients with metastatic colorectal cancer received lomeguatrib (10–80 mg PO) on days 1–5 with irinotecan (250–350 mg/m^2 IV) on day 4 of a 21-day cycle.
Results Twenty-four patients, pre-treated with a median of 2 lines of chemotherapy, received 104 cycles of treatment. The MTD was defined as 80 mg/day lomeguatrib with 300 mg/m^2 irinotecan. The main toxicities observed were neutropaenia and diarrhoea. Lomeguatrib of 80 mg/day produced complete MGMT depletion in all available peripheral blood mononuclear cells (PBMCs) and paired tumour biopsies (one patient). There was no pharmacokinetic interaction between the drugs. In 22 patients assessable for tumour response, one achieved a partial response and 16 had stable disease.
Conclusion This study defined a tolerable dose of irinotecan in combination with lomeguatrib in patients with metastatic colorectal cancer. Combination treatment gave a similar response rate to irinotecan monotherapy in this heavily pre-treated patient group.

Keywords Lomeguatrib · Irinotecan · Colorectal cancer · Phase I trial · O^6-methylguanine-DNA methyltransferase · DNA repair

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Background

A third of patients with colorectal cancer present with metastatic disease which, except for a small subset with isolated hepatic involvement, cannot be cured by surgery. For all other patients, treatment is palliative and involves systemic chemotherapy, possibly with additional local measures such as surgery, ablation or radiotherapy.

Irinotecan, a camptothecin derivative, acts by inhibiting topoisomerase I and has activity in stage 4 colorectal cancer in combination with fluoropyrimidines or as monotherapy [1–4]. Sequential use of chemotherapies and targeted agents has improved median survival in metastatic colon cancer to more than 20 months, but response rates for second- and third-line treatments remain low [5].

Treatment with irinotecan might be improved by targeting specific mechanisms of cellular drug resistance. Preclinical data indicate that the DNA repair protein O^6-methylguanine-DNA methyltransferase (MGMT) may be one such target. MGMT expression was closely correlated with sensitivity to irinotecan and its active metabolite SN-38 in a panel of 17 cell lines including 4 colorectal cancer lines [6]. Furthermore, inactivation of MGMT by the pseudosubstrate O^6-benzylguanine (O6-BG) enhanced irinotecan activity. Increasing *MGMT* expression by transfection decreased sensitivity to irinotecan and SN-38, whereas reduced *MGMT* expression sensitised cells to the topoisomerase I inhibitor.

Lomeguatrib is an orally bioavailable inactivator of MGMT. Regimens combining lomeguatrib with temozolomide, an O^6-alkylating agent, have been evaluated in melanoma and colorectal cancer, but results have been disappointing [7–9]. In the present report, we sought to establish the potential for lomeguatrib to enhance the activity of a different class of chemotherapeutic agent. Lomeguatrib was administered daily for 5 days, as previously used [7–9], with a single dose of irinotecan given on day 4. This dosing regimen was chosen to reflect previous dosing schedules with both agents and to administer irinotecan in the context of MGMT depletion, as well as ensure that depletion persisted for a further 24 h.

The primary aim of this study was to define the maximum tolerated dose (MTD) of lomeguatrib in combination with irinotecan in patients with metastatic colorectal cancer. Secondary objectives included assessing the efficacy, safety, toxicity and clinical pharmacology of combination treatment.

Patients and methods

Inclusion and exclusion criteria

Individuals over the age of 18 with stage 4 histologically confirmed colorectal cancer deemed to have the potential for clinical benefit from treatment and with a life expectancy of at least 12 weeks were eligible for the study, designated PAT103. ECOG performance status of 2 or better, adequate hepatic (AST or ALT levels $\leq$2.5 $\times$ upper normal limit (ULN) and total bilirubin levels $\leq$1.5 $\times$ ULN), renal (serum creatinine $\leq$1.5 $\times$ ULN) and bone marrow function (absolute neutrophil count $\geq$1,500/mm^3 and platelet count of $\geq$100,000/mm^3) were required.

Patients were excluded if they had recent major thoracic or abdominal surgery; chemotherapeutic or investigational agents, or radiotherapy in the preceding 4 weeks; mitomycin C or nitrosureas within previous 6 weeks; an active infection or significant non-malignant intercurrent illness; known central nervous system metastases; a history of seizures; unresolved gastrointestinal symptoms; were pregnant or lactating; were serologically positive for hepatitis B, hepatitis C or HIV; were unable to swallow capsules; or were receiving concurrent antacid medication. A negative serum pregnancy test was required in women with childbearing potential, and all patients were required to use medically approved contraceptive precautions during the study and for 4 weeks afterwards.

