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ORIGINAL ARTICLE

Dose finding study of erlotinib combined to capecitabine and irinotecan in pretreated advanced colorectal cancer patients

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Abstract
Purpose This study evaluated the maximum tolerated dose (MTD) and the dose limiting toxicity (DLT) of erlotinib when combined to irinotecan and capecitabine in pretreated metastatic colorectal cancer patients.
Methods Five dose level combinations with irinotecan (from 180 to 240 mg/m^2, day 1, q21), capecitabine (1,500–2,000 mg/m^2 per day, days 2–15, q21) and erlotinib (50–150 mg per day, continuously) were planned. Patients were enrolled in cohorts of three, and evaluated for first cycle acute toxicity.
Results Twenty-one patients were treated. In the first cohort, no DLT was reported, in the second: one DLT (G4 neutropenic fever associated with G3 cutaneous rash and mucositis); in the third dose level: two DLT (G3 diarrhea and G4 neutropenic fever). To confirm these results, other six patients were additionally included and no DLT was observed.
Conclusions The results documented that erlotinib at the dose of 100 mg per day, irinotecan 180 mg/m^2 and capecitabine 1,500 mg/m^2 per day for 14 days has an acceptable safety profile and appears suitable for further phase II studies.

Keywords Erlotinib · Irinotecan · Capecitabine · Colorectal cancer

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Introduction

Colorectal cancer is the third most common solid tumor. Due to better cancer care, disease mortality has fallen over past three decades [1]. Metastatic disease is present at first diagnosis in 20% of cases. In 40% of cases, it will develop distant metastasis over time. Usually these patients receive a combination chemotherapy containing oxaliplatin (L-OHP) or irinotecan (CPT-11) in association to fluorouracil (FOLFOX-FOLFIRI) [2]. However, introduction of new biomolecular agents (bevacizumab and cetuximab) in the clinical practice has dramatically changed therapeutic outcome in terms of progression-free survival and overall survival [3, 4] .

Oral fluoropyrimidines represent another possible choice in the treatment of colorectal cancer with clinically meaningful safety advantages over 5-FU/LV i.v. combination [5, 6]. Numerous studies of capecitabine combined with L-OHP or CPT-11 demonstrate to be safe and efficient and it is currently used in routine management of colorectal cancer patients [7, 8].

EGFR is a transmembrane glycoprotein, which belongs to the family of four closely related receptors such as

HER-1/ErbB1, HER-2/*neu*/ErbB2, HER-3/ErbB3, and HER-4/ErbB4. Structurally, each receptor is composed of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain [9]. The currently available agent targeting EGFR include tyrosine kinase inhibitors (erlotinb/gefitinib) and monoclonal antibodies (cetuximab/panitumumab). Erlotinib is an orally active, potent, selective inhibitor of the EGFR tyrosine kinase, which inhibits human EGFR tyrosine kinase with an IC50 of 2 nM (0.786 ng/mL) in an in vitro enzyme assay and reduces EGFR autophosphorylation in intact tumor cells with an IC50 of 20 nM (7.86 ng/mL). Erlotinib inhibits EGF-dependent proliferation of cells at submicromolar concentrations and blocks cell-cycle progression in the G1 phase [10, 11].

Pre-clinical data confirms that erlotinib and capecitabine have at least additive activity in tumor models. The antitumor effect of this combination was greater than capecitabine alone. In particular, erlotinib treatment acts on thymidine phosphorylase (TP), enzyme that activates capecitabine [12]. Regards the combination with CPT11, some data proved the existence of complementary mechanisms of action between EGFR inhibitor and CPT11. In addition, the two drugs are partially metabolized by P450 3A4, making a potentially safety concern [13].

Considering such data, a phase I study to evaluate the maximum tolerated dose (MTD), the dose limiting toxicity (DLT) and the recommended dose of erlotinib in combination with CPT-11 and capecitabine was started. Secondary objectives were the evaluation of safety, the assessment of response rate (RR) and time to progression (TTP).

