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SHORT COMMUNICATION

A dose finding and pharmacokinetic study of capecitabine in combination with oxaliplatin and irinotecan in metastatic colorectal cancer

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Abstract
Purpose The GONO-FOLFOXIRI regimen demonstrated higher activity and efficacy than FOLFIRI in metastatic colorectal cancer patients. The aim of this study was to determine the maximum tolerated dose of capecitabine, in substitution of 5-fluorouracil, combined with oxaliplatin and irinotecan and to evaluate the pharmacokinetics of the drugs.
Patients and methods We treated 15 patients with escalating doses of capecitabine (from day 1 to 7) and fixed doses of oxaliplatin (85 mg/m^2) plus irinotecan (165 mg/m^2) (both administered on day 1), repeated every 2 weeks. Pharmacokinetic analysis was performed on plasma samples collected at the first cycle of treatment.
Results The maximum tolerated dose of capecitabine resulted 2,000 mg/m^2/day, with diarrhea being the only dose-limiting toxicity. Large interpatient variability in the pharmacokinetic parameters of investigated drugs was observed. Results in terms of activity are promising.
Conclusions At the maximum tolerated dose of capecitabine of 2,000 mg/m^2/day the combination is feasible with promising activity and deserves further investigations.

Keywords Metastatic colorectal cancer · Capecitabine · Oxaliplatin · Irinotecan · Triplet regimen · Dose finding

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Introduction

In the setting of unresectable metastatic colorectal cancer (mCRC) the best outcome is achieved in patients receiving fluoropyrimidines, oxaliplatin (LOHP) and irinotecan (CPT-11) in the course of their disease [1]. However, in a sequential strategy 25–50% of patients cannot receive second-line chemotherapy; therefore, if feasible and tolerable, the best way to expose all patients to all the three most active agents might be to administer them up-front.

Phase I–II studies demonstrated the feasibility and the promising activity of biweekly 5-fluorouracil (5-FU) infusion combined with LOHP and CPT-11 in this setting [2, 3]. A phase III study conducted by the GONO group comparing FOLFOXIRI (CPT-11 165 mg/m^2, LOHP 85 mg/m^2 and leucovorin 200 mg/m^2 day 1, 5-FU 3,200 mg/m^2 48-h continuous infusion starting on day 1, every 2 weeks) to FOLFIRI demonstrated that FOLFOXIRI was feasible with manageable toxicities and significantly improved response

rate (RR) (66 vs.41%; $P = 0.0002$), progression-free survival (PFS) (9.8 vs. 6.9 months; $P = 0.0006$) and overall survival (OS) (22.6 vs. 16.7 months; $P = 0.032$). The FOLFOXIRI regimen increased also the rate of radical surgical resections of metastases in initially unresectable patients (15 vs. 6%; $P = 0.033$) [4].

Several studies demonstrated that capecitabine, an oral fluoropyrimidine, is as effective as 5-FU and better tolerated [5, 6]. The oral administration can simplify the treatment regimen and reduce the complications related to the central venous catheters. In particular, a biweekly days 1–7 schedule of capecitabine has promising activity and a favorable toxicity profile also in combination with either LOHP or CPT-11. A phase II randomized trial by Scheithauer et al. [7] demonstrated that a dose-intensified bimonthly combination of capecitabine 3,500 mg/m^2/day days 1–7 and LOHP 85 mg/m^2 day 1 every 2 weeks is as safe and feasible as the combination of capecitabine 2,000 mg/m^2/day days 1–14 and LOHP 130 mg/m^2 day 1 every 3 weeks, with higher RR (54.5 vs. 42.2%) and PFS (10.5 vs. 6.0 months).

Therefore, moving from the biweekly GONO-FOLFOXIRI regimen, we designed the present dose finding trial to evaluate the feasibility of a three-drug regimen by substituting 5-FU with capecitabine (XELOXIRI). In particular, our objective was to determine the recommended dose (RD) of capecitabine in combination with fixed doses of CPT-11 and LOHP, as used in the GONO-FOLFOXIRI regimen, to evaluate the pharmacokinetics of investigated drugs and to preliminary assess the activity of this regimen as first-line treatment of mCRC patients.