The study was conducted in accordance with the Principles of the International Conference on Harmonisation of Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by an independent ethics committee, according to UK and local requirements. All patients enrolled in the study gave informed written consent.

Treatment

Lomeguatrib (supplied by KuDOS Pharmaceuticals Ltd, Cambridge, UK) was orally administered at a starting dose of 10 mg/day in the evening on days 1–5 of each treatment cycle, with the patient fasting for 2 h before and after dosing. In the absence of dose-limiting toxicity, lomeguatrib was escalated by 100% in successive patient cohorts to a maximum of 80 mg/day.

Irinotecan (Rhone-Poulenc Rorer, Vitry-sur-Seine, France) was administered by intravenous infusion over 90 min on the morning of day 4 at a starting dose of 350 mg/m^2. Early results mandated a reduction in the irinotecan dose to 250 mg/m^2, with the option to increase to 300 mg/m^2 if the lower dose proved tolerable with 80 mg/day lomeguatrib. Cycles were repeated every 21 days, with a total of 6 cycles planned. Concomitant treatment with cytochrome P450 inducers during the study period was not permitted.

A treatment delay of up to 2 weeks was allowed for the resolution of drug-related toxicity to grade 1. Dose reduction in irinotecan was permitted in this event or in the event of a dose-limiting toxicity (DLT) in the preceding cycle. Patients could be withdrawn from the study for progressive disease, unacceptable toxicity, serious violation of the study protocol or withdrawal of consent.

At least three patients were treated at each dose level, and any patient withdrawn before day 21 was replaced. The first patient at each dose level was observed for at least 1 week following irinotecan administration, i.e. day 11, before enrolment of subsequent patients at that dose level. All three patients at a dose level were required to complete one treatment cycle before a decision to dose escalate lomeguatrib or irinotecan could be made. DLT was defined as any of the following study drug-related events experienced during cycle 1: grade 4 haematological toxicity lasting

>5 days; grade 3 or 4 febrile neutropaenia; grade 3 or 4 non-haematological toxicity including diarrhoea, nausea or vomiting despite adequate treatment. Patients were followed up for 30 days after the last dose of study drug. If one of three patients at a dose level developed a DLT, up to three additional patients were treated at that dose level. If one of the three additional patients developed a DLT, dose escalation ceased and a total of six patients were treated at the preceding dose level. This lower dose was defined as the maximum tolerated dose (MTD) unless ≥2 of 6 patients developed a DLT.

Toxicity and response evaluation

Pre-treatment evaluations included a complete medical history and physical examination, full blood count, biochemical profile including carcinoembryonic antigen (CEA), urinalysis and electrocardiogram. CT scans were performed to evaluate tumour sites, using RECIST, prior to commencing treatment, after two complete cycles, and at the end of six cycles of treatment. Toxicities were evaluated at least weekly during the study period, and toxicities graded according to the National Cancer Institute Common Toxicity Criteria version 2.

Pharmacodynamics

Blood samples for peripheral blood mononuclear cell (PBMC) isolation and MGMT assessment were obtained prior to treatment on day 1 of cycle 1, prior to irinotecan dosing on day 4 and at the end of treatment, on day 6. Eight millilitres of blood was taken in each of two tubes containing 320 μmol EDTA. Optional tumour core biopsies were obtained on day 1 pre-treatment and post-treatment on day 6. Tumour biopsies were taken under local anaesthetic, immediately frozen on dry ice and stored at −70°C before determination of MGMT activity according to the method of [10].

Pharmacokinetics

Five millilitres of venous blood was drawn into lithium heparin vacutainers for the determination of lomeguatrib and 8-hydroxy-lomeguatrib concentration immediately prior to the start of the irinotecan infusion (approximately 12 h after the day 3 dose of lomeguatrib). Venous blood samples were also collected prior to the start of the irinotecan infusion, and immediately, 30 min, 1, 2, 4, 6–8 and 24 h after the end of infusion to quantify plasma levels of irinotecan and its major circulating metabolite SN-38. Plasma drug concentrations were determined by high performance liquid chromatography with tandem mass spectrometric detection (HPLC–MS-MS). Data collection and peak area integration were performed using Analyst software (version 1.3.1) associated with the mass spectrometer. Standard regression and quantification were performed using Watson LIMS (version 7.0).

