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ORIGINAL ARTICLE

# Feasibility of biweekly combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in patients with metastatic solid tumors: results of a two-step phase I trial: XELIRI and XELIRINOX

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**Abstract**
*Background* Biweekly schedule of capecitabine combined with irinotecan (XELIRI), consecutively with irinotecan and oxaliplatin (XELIRINOX), was evaluated in patients with metastatic cancer from any solid tumors.
*Patients and methods* In this two-step phase I trial, seventeen and eleven patients were enrolled in the XELIRI and XELIRINOX stages, respectively.
*Results* In XELIRI, a total of 136 chemotherapy cycles were administered with a median number of 8 cycles per patient (2–16). Main dose-limiting toxicities (DLT) were grade 3–4 neutropenia, with one toxicity-related death. Maximum tolerated dose (MTD) for capecitabine combined with 180 mg/m$^2$ of irinotecan was 3,500 mg/m$^2$/day. In XELIRINOX, capecitabine starting dose was 2,500 mg/m$^2$/day. Fifty-eight chemotherapy cycles were administered with a median of 4 cycles per patient (1–16). DLT included 3 grade 4 neutropenia, associated with 1 grade 3 diarrhea, and 1 grade 4 pneumopathy leading to patient death. MTD for capecitabine with 180 mg/m$^2$ of irinotecan and 85 mg/m$^2$ of oxaliplatin was 3,000 mg/m$^2$/day. The recommended doses for capecitabine were 3,000 and 2,500 mg/m$^2$/day D1–D7 in combination with 180 mg/m$^2$ of irinotecan in XELIRI, plus 85 mg/m$^2$ of oxaliplatin in XELIRINOX (D1 = D14), respectively.
*Conclusion* XELIRI and XELIRINOX regimens are feasible and warrant further investigation in combination with targeted therapy in metastatic colorectal cancer patients.

**Keywords** Biweekly · Capecitabine · Irinotecan · Metastatic colorectal cancer · Oxaliplatine · Recommended dose

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## Introduction

Colorectal cancer is the fourth most common cancer worldwide. In 2008, with an estimated incidence of 39,000 cases in France, colorectal cancer was responsible for more than 17,000 deaths [1]. Despite significant progress made in screening and early management of the disease, 30% of patients present with synchronous metastases, and 50–60% will develop metastases requiring in most cases chemotherapy. Fluorouracil (5-FU) has been the mainstay of chemotherapy over several decades. Primarily used as single agent, 5-FU allowed improvement in overall survival (OS) by 3–6 months as compared with classical symptomatic therapy [2]. Afterward, response rates (RR) and survival have been significantly increased by first-line 5-FU in combination with other cytotoxic agents such as oxaliplatin and irinotecan [3–5]. Capecitabine (Xeloda®) is

an oral fluoropyrimidine carbamate designed to generate 5-FU preferentially in tumor cells due to high concentration level of thymidine phosphorylase enzyme [6–8]. This allows to mimic continuous 5-FU infusion at the tumor site and to reduce exposure of adjacent healthy tissues without causing discomfort and complications related to intravenous (IV) administration. Two large phase III trials with more than 600 patients [9, 10] showed that the administration of 2,500 mg/m$^2$/day of capecitabine for 14 days every 3 weeks provides equivalent disease-free and overall survivals as IV 5-FU plus leucovorin regimen, with meaningful tolerance benefits and reduced occurrence of diarrhea, mucositis, alopecia, and severe neutropenia [11]. A recent meta-analysis of six randomized trials comparing oxaliplatin in combination with either IV 5-FU or capecitabine (XELOX) demonstrated similar survivals in both arms although higher RR were observed in the IV 5-FU-based regimens [12]. Limited study data are available to compare irinotecan in combination with capecitabine (XELIRI) or IV 5-FU. The only phase III trial comparing irinotecan plus infusional 5-FU/LV (FOLFIRI), irinotecan plus bolus FU/LV (mIFL), and irinotecan plus oral capecitabine (CapeIRI) reported inferior results in terms of tolerance and progression-free survival (PFS) for the CapeIRI regimen in comparison with FOLFIRI [13]. Similarly, another phase III trial comparing the FOLFIRI and CapeIRI regimens was prematurely stopped due to high death rate in the CapeIRI arm [14]. These data suggest that the optimal doses and most appropriate modalities of treatment combining capecitabine and irinotecan are not yet defined. The current tendency toward chemotherapy intensification with 5-FU, oxaliplatin, and irinotecan tritherapy can significantly improve PFS [15] and objective RR providing the chance for secondary surgical resection in patients with metastases initially unresectable. A recent systematic review of the literature [16] on FOLFOXIRI chemotherapy confirmed a significant benefit in progression-free survival, survival, response, and R0 resection rates but more toxicities compared with FOLFIRI. Another triplet combination (FOLFIRINOX) has been tested in a phase I [17] on various solid tumors and in a phase II [18] on potentially resectable liver metastases from colorectal cancer. So, we wanted to explore the possibility to replace the IV 5-FU plus leucovorin regimen by capecitabine in this triplet.