Patients and methods

Patients selection

Patients with unresectable metastatic colorectal adenocarcinoma were eligible for the trial. Main selection criteria were: age 18–75 years, ECOG PS $\leq$2, PS = 0 in patients aged 71–75 years, measurable disease (RECIST criteria), adequate bone marrow, kidney and liver functions, previous fluoropyrimidine-based adjuvant chemotherapy ended >6 months before study enrollment, no previous palliative chemotherapy, no previous chemotherapy including CPT-11 or LOHP, no symptomatic cardiac disease or myocardial infarction in the last 24 months or uncontrolled arrhythmia, active infections, inflammatory bowel disease and no total colectomy. The study was conducted in accordance to Helsinki declaration and to Good Clinical Practice guidelines. Patients provided their written informed consent before registration. The protocol was approved by the Ethics Committee of all participating institutions.

Study design and treatment schedule

Treatment consisted of fixed doses of CPT-11 (165 mg/m^2 intravenous over 1 h) immediately followed by LOHP (85 mg/m^2 intravenous over 2 h) on day 1 (as used in the GONO-FOLFOXIRI regimen), in association with variable doses of capecitabine (orally from day 1 to 7, starting from the evening of day 1). We defined as dose-limiting toxicity (DLT) any National Cancer Institute-Common Toxicity Criteria (NCI-CTC vers. 3.0) grade 3–4 non-hematological toxicity, except for alopecia, nausea and vomiting, any grade 4 neutropenia lasting more than 5 days and grade 4 neutropenia associated with fever $\geq$38°C and any grade 4 thrombocytopenia occurring during the first two cycles of treatment. We treated consecutive cohorts of three to six patients with escalating doses of capecitabine: the starting dose of capecitabine was 2,500 mg/m^2/day. The dose was increased to 3,000 mg/m^2/day if <2 DLTs out of three to six patients were observed; if $\geq$2 DLTs were observed, capecitabine dose was reduced to 2,000 mg/m^2/day. At this dose level, if we still observed $\geq$2 DLTs out of three to six patients, a reduction of CPT-11 dose to 150 mg/m^2 was planned. The RD was defined as the dose at which six patients could be treated reporting $\leq$1 DLTs.

Treatment was administered until evidence of disease progression, unacceptable toxicity, patient refusal or for a maximum of 12 cycles. Treatment was delayed until recovery in case of neutrophils <1,000 mm^{-3}, platelets <100,000 mm^{-3} or diarrhea or stomatitis grade >1 on the planned day of treatment. LOHP was interrupted if grade >2 peripheral neurotoxicity occurred. In the case of previous DLT, treatment was continued after resolution of the event with doses of LOHP, CPT-11 and capecitabine reduced by 25%, except in the case of grade 3–4 diarrhea, when only CPT-11 and capecitabine doses were reduced by 25%. In the case of life-threatening toxic effects, treatment was definitively interrupted or continued at doses reduced by 50%.

Assessment of safety and activity

Pre-treatment evaluation included complete blood profile, carcinoembryonic antigen, electrocardiogram, chest and abdominal tomography scan and any other appropriate diagnostic procedure to evaluate metastatic sites. During treatment, a physical examination and a complete blood cell count, AST, ALT, total bilirubin and creatinine were performed every 2 weeks. Sites of metastatic disease were radiologically re-evaluated every 8 weeks. Toxicities were evaluated according to NCI-CTC vers. 3.0 and responses were scored according to standard RECIST criteria. PFS and OS were calculated from the first day of treatment to the date of first observation of progressive disease, death or last contact.

Pharmacokinetics

Plasma samples were obtained at the first cycle of chemotherapy, before and 0.5, 1, 2, 3, 4, 5, 6, 24, 48 and 144 h after the beginning of CPT-11 infusion. Samples were centrifuged and plasma was stored at −20°C until the laboratory analyses for the measurement of drugs plasma concentrations. Free LOHP levels were measured following a previous described method [8], with a mobile phase consisting of acetonitrile/water (60/40, vol/vol) and a flow of 1 ml/min. Plasma levels of CPT-11 and its metabolites (SN-38 and SN-38 glucuronate) were measured using a HPLC method with fluorimetric detection [9], while 5-FU and 5-FDHU concentrations in plasma samples were obtained using an UV–HPLC technique [10].