Materials and methods

Patient selection

The eligibility criteria included histologically or cytologically proven diagnosis of colorectal carcinoma with metastatic measurable and/or evaluable lesions, aged between 18 and 65 years, ECOG performance status (PS) 0–2, neutrophils count $\geq 2 \times 10^9$/L, platelets count $\geq 100 \times 10^9$/L, total bilirubin $\leq$1.5 time the upper-normal limits (UNL) of the Institutional normal values, aspartate aminotransferase/alanine aminotransferase $\leq 2 \times$ UNL ($\leq$five times the UNL for patients with liver metastasis), alkaline phosphatase $\leq 2.5 \times$ UNL (unless bone metastasis are present in the absence of any liver disorders), serum creatinine <140 μmol/L (1.6 mg/dL). Patients may have had only one previous chemotherapy treatment including oxaliplatin regimen for metastatic disease, other than adjuvant fluoropyrimidines in combination with leucovorin.

Exclusion criteria included congestive hearth failure or angina pectoris even if medically controlled, previous history of myocardial infarction within 1 year from study entry, uncontrolled high risk hypertension or arrhythmia, history of significant neurologic or psychiatric disorders including dementia or seizures, active infection, concurrent treatment with other experimental drugs, pregnant or lactating women or women of childbearing potential (e.g. not using adequate contraception), past or current history of neoplasm other than curatively treated non-melanoma skin cancer or carcinoma in situ of the uterine cervix. A malabsorption syndrome or any other disorder that would affect gastrointestinal absorption was also included in exclusion criteria.

In all patients, a tumor tissue sample was provided for HER1/EGFR assessment. HER1/EGFR expression was assessed by immunohistochemistry.

This study was approved by Institutional Ethical Review Board. All patients gave a written consent to participate in the study.

Study design and treatment

This is a phase I study with the primary objective to identify the MTD of erlotinib, capecitabine and CPT11 when given in combination in pre-treated metastatic colorectal cancer patients.

The MTD was defined as the highest dose at which DLT did not exceed a 30% target rate of occurrence. Dose-limiting toxicity is defined as the occurrence of Absolute Neutrophyl Count (ANC) $<0.5 \times 10^9$/L of $\geq$7 days duration, or ANC $< 0.1 \times 10^9$/L of >3 days duration, or neutropenic fever defined as ANC $< 0.5 \times 10^9$/L with fever $\geq$ 38.5°C (single evaluation), or fever >38°C in two evaluations lasting 12 h each other, or platelets count $<25 \times 10^9$/L of $\geq$7 days duration or with bleeding requiring transfusions. All DLT were evaluated during a minimum of 3 weeks follows the first cycle.

The intensity of clinical adverse events was graded according to the National Cancer Institute-Common Toxicity Criteria (NCT-CTC).

Any grade, 3–4 non-hematologic toxicity (nausea, vomiting or diarrhea) if patients had received optimal antiemetics and antidiarrheal premedication and management were considered DLT.

Dose levels and corresponding drugs are shown in Table 1. The trial was designed using a conventional dose-escalation scheme based on the 3 + 3 algorithm. In practice, cohorts of thee patients were evaluated at each dose level combination, and sequential dose levels were studied in the absence of DLT. If one of three patients at any level developed treatment-related DLT, three additional patients were studied at the level before escalation. The stopping rule was

Table 1 Dose escalation protocol

Dose level	Drug			No. of patients evaluable
	mg per day continuously	mg/m^2 day 1 q21	mg/m^2 days 2–15	
I	Erlotinib 50	CPT11 180	Capecitabine 1,500	3
II	Erlotinib 100	CPT11 180	Capecitabine 1,500	6 + 3[a]
III	Erlotinib 100	CPT11 240	Capecitabine 1,500	6 + 3[a]
IV	Erlotinib 100	CPT11 240	Capecitabine 2,000	–
V	Erlotinib 150	CPT11 240	Capecitabine 2,000	–

[a] Additional patients entered after defining MTD

the occurrence of two or more DLT over three or six patients. At the end of the study, according to this approach, considering all the toxic events occurred, six additional patients were therefore entered, three in each of Group II and III. Dose intensity (DI) was calculated by summing each cycle dose divided by the number of weeks from the first day of cycle one to the date of the last cycle plus a fixed time of three weeks. The relative DI was calculated as the ratio between the DI for each drug as received and the planned DI.