Moreover, Scheithauer has proposed to shorten the duration of capecitabine administration considering that shorter exposure would increase dose intensity, an essential parameter in tumor growth inhibition, without making worse toxicity because of longer drug-free periods. He has demonstrated, in consecutive phase I and II studies [19, 20], the feasibility of a biweekly regimen of capecitabine and oxaliplatine. Therefore, we decided to replicate this method of administration of capecitabine in combination with irinotecan only on one hand and with irinotecan and oxaliplatin on the other. In this context, we designed a phase I trial to determine the recommended dose of capecitabine associated with irinotecan (XELIRI), consecutively with irinotecan and oxaliplatin (XELIRINOX) in a biweekly schedule for patients with metastatic solid tumors.

## Materials and methods

We undertook a prospective monocentric phase I trial (NCT 00544063, ClinicalTrials.gov) whose protocol was approved by the local ethics committee and French competent authority.

### Patient selection

Patients with histologic confirmation of metastatic carcinoma, independently the site of primary tumor, evaluable or not according to RECIST criteria were eligible. Main additional inclusion criteria were age between 18 and 75 years, WHO performance status $\leq$2, life expectancy $\geq$16 weeks, adequate hematological, liver, and renal functions, rest period of at least 4 weeks in case of prior myelosuppressive chemotherapy, and no previous treatment with irinotecan or oxaliplatin or capecitabine. Patients who presented with symptomatic brain metastases or carcinomatous meningitis, concurrent severe infection or major organ failure, malabsorption syndrome or dysphagia, prior history of major gastrointestinal resection, bowel obstruction, or uncontrolled epilepsy were not eligible. Written informed consent was obtained from each patient before study entry.

### Treatment procedures

This was a two-step trial. In the first stage, a fixed dose of irinotecan was administered in combination with increasing dose of capecitabine (XELIRI). A dose of 180 mg/m$^2$ of irinotecan was delivered intravenously on Day 1 over 90 min. Capecitabine was administered from D1 to D7 orally twice daily for 7 days according to five dose levels: 2,000; 2,500; 3,000; 3,500, and 4,000 mg/m$^2$/day. The same treatment procedure was repeated every 2 weeks. One treatment course included 2 chemotherapy cycles for 4-week duration. In consecutive XELIRINOX stage, oxaliplatin was delivered intravenously at fixed dose of 85 mg/m$^2$ over 2 h on Day 1, followed by 180 mg/m$^2$ of irinotecan. Increasing doses of capecitabine were given according to the same modalities, the starting dose being two dose levels below the maximum tolerated dose (MTD)

determined in the first stage. Seven dose levels were investigated: 1,000; 1,500; 2,000; 2,500; 3,000; 3,500, and 4,000 mg/m$^2$/day. Treatments were delivered until unacceptable toxicity, patient's refusal, or disease progression and could be discontinued in the absence of full recovery from any limiting toxicity within 4 weeks after the treatment starts. A maximum of 12 cycles was planned, and subsequent treatment was left at the investigator's discretion. Patients were followed every 3 months until death or data cutoff date.