Results

Twenty-five patients were enrolled in the study at two centres. One patient, enrolled into cohort 1, withdrew his consent prior to receiving treatment. The characteristics of the other 24 patients are summarised in Table 1. All patients had received previous chemotherapy (median 2 lines). All 24 patients were evaluable for toxicity following treatment with lomeguatrib and irinotecan, and 22 were evaluable for tumour response.

Dose escalation and extent of exposure

Two of the three patients treated in cohort 1 with irinotecan 350 mg/m^2 and lomeguatrib 10 mg/day experienced grade 3 diarrhoea. One of these patients was admitted as an emergency with a 3-day history of severe diarrhoea, having ignored instructions to contact the study centre in that event, and grade 4 neutropaenia. Despite aggressive resuscitation, the patient died from presumed neutropaenic sepsis. For subsequent cohorts, 250 mg/m^2 irinotecan was given with escalating lomeguatrib doses (cohorts 2, 3, 4 and 5) and escalated to 300 mg/m^2 at the highest lomeguatrib dose (cohort 6, see Table 2). One further dose-limiting toxicity was observed in the study: one of three patients in cohort 4 (lomeguatrib 40 mg and irinotecan 250 mg/m^2) had grade 4 neutropaenia for more than 5 days resulting in the expansion of the cohort to 6 patients with no additional

Table 1 Patient demographics

Number of patients	24
Median age (range)	62.5 (40–75)
Gender (male/female)	15/9
PS (0/1)	21/3
Extent of disease	
1 organ involved	4
2	9
≥3	11
Liver	20
Lung	19
Other viscera	15
Prior chemotherapy	
Irinotecan-based	11
Oxaliplatin and 5-FU/capecitabine	21
5-FU/capecitabine	10

Table 2 Drug doses for each cohort

Cohort	Irinotecan dose (mg/m^2)	Lomeguatrib dose (mg/day)	Number of patients
1	350	10	3
2	250	10	3
3	250	20	3
4	250	40	6
5	250	80	3
6	300	80	6

DLTs. The MTD for the combination was determined to be 300 mg/m^2 irinotecan with 80 mg/day lomeguatrib.

A total of 104 cycles (median 6 cycles per patient) of lomeguatrib and irinotecan were administered across the study. In keeping with the protocol, there were no dose reductions in lomeguatrib, but five patients required irinotecan dose reductions of 50 mg/m^2 (in two patients, two dose reductions were needed) for haematological toxicity and/or diarrhoea. Four treatment cycles were delayed to allow for the recovery of neutropaenia.

Safety

Adverse events were as anticipated for irinotecan (Table 3). The most significant toxicities were neutropaenia and diarrhoea, although nausea, fatigue, anorexia and alopecia were common. Neutropaenia was recorded in a third of treatment cycles, but was of grade 3 or 4 severity in only three patients. There was one episode of neutropaenic sepsis (as described above) and one of febrile neutropaenia without sepsis. Diarrhoea occurred in 46% of cycles, affecting four-fifths of the patients, but was grade 3 or 4 severity in only five individuals. No significant cumulative toxicities were seen, and toxicities all resolved on cessation of treatment.

Efficacy

Two patients were not evaluable for response since they did not complete cycle 1 of treatment. One partial response was documented, and 16 patients had stable disease, with the other five progressing on treatment. The partial response was seen in an irinotecan-naïve patient, previously treated with oxaliplatin-based therapy. Median time to progression was 4.0 months (range 1.2–16.2 months). Median overall survival was 5.4 months (0.4–16.2 months).

Pharmacokinetics

Lomeguatrib plasma concentration 12 h after dosing on day 3 was available for 21 of the 24 patients. This confirmed no detectable lomeguatrib at the time of irinotecan administration. Irinotecan and SN-38 plasma concentrations were obtained for 22 of the patients (Table 4). Maximum plasma concentrations were seen at the end of infusion after which concentrations declined in a biphasic fashion. The terminal half-life of irinotecan was 5–7 h, but it was not possible to derive the terminal half-life for SN38.