Then starting from Group I, patients were entered into the study in cohorts of three. The patients received irinotecan in 90 min infusion on day 1, followed by capecitabine on day 2 for 14 consecutive days. The capecitabine dose was taken as two equally divided daily doses approximately 12 h apart, and were administered within 30 min after ingestion of food, after breakfast and evening meal. Erlotinib was given continually daily starting on day 1 throughout the 21-day cycle. Patients were instructed to take erlotinib 1 h before lunch. Tumor assessment was performed using conventional methods and disease evaluation was done based on RECIST criteria [14]. In case of disease progression (PD), patient was removed from the study. In presence of stable disease (SD), treatment was continued until 6 cycles and, patients with partial (PR) or complete response (CR) received up to 8 cycles. Erlotinib assumption was continued after termination of chemotherapy and discontinuation was done in case of PD, severe toxicity, or consent withdrawal.

Baseline and treatment assessment

Baseline assessment included complete medical history, physical examination and performance status (PS) evaluation according to ECOG scale. Complete blood count (CBC) and blood chemistry were monitored before each cycle. CT scan was ordered at the baseline assessment and was repeated after every three cycles of chemotherapy.

All adverse events encountered during the clinical study were documented in clinical case report forms (CRFs). Any change from the patient's baseline in course of treatment was considered as adverse event (AE).

Treatment modifications

No treatment interruptions or dose reductions were indicated in individual patients for reactions that were unlikely to become serious or life threatening, or in the case of grade 1 toxicity. Treatment was interrupted in cases of grade 2 toxicity or worse, and then restarted once the adverse event had resolved or improved to grade 1. In the case of patients experiencing hematologic toxicities other than neutropenia (leukopenia, anemia or thrombocytopenia) or diarrhea, a new course of therapy could not begun until the neutropenia count had returned to $\geq 1.5 \times 10^9$/L and the platelet count to $\geq 100 \times 10^9$/L, and the treatment-related diarrhea had fully recovered. Treatment was delayed for 1–2 weeks, to allow for recovery, and the dose was reduced by 25% in patients experiencing a second occurrence of a grade 2 toxicity or any grade 3 toxicity. Treatment reduction was 50% in those experiencing a third occurrence of a grade 2 toxicity, a second occurrence of a given grade 3 toxicity or any occurrence of grade 4 toxicity. Treatment was definitely discontinued in cases experiencing a fourth episode of grade 2 toxicity, a third episode of grade 3 toxicity, or a second episode of grade 4 toxicity.

The adverse events not listed by the NCT-CTC grading system were evaluated and scored as mild (grade 1), moderate (grade 2), severe (grade 3) or life threatening (grade 4). Hand-foot syndrome (HFS or palmar–plantar erythrodysesthesia) was classified as grade 1 (numbness, dysesthesia, painless swelling or erythema not disrupting normal activity), grade 2 (painful erythema with swelling or affecting daily living activities), or grade 3 (moist desquamation, ulceration, blistering or severe pain or any symptoms leading to an inability to work or to perform daily living activities).

Results

Patients' characteristics

Between May 2004 and July 2005, 21 consecutive patients were enrolled into the study. Table 2 shows the main

Table 2 Main patient and disease characteristics

Total analyzed	*N* (%)
Median age, years (range)	55 (39–69)
Gender: male/female	12/9
PS (ECOG): 0	21 (100)
Site of primary lesion:	
Colon	14 (67)
Rectum	7 (33)
Number of metastatic sites:	
1	6 (29)
≥2	15 (71)
Status at first diagnosis:	
Primary operable	20 (95)
Metastatic	1
Prior treatment:	
Surgery	20 (95)
Adjuvant chemotherapy	7 (33)
L-OHP containing chemotherapy	21 (100)
EGFR status:	
Missing	3
Negative	3
Positive	15

patients and tumor characteristics. The median age was 55 years (range 39–69), all patients had a baseline ECOG PS of 0, and they had previously received chemotherapy for metastatic disease with an oxaliplatin-containing regimen.