Dose escalation was performed as below:

At the start of the study and before the first limiting toxicity is observed during the first three cycles, a minimum of 2 patients will be treated at each dose level. If no limiting toxicity is observed among 2 patients, escalation to the next dose level is permitted. When the first DLT is observed at a dose level, the recommended dose level for all subsequent patients will be evaluated by the continual reassessment method [21], which will determine the dose level nearest the maximum tolerated dose (MTD). The MTD was defined as the dose level for which at least one DLT occurred for 50% of patients during the first three treatment cycles. The biostatistics unit will then be provided with this information as soon as it becomes available, since it is necessary in determining all subsequent dose escalation recommendations. Patients should be treated according to the recommendations of this method, but dose increases of more than one level will not be allowed. In the first step, when the MTD is reached, a total of 6 patients should be treated at the dose level just below the MTD, if this is not already the case.

In the second step, the starting dose level of Xeloda (Capecitabine) in the biweekly association with irinotecan and oxaliplatin will be two dose levels below the MTD level reached in the first step of the study.

DLT included any grade 4 toxicity (except for vomiting in the absence of adequate prophylaxis, and alopecia), any toxicity requiring a cycle delay of more than 15 days, any grade 3 febrile neutropenia, any grade 3 neutropenia with infection, any symptomatic thrombocytopenia, any grade $\geq$2 diarrhea associated with grade 4 neutropenia, and any grade 3 peripheral neuropathy at the dose level of 60 mg/m$^2$ for oxaliplatin.

## Dose modification and cycle delay

Dose reduction was planned in case of severe hematological or non-hematological toxicities evaluated according to the National Cancer Institute Common Toxicity Criteria version 3.0 (NCI-CTC v 3.0). Granulocyte colony-stimulating factor (G-CSF) was added for the subsequent cycles in case of grade 4 neutropenia, febrile neutropenia, or concomitant sepsis with grade 3–4 neutropenia. If the same toxicity persisted, the doses of irinotecan and oxaliplatin were reduced to 150 and 70 mg/m$^2$, respectively. In case of grade 3–4 delayed diarrhea or diarrhea associated with fever, irinotecan was reduced to 150 mg/m$^2$. In case of grade 3 peripheral neuropathy persisting on Day 15, oxaliplatin was adjusted to 60 mg/m$^2$. In case of grade 2 mucositis, hand-foot syndrome, and conjunctivitis, the dose of capecitabine was reduced by 25%. A dose reduction of 50% was planned if these toxicities were higher than a grade 3. The treatment was discontinued in patients with angor or myocardial infarction. Treatment course could be delayed for a maximum of 15 days in the absence of full recovery from any toxicity or resolution to grade $\leq$1. Intrapatient dose escalation was not permitted.

## Study assessment

Before inclusion, patients were subjected to a pretrial evaluation including physical examination, assessment of medical history, hematological and biochemical tests, and tumor assessment by computed tomography scan. During therapy, clinical examination and complete blood counts were performed every 2 weeks during treatment. All adverse events experienced during the study were recorded and graded according to the National Cancer Institute common toxicity criteria. Oncologic outcome was assessed every 8 weeks using thoraco-abdomino-pelvic computed tomography, and tumor response was determined using RECIST criteria (version 1.0).

## Pharmacological analysis

### *Pharmacokinetics*

Pharmacokinetics (PK) of capecitabine, irinotecan, and their metabolites was only performed at cycle 1 for both study phases. Blood samples were collected at different times on lithium-heparin and dry tubes. Following sampling, cold centrifugation was rapidly performed, and the plasma obtained was placed in 2 tubes immediately frozen. Samples were collected on Day 1 (T0 and T1: before the start and at the end of the irinotecan infusion, respectively; T2/T3/T4/T5/T6/T7/T8: 30 min/1H/2H/3H/4H/6H and 12 H after the first capecitabine intake) and on Day 3 (T9: 44 H after the start of irinotecan infusion).