Plasma concentrations of CPT-11, its metabolites and LOHP were analyzed by means of a pharmacokinetic dedicated software (Apo2pr, Mediware, Groeningen, The Nederlands) in order to obtain the following main pharmacokinetic parameters: area under the time/concentration curve (AUC), total body clearance (Cl) and volume of distribution (Vd), while maximum plasma concentration (C_{max}) and time to peak (T_{max}) were obtained from direct visual inspection of plasma profiles. Moreover, for 5-FU and 5-FDHU the C_{max} values were obtained.

Results

Patients' characteristics

A total of 15 patients were enrolled into the study. Patients' main characteristics are listed in Table 1.

Toxicity and dose finding

A total of 164 cycles of chemotherapy were administered with a median of 12 cycles per patient (range 3–14). Grade 3–4 diarrhea was the only DLT observed and it was reported in six out of 15 (40%) patients enrolled. In particular, as reported in Table 2, none of the first three patients treated at the dose of 2,500 mg/m^2/day experienced DLT, so the following three patients were treated at the dose of 3,000 mg/m^2/day, reporting two DLTs. For this reason, another group of three patients was treated at the dose of 2,500 mg/m^2/day; two out of these three patients experienced grade 3–4 diarrhea. Then, we treated six patients at the dose of 2,000 mg/m^2/day, observing only one DLT. Therefore we defined the RD of capecitabine 2,000 mg/m^2/day on days 1–7, administered in association with LOHP 85 mg/m^2 and CPT-11 165 mg/m^2 on day 1, every 2 weeks (Fig. 1). Overall maximum per patient grade 3–4 toxicities observed are reported in Table 3. Three patients were hospitalized because of G3-4 diarrhea, but no toxic deaths occurred.

Table 1 Patients characteristics

	N	%
Patients	15	100
Age, median (range)	60	(42–75)
Sex (male/female)	8/7	53/47
ECOG PS 0/1–2	12/3	80/20
Primary colon/rectum	12/3	80/20
Previous adjuvant chemotherapy	3	20
Multiple sites of disease	7	47
Liver only metastases	4	27

Table 2 Capecitabine dose levels and dose-limiting toxicity

Dose (mg/m^2/day)	No. of pts.	No. of DLT	Type of DLT
2,500	3	0	–
3,000	3	2	Diarrhea G3
2,500	3	2	Diarrhea G3-4
2,000	6	1	Diarrhea G3

DLT dose-limiting toxicity

Antitumor activity and survival

All 15 patients were evaluable for response. We observed eight (53%) partial responses (RR = 53%) and seven (47%) stabilizations. Post-chemotherapy resection of metastases

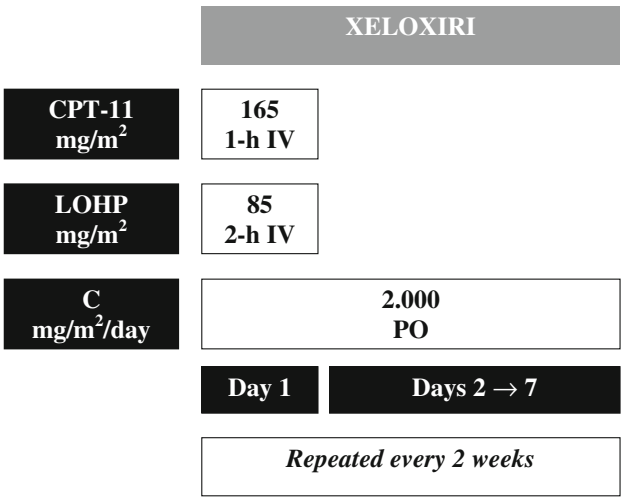

Fig. 1 XELOXIRI regimen: treatment schedule at recommended dose. *CPT-11* irinotecan, *LOHP* oxaliplatin, *C* capecitabine, *1-h* 1 hour, *2-h* 2 hour, *IV* intravenous, *PO* per os

Table 3 Maximum toxicities per patient ($N = 15$)

Adverse event	G1 N (%)	G2 N (%)	G3 N (%)	G4 N (%)
Nausea	9 (60)	4 (27)	–	–
Diarrea	6 (40)	2 (13)	4 (27)	2 (13)
Neutropenia[a]	3 (20)	3 (20)	3 (20)	1 (7)
Thrombocytopenia	2 (13)	3 (20)	1 (7)	–
Neurotoxicity	7 (47)	1 (7)	3 (20)	–
Hand-foot syndrome	1 (7)	1 (7)	–	–

[a] Febrile neutropenia: 0 (0%)

was considered in three (20%) patients and a radical (R0) resection was performed in two (13%) of them. After a median follow-up of 21.4 months, median Kaplan–Meyer estimates of PFS and OS are 9.5 and 21.0 months, respectively.