Safety analysis

The description of the overall toxicity profile is shown in Table 3. Three cases received the first dose level (Group I) without any DLT. At dose level two, among the first three patients treated, one DLT with neutropenic fever associated with mucositis and G3 cutaneous rash was reported. In the second cohort (other three patients), no DLT was documented. At dose level three-one DLT consisting of G3, diarrhea was observed in the first cohort and another DLT (G4 febrile neutropenia) was reported among the subsequent three treated cases. To confirm the results, other three patients were enrolled into level two and the remaining three patients into level three, no DLT was reported. Consequently, dose level III combination was defined as the MTD (Table 3). Detailed description of all toxicities observed within the Group treated is presented in Tables 4 and 5. High dose levels had more frequent incidence of AEs. No G3-G4 toxicity was reported at the first dose level. Chemotherapy was definitely discontinued in five patients (2 in dose level two and 3 in dose level three) due to adverse reactions.

Table 3 Dose escalation protocol and dose-limiting toxicity

Dose level	No. of patients		Description
	Overall	With DLT	
I	3	–	–
II	9	1	Neutropenic fever G4, mucositis G3, rash G3
III	9	2	Diarrhea G3, neutropenic fever G4

No dose modification was done in dose level I (18 cycles delivered). In dose level II, one out of 40 administered cycles was given at 75% of the dose. In dose level III, 20 out of 45 were administered at 75% of the dose, so 6 out of 9 patients received a dose reduction. All dose reductions regarded irinotecan and capecitabine. No erlotinib reduction was needed. Table 6 summarizes dose intensity (DI) data for each drug according to dose level.

As shown, DI was always above 90% in Group I. DI figures tended to be lower in the remaining Groups. Regarding irinotecan, the higher starting dose in dose level III (240 mg/m^2) compared to dose level II (180 mg/m^2) was partly changed by the lower dose intensity (83 vs. 95%, respectively). No such trade off occurred for capecitabine, as far as the starting dose was the same in the two Groups and the dose intensity was lower in Group III (70%) compared to dose level II. Finally, no important difference was observed for erlotinib dose intensity. Consequently, the overall treatment dose was not much different in dose level II and III.

Tumor response

Eighteen patients were evaluable for efficacy (three patients interrupted treatment before first disease evaluation reporting side effects without any clinical benefit). Out of these described patients, one had a partial response (Group I), whereas 15 showed disease stabilization at the end of chemotherapy of whom two patients in Group I, six in Group II and seven patients in Group III and two cases in Group II reported a disease progression. The median duration of SD was 4 months (range 2–9 months). The time-to-progression (TTP) of all treated patients was 6.5 months (range 2–10 months).

Discussion

Capecitabine and CPT-11 have different mechanism of action and show a partial overlap of key toxicities. Several phase II studies documented that the schedule, when CPT-11 was administered in one day, resulted highly active as first-line therapy and with an acceptable safety profile [8, 15].

Table 4 Toxicities related to dose level (grade 1–2 per patient and cycle according to NCI CTC)

Dose Level	I		II		III	
Event	Patient ($n = 3$)	Cycles ($n = 18$)	Patient ($n = 9$)	Cycles ($n = 40$)	Patient ($n = 9$)	Cycles ($n = 45$)
Diarrhea	3	11	7	20	8	24
Nausea/emesis	1	1	7	21	7	21
Mucositis	–	–	1	2	1	1
Asthenia	–	–	4	9	2	5
Hand-foot syndrome	1	1	1	3	1	2
Leukopenia	2	7	1	1	–	–
Neutropenia	2	6	1	1	1	4
Rash	1	7	5	18	7	24
Any type	3	16	9	39	9	43

Table 5 Toxicities related to dose level (grade 3–4 per patient and cycle according to NCI CTC)