Irinotecan and its metabolites (SN38, SN38G, APC, NPC) were dosed using high-performance liquid chromatography (HPLC) with fluorescence detection [22]. Samples pretreated consisted in precipitation using methanol–acetonitrile mixture (50:50, v/v), followed by the addition of hypochloric acid (1 mol/l) to shift the carboxylate-lactone equilibrium toward the lactone form. Camptothecin was used as internal standard. Capecitabine and its

metabolites (5′-DFCR, 5′-DFUR) were dosed using HPLC mass spectrometry [23]. Plasma samples were pretreated by liquid–liquid extraction and the addition of a 5-ml ethyl acetate/methanol mixture (95/5). 5-FC was used as internal standard, and individual PK parameters were determined according to the same Bayes approach.

*Pharmacogenetics*

Pharmacogenetics focused on the analysis of the UGT 1A1 (UGT1A1*28) gene mutation. Sequencing was performed on DNA extracted from blood samples collected in EDTA tube at cycle 1 (T0).

## Results

### Patient characteristics

A total of 17 patients were included in the XELIRI stage. Six patients were diagnosed with pancreatic adenocarcinoma, 3 with pancreatic endocrine carcinoma, 2 with cholangiocarcinoma, 2 with unknown primary tumor, 1 with anal canal squamous carcinoma, 1 with gastric cardia adenocarcinoma, and 2 with gastrointestinal endocrine carcinoma. In XELIRINOX, 11 patients were enrolled including 3 diagnosed with pancreatic adenocarcinoma, 3 with gastric adenocarcinoma, 2 with esophageal squamous carcinoma, 1 with cholangiocarcinoma, 1 with pancreatic endocrine carcinoma, and 1 with hepatocellular carcinoma.

In the XELIRI stage, 9 patients had received one line of treatment, 5 patients had received two lines of treatment, and 3 patients had received three lines of treatment.

In the XELIRINOX stage, 2 patients had received one line of treatment, 5 patients had received two lines of treatment, and 4 patients had received three lines of treatment.

The main drugs used in these previous chemotherapies were 5FU IV, gemcitabine, and cisplatine.

Further patient details are summarized in Table 1.

**Table 1** Patient characteristics

| | XELIRI | | XELIRINOX | |
|---|---|---|---|---|
| | *N* | % | *N* | % |
| Patients | 17 | 100 | 11 | 100 |
| Median age (range) | 59 | (50–73) | 56 | (35–76) |
| Gender | | | | |
| M | 10 | 59 | 11 | 100 |
| W | 7 | 41 | 0 | 0 |
| ECOG PS | | | | |
| 0 | 11 | 65 | 8 | 73 |
| 1–2 | 6 | 35 | 3 | 27 |
| Prior chemotherapy lines | | | | |
| 1 | 9 | 53 | 2 | 18 |
| 2 and + | 8 | 47 | 9 | 82 |
| Nb of metastatic sites | | | | |
| 1 | 5 | 29 | 1 | 9 |
| 2 | 9 | 53 | 5 | 45.5 |
| 3 and + | 3 | 18 | 5 | 45.5 |

**Table 2** Dose of capecitabine and dose-limiting toxicity (DLT)

| Dose ($mg/m^2$/day) | Nb of patients | Nb of DLT | Type of DLT |
|---|---|---|---|
| XELIRI | | | |
| 2,000 | 3 | 1 | Grade 4 neutropenia >7 days |
| 2,500 | 4 | 0 | |
| 3,000 | 6 | 1 | Grade 3 febrile neutropenia |
| 3,500 | 4 | 2 | Grade 3 febrile neutropenia |
| | | | Grade 4 febrile neutropenia and grade 2 diarrhea (death) |
| XELIRINOX | | | |
| 2,500 | 7 | 2 | Grade 3 febrile neutropenia |
| | | | Grade 3 diarrhea + grade 4 neutropenia |
| 3,000 | 4 | 2 | Grade 4 neutropenia |
| | | | Grade 4 pneumopathy (death) |