Pharmacodynamics

MGMT activity was detectable in the 22 available pre-treatment PBMC samples; mean activity 11.7 fmol/μg DNA (range 6.2–22.9 fmol/μg DNA) but not detectable in any of the 17 pre-irinotecan (day 4) or 13 end of treatment

Table 3 Commonest treatment-related toxicities

Irinotecan dose	All adverse events				Grade 3/4 adverse events
	Total $N = 24$ (%)	350 mg/m^2 $N = 3$ (%)	250 mg/m^2 $N = 15$ (%)	300 mg/m^2 $N = 6$ (%)	All $N = 24$ (%)
Neutropaenia	5 (21)	2 (67)	2 (13)	1 (17)	3 (13)
Anaemia	6 (25)	1 (33)	5 (33)	0	1 (4)
Nausea	11 (46)	2 (67)	7 (47)	2 (33)	
Vomiting	9 (38)	1 (33)	4 (27)	4 (67)	2 (8)
Constipation	4 (17)	1 (33)	3 (20)	0	
Diarrhoea	19 (79)	2 (67)	12 (80)	5 (87)	5 (21)
Fatigue	16 (67)	2 (67)	11 (73)	3 (50)	2 (8)
Cough	4 (17)	0	3 (20)	1 (17)	
Anorexia	11 (46)	2 (67)	6 (40)	3 (50)	
Headache	7 (29)	0	5 (33)	2 (33)	
Fever	4 (17)	0	4 (27)	0	
Abdominal pain	8 (33)	1 (33)	5 (33)	2 (33)	
Alopecia	20 (83)	3 (100)	13 (65)	8 (89)	

Adverse events considered possibly, probably or highly probably related to treatment occurring in 15% or more patients

Table 4 Derived pharmacokinetic parameters for irinotecan and SN-38

Irinotecan dose	250 mg/m^2 (N = 14)		300 mg/m^2 (N = 5)		350 mg/m^2 (N = 3)	
	Irinotecan	SN-38	Irinotecan	SN-38	Irinotecan	SN-38
C_{max} (ng/ml) (CV%)	2,530 (28)	40.9 (53)	3,510 (32)	35.7 (60)	4,190 (34)	36.7 (38)
T_{max} (h) (range)	1.72 (1.53–2.65)	1.72 (1.53–2. 58)	1.68 (1.65–2.33)	1.76 (1.67–2.67)	2.37 (1.80–2.38)	1.87 (1.80–1.90)
AUC0-t (ng.h/ml) (CV%)	14.9 (32)	260.9 (62)	17.4 (12)	303.5 (62)	33.5 (52)	395.3 (38)

C_{max} peak plasma concentration, T_{max} time to peak plasma concentration, AUC area under plasma concentration–time curve, CV coefficient of variation

(day 6) samples. Similarly, MGMT activity was detected in the single pre-treatment tumour biopsy (6.9 fmol/μg DNA), but not in the corresponding end of treatment sample.

Discussion

The patients treated in this study, a representative population in terms of their age, performance status and prior therapies, did not tolerate the standard irinotecan dose of 350 mg/m^2 when combined with 10 mg/day lomeguatrib, indicating a biological effect of the latter agent. Irinotecan at 250 or 300 mg/m^2 was well tolerated across a range of lomeguatrib doses including at 80 mg/day, a dose which has been shown reliably to deplete colorectal tumour MGMT [11].

T_{max} and C_{max} for irinotecan and SN-38 were consistent with prior studies, indicating no interaction between lomeguatrib and irinotecan [12]. The area under the concentration–time curve for both irinotecan and SN-38 was lower than some previous reports, but this is a consequence of the reduced duration of sampling in our study—as has been described previously [13].

The spectrum of toxicities observed was as expected for irinotecan. The incidence of grade 3 and 4 diarrhoea was very similar to that previously reported with single-agent irinotecan in metastatic colorectal cancer, affecting 21% of patients compared with 21 and 22% [14, 15]. Once the dose of irinotecan was reduced, the incidence of grade 3 or 4 neutropaenia, at 10%, was lower than that previously reported for irinotecan alone, at 22 and 14%. The inability to combine irinotecan at full dose with lomeguatrib was not surprising, as the latter has been reported to increase haematological toxicity when used in combination with other myelotoxic chemotherapeutic agents [7]. Complete inactivation of PBMC MGMT was seen at the lowest lomeguatrib dose administered. Since expression of the repair protein in PBMCs is very similar to that in myeloid precursor cells, this could explain why increasing doses of lomeguatrib were not associated with increasing myelotoxicity. In general, haematological and non-haematological side effects were readily managed and despite these toxicities, compliance with treatment was good with only one patient discontinuing treatment due to unacceptable side effects. No lomeguatrib-specific toxicity was encountered.