Pharmacokinetics

A complete plasma sampling for pharmacokinetic analysis was available in eight out of 15 patients, who received capecitabine 3,000 and 2,000 mg/m^2/day (two and six subjects, respectively). Because of the large interpatient variability in plasma levels of 5-FU and 5-FDHU generated from capecitabine, plasma levels of both metabolites were normalized by the lowest dose of the drug [2,000 mg/m^2/day]. Maximal plasma concentrations of 5-FU and 5-FDHU were 0.51 ± 0.95 and 1.02 ± 1.12 μg/ml, respectively, while pharmacokinetic parameters of CPT-11, its metabolites and unbound LOHP are presented in Table 4.

Discussion

Several phase I–II studies demonstrated the feasibility of a three-drug regimen with infusional 5-FU, LOHP and CPT-11 and a phase III trial showed that the GONO-FOLFOXIRI regimen was significantly more active and effective than FOLFIRI [2–4].

In the present dose finding study we evaluate the feasibility and determine the RD of a triple drug combination with capecitabine instead of 5-FU (XELOXIRI), administered with the same biweekly schedule as in the GONO-FOLFOXIRI regimen. The XELOXIRI regimen was feasible, with diarrhea being the DLT. The RD of capecitabine was 2,000 mg/m^2/day in combination with LOHP 85 mg/m^2 and CPT-11 165 mg/m^2 day 1 every 2 weeks.

The safety profile of XELOXIRI demonstrated a relatively low rate of hematological toxicity, with few cases of grade 3–4 neutropenia and no cases of febrile neutropenia, but a relatively high incidence of grade 3–4 diarrhea. For these reasons, the regimen allows the administration of a reduced dose intensity of capecitabine (7.0 g/m^2/week) compared to those achieved in the XELOX/XELIRI regimens (9.3 g/m^2/week) [11, 12]. Notably, the RD of capecitabine is below the starting dose level which was completed without any DLT (Table 2): considering single patient data and characteristics, a younger age and better PS in the first three patients, in association with the small sample size of each dose level, can explain this apparently discrepancy of the reported results.

These data are consistent with those reported in previous phase I–II studies testing the combination of different schedules of capecitabine with LOHP and CPT-11 [13, 14], with grade 3–4 diarrhea (and febrile neutropenia in the study by Maroun [13]) as the most common DLTs. The XELOXIRI regimen we studied produced a higher incidence of grade 3–4 neutropenia if compared to the COI regimen reported by Bajetta (27 vs. 0%, respectively) [14], but a higher dose intensity of capecitabine (7.0 vs. 5.0 g/m^2/week) in our study and a strict monitoring of blood cell count during treatment may explain the increased incidence of neutropenia observed.

Although the large interpatient variability observed for investigated drugs, the present pharmacokinetic values were superimposable with those previously reported [2, 9, 15, 16], suggesting a predictable pharmacokinetic behavior of LOHP and CPT-11. It is worth of note the large variability of plasma levels of capecitabine metabolites among subjects, but it could be explained by the complex metabolic activation of the drug.

On the basis of these results, we are now completing a phase II trial to better define the safety profile and to evaluate the activity of the XELOXIRI regimen with capecitabine at the RD of 2,000 mg/m^2/day.

Table 4 Main pharmacokinetic parameters of oxaliplatin (L-OHP), irinotecan (CPT-11) and its metabolites (SN-38 and SN-38glu)

Parameter	L-OHP	CPT-11	SN-38	SN-38glu
AUC (h × μg/ml)	12.5 ± 3.9	12.13 ± 1.20	0.161 ± 0.015	0.408 ± 0.075
C_{max} (μg/ml)	1.17 ± 0.21	1.90 ± 0.20	0.041 ± 0.010	0.066 ± 0.007
T_{max} (h)	2.11 ± 0.33	1	1.11 ± 0.33	1.22 ± 0.44
Cl (l/h/m^2)	7.43 ± 2.82	13.73 ± 1.44	–	–

AUC area under the time/concentration curve, C_{max} maximal plasma concentration, T_{max} time to peak, *Cl* systemic clearance

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