### Maximum tolerated dose, recommended dose, and toxicity

A total of 136 cycles of capecitabine and irinotecan combination were administered with a median number of 8 cycles per patient (2–16). DLT included two grade 3 febrile neutropenia, one grade 4 neutropenia lasting for more than 7 days, and one grade 3 neutropenia associated with a grade 2 diarrhea leading to the patient death (Table 2). The MTD for capecitabine given with 180 mg/$m^2$ of irinotecan in a biweekly combination was 3,500 mg/$m^2$/day, and the recommended dose was determined to be 3,000 mg/$m^2$/day D1–D7 (D1 = D14).

In the second stage, the starting dose was 2,500 mg/$m^2$/day. A total of 58 cycles were administered with a median number of 4 cycles per patient (1–16). DLT included two grade 4 neutropenia, one grade 3 febrile neutropenia, and one grade 4 bilateral pneumopathy leading to the patient death. The MTD for capecitabine given with 180 mg/$m^2$ of irinotecan and 85 mg/$m^2$ of oxaliplatin was 3,000 mg/$m^2$/day, and the recommended dose was determined to be 2,500 mg/$m^2$/day D1–D7 (D1 = D14).

The most common type of toxicity reported in either stage was nausea, vomiting, bowel dysfunction, abdominal pain, hand-foot syndrome, and neutropenia. Additional peripheral neuropathy could be observed in patients treated

**Table 3** Maximum toxicity grade

| Toxic events | Grade 1 *N* (%) | Grade 2 *N* (%) | Grade 3 *N* (%) | Grade 4 *N* (%) |
|---|---|---|---|---|
| XELIRI | | | | |
| Nausea | 11 (65) | 1 (6) | 1 (6) | |
| Vomiting | 7 (41) | 2 (12) | 1 (6) | |
| Diarrhea | 3 (18) | 8 (47) | 1 (6) | |
| Constipation | 3 (18) | 1 (6) | | |
| Abdominal pain | 2 (12) | 5 (29) | | |
| Hand-foot syndrome | 5 (29) | 5 (29) | | |
| Neutropenia | 3 (18) | 4 (24) | 3 (18) | 4 (24) |
| XELIRINOX | | | | |
| Nausea | 6 (55) | 1 (9) | 3 (27) | |
| Vomiting | 6 (55) | 2 (18) | | |
| Diarrhea | 2(18) | 7 (64) | 2 (18) | |
| Constipation | 2 (18) | | | |
| Abdominal pain | 4 (36) | 2 (18) | | |
| Hand-foot syndrome | | 1 (9) | | |
| Peripheral neuropathy | 3 (27) | 4 (36) | | |
| Neutropenia | | 3 (27) | 2 (18) | 4 (36) |

by XELIRINOX. Maximum intensity and frequency of toxicity events are described in Table 3.

Two patients in the XELIRI stage and 3 patients in the XELIRINOX stage had a 25% dose reduction of capecitabine. However, no patient had a 50% reduction.

## Tumor response

Fifteen out of seventeen patients were evaluable in the XELIRI study. Three patients achieved partial response (PR) (20%), eight had stable disease (53%), and 4 tumor progression (27%). At the end of treatment, disease had progressed in 12 patients and was stabilized in 2 patients and one patient had still PR. Seven out of eleven patients were evaluable in the XELIRINOX study. PR was observed in 3 patients (43%), stable disease in 2 (28%), and progression in 2 others (28%). At the end of the treatment, the 3 responders had still PR, 2 patients had stable disease, and 2 had progressed.