Combination treatment with irinotecan and lomeguatrib yielded only one partial response. These patients had all received prior chemotherapy with a median 2 (range 1–6) regimens. Eleven (46%) had previously been treated with irinotecan. The responding patient was irinotecan naïve, so evidence for the reversal of resistance to the topoisomerase inhibitor was not seen. In this setting, in which most patients were receiving third-line treatment, a response rate of 4–6% would be expected, equivalent to one responder in a study of this size [4]. Thus, lomeguatrib did not appear to improve patient outcomes, but this might better be assessed in patients receiving irinotecan as part of first- or second-line treatment.

The MTD was defined as irinotecan 300 mg/m^2 with lomeguatrib 80 mg/day for 5 days. It might be possible to escalate the dose of lomeguatrib used in combination with irinotecan further. However, a single dose of 80 mg lomeguatrib inactivated over 96.5% of MGMT in colorectal tumours at 12 h [11], so that one might reasonably anticipate complete depletion of MGMT in tumour at the time irinotecan was administered in this study. Greater duration of MGMT depletion, so as to ensure no recovery in MGMT activity before replication, might also be considered. However, such prolonged lomeguatrib administration was associated with much greater myelotoxicity, without improvement in efficacy, when combined with temozolomide [16]. This might not be the case with irinotecan since topoisomerase I inhibitors do not generate DNA alkylation damage.

Addition of a methylating agent, such as temozolomide, to combination treatment with lomeguatrib and irinotecan could also be explored. Pre-clinical data show that treatment with an O^6-alkylating agent prior to irinotecan increases its cytotoxicity in a schedule-dependent manner [17, 18]. The basis of this effect is an enhancement in topoisomerase I-mediated DNA strand cleavage in the presence of O^6-methylguanine and a decreased rate of religation.

O^6-alkylating agent therapy, therefore, induces topo1-DNA cleavage complexes. Such complexes are susceptible to trapping by topoisomerase I inhibitors resulting in DNA damage, which is ultimately cytotoxic. The presence of O^6-methylguanine in DNA enhances topoisomerase I inhibitor cytotoxicity. Depletion of MGMT, which repairs O^6-methylguanine, considerably enhances the cytotoxicity of topoisomerase I inhibitors in cells. This enhancement appears to be independent of the cytotoxicity of the DNA lesion itself, in that it is observed in mismatch repair-deficient (i.e. O^6-methylguanine tolerant) cells. The effect of MGMT on this interaction has not yet been fully elucidated, but in vitro studies have shown that adding O^6-benzylguanine to combination treatment with temozolomide and irinotecan results in a significant reduction in the growth of human tumour xenografts compared with either temozolomide or irinotecan alone or together [19].

A number of clinical studies have reported disappointing results for O^6-alkylating agent and irinotecan combination treatment, with no improvement in the efficacy of irinotecan alone, but these have used regimens in which the topoisomerase inhibitor was given first [20, 21]. More encouraging results have been seen when drug scheduling is optimised in accordance with pre-clinical data, and the alkylating agent is administered prior to irinotecan. For example, in a phase I study in recurrent malignant glioma, patients were given temozolomide (days 1–5) and then irinotecan (day 6), and 10 of 32 (31%) achieved a complete or partial response [22].

Although responses to high-dose therapy with the chloroethylating agent BCNU have been reported in patients with metastatic colorectal cancer [23], combination treatment with lomeguatrib and temozolomide was found to be ineffective in this patient group [8]. Temozolomide may still have a role in colorectal cancer chemotherapy through the effects of O^6-methylguanine on topoisomerase I activity and the efficacy of irinotecan as described earlier. However, given the overlapping toxicity profiles for temozolomide and irinotecan, in particular haematological toxicity, any future studies will require careful design.

In conclusion, this phase I study successfully identified doses of lomeguatrib and irinotecan for use in combination therapy in patients with metastatic colorectal cancer. While the focus of colorectal cancer systemic therapy has now shifted towards integration of targeted biological agents with cytotoxic chemotherapy, exploration of this novel regimen could be considered in patients receiving first- or second-line irinotecan.

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