Dose Level	I		II		III	
Event	Patients ($n = 3$)	Total number of cycles ($n = 18$)	Patients ($n = 9$)	Total number of cycles ($n = 40$)	Patients ($n = 9$)	Total number of cycles ($n = 45$)
Diarrhea	–	–	1	1	4	5
Nausea/emesis	–	–	3	3	1	1
Mucositis	–	–	1	1	–	–
Asthenia	–	–	1	1	1	1
Hand-foot syndrome	–	–	–	–	–	–
Bilirubin	–	–	1	1	–	–
Leukopenia	–	–	–	–	2	–
Neutropenia	–	–	–	–	6	5
Fever Neutropenic	–	–	1	–	2	4
Skin rash	–	–	1	1	4	4
Vasculitis	–	–	1	1	–	–
Any type			8	17	9	21

Table 6 Dose intensity to dose level

Group	Drug	Mean	Median	Minimum	Maximum
I	Erlotinib	0.93	0.99	0.79	1.00
	Irinotecan	0.99	0.99	0.98	1.00
	Capecitabine	0.94	0.99	0.83	1.00
II	Erlotinib	0.86	0.95	0.24	1.10
	Irinotecan	0.95	0.96	0.80	1.00
	Capecitabine	0.81	0.88	0.29	1.00
III	Erlotinib	0.83	0.83	0.59	1.00
	Irinotecan	0.83	0.88	0.60	1.00
	Capecitabine	0.70	0.72	0.47	1.00

This is the first study where three drugs, combination of erlotinib, capecitabine and CPT-11, are evaluated. This dose finding exploration did not document unexpected severe toxicities. The most common grade 3–4 side effects were diarrhea, cutaneous rash, neutropenia, and neutropenic fever. The incidence was greater at higher doses; in fact, no grade 3–4 side effect was reported at the first dose level. Any type of grade 3–4 adverse reactions were documented in all the cases treated in the dose level III and in eight patients in dose level II. The safety profile of the dose level II and III were similar but the DI of CPT-11 and capecitabine were lower in dose level III compared to those of Group II. Considering that the overall treatment dose was similar in level II and III, the combination of erlotinib at 100 mg per day, capecitabine 1,500 mg/m^2 for 14 days, and CPT 11 180 mg/m^2, can be considered for future evaluations.

Previous Phase I studies have evaluated the pharmacodynamic and pharmacokinetic effects of erlotinib given as continuous administration at a daily dose of 150 mg [16, 17]. More recently, a Phase I study evaluated the MTD of erlotinib, in combination with FOLFIRI. This trial was interrupted at lowest dose level when six patients included expressed severe toxicity. No pharmacokinetic interaction

of FOLFIRI and erlotinib was reported [18]. A phase II study documented the efficacy and safety of erlotinib alone in colorectal cancer patients [19]. At a continuous daily oral dose of 150 mg, 39% of patients achieved a SD. The most common toxicities were rash and diarrhea reported in 90 and 61% of the treated patients, respectively. Different data were obtained from studies that evaluated the MTD of erlotinib when combined to oxaliplatin. A study documented that the standard doses for oxaliplatin and 5-FU, when administered according to FOLFOX-4 regimen, with the known MTD for erlotinib, 150 mg total dose daily, can be given without causing unacceptable incidence of DLTs [20]. Thus, each of the drugs could be administered at a clinically active dose, maximizing the antitumor effect of the combination. On the other hand, the safety profile of capecitabine, oxaliplatin and erlotinib, according to the standard recommended dose of each drug, has been reported in Phase I–II studies [21, 22]. The MTD was capecitabine 825 mg/m^2 twice-daily, days 1–14, oxaliplatin 130 mg/m^2 day 1 and erlotinib 100 mg per day of a 21-day cycle.

In our study, erlotinib dose was lower that standard single agent dose. However, results from previous erlotinib dose finding studies confirm that the dose of 100 mg per day is also efficient. Based on published data, we can state that erlotinib activity is not affected by concomitant administration with other drugs such as capecitabine and CPT11.

Observed evidence will allow the use of this triple drug combination in phase I/II study combined with bevacizumab as first line therapy for colorectal cancer patients.

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