## Pharmacological analysis

PK parameters could be determined in 26 patients. Inter-individual variability was found for irinotecan and its metabolites (26% variation for irinotecan clearance) (Table 4), as well as for capecitabine where variability was even higher (157% variation for capecitabine clearance) (Table 5). Linear relationship was obtained between the area under curve (AUC) of both products (irinotecan plus SN38) and the percentage of decrease in neutrophil count ($P = 0.0267$, $r = 0.44$), as well for separate products (irinotecan: $P = 0.031$, $r = 0.4285$; SN38: $P = 0.0477$, $r = 0.396$). Nevertheless, no correlation could be established between PK parameters and diarrhea.

The mutation prevalence of the UGT1A1 promoter was 8% in homozygotous (7/7) and 33% in heterozygotous

**Table 4** Pharmacokinetic parameters of irinotecan and its metabolites ($n = 26$ patients)

| Product | Mean | CV% |
|---|---|---|
| Irinotecan | | |
| V1 (l) | 15.2 | 7.5 |
| CL (l/h) | 25.6 | 26.3 |
| AUC (mg*h/l) | 13.9 | 34 |
| $t_{1/2}$ $\beta$ (h) | 11.6 | 11.8 |
| SN38 | | |
| AUC (mg*h/l) | 0.43 | 45 |
| $t_{1/2}$ $\beta$ (h) | 26.3 | 35 |
| APC | | |
| AUC (mg*h/l) | 3.3 | 57 |
| $t_{1/2}$ $\beta$ (h) | 7.8 | 28 |
| NPC | | |
| AUC (mg*h/l) | 0.43 | 64 |
| $t_{1/2}$ $\beta$ (h) | 8.24 | 49 |
| SN38G | | |
| AUC (mg*h/l) | 2.3 | 58 |
| $t_{1/2}$ $\beta$ (h) | 14.6 | 38 |

*CL* total clearance, $V_1$ initial volume of distribution, *AUC* area under curve, $t_{1/2}$ half-life, *CV* coefficient of variation

**Table 5** Pharmacokinetic parameters of capecitabine and its metabolites ($n = 26$ patients)

| Product | Mean | CV% |
|---|---|---|
| Capecitabine | | |
| Vd (l) | 507 | 203 |
| CL (l/h) | 272 | 157 |
| Tmax | 1.46 | 67 |
| AUC (mg*h/l) | 19.1 | 79 |
| $t_{1/2}$ (h) | 1.1 | 62 |
| 5′-DFCR | | |
| AUC (mg*h/l) | 5.3 | 100 |
| $t_{1/2}$ (h) | 1.68 | 53 |
| Tmax | 1.52 | 47 |
| 5′-DFUR | | |
| AUC (mg*h/l) | 49.9 | 51 |
| $t_{1/2}$ (h) | 0.93 | 39 |
| Tmax | 1.62 | 47 |

*CL* total clearance, *Vd* volume of distribution, *AUC* area under curve, $t_{1/2}$ half-life, *CV* coefficient of variation, *Tmax* time to maximum plasma concentration

genotypes (6/7). No correlation with toxicity was observed, maybe because of the small sample size.

## Discussion

The present study confirms the feasibility of XELIRI and XELIRINOX in a biweekly scheduling. No phase I trial has been published to date on the biweekly delivery of capecitabine in XELIRI combination. For XELIRINOX regimen, our results are consistent with two recently published data reporting acceptable toxicity profile with similar regimens [24, 25]. The recommended dose of 2,500 mg/m$^2$/day D1–D7 for capecitabine is higher than the dose of 2,000 mg/m$^2$/day proposed by Bajetta [24] and Fornaro [25] from D2 to D6 and D1 to D7, when combined with 180 and 165 mg/m$^2$ of irinotecan and 85 mg/m$^2$ of oxaliplatin, respectively.

Dose intensity values obtained were widely higher than in conventional 3-week schedules, regardless of the type of chemotherapy. Indeed, dose intensity reached 10,500 and 90 mg/m$^2$/week for capecitabine and irinotecan in the XELIRI regimen, while the different phase II/III trials of conventional schedules recorded maximum values of 9,333 and 83.3 mg/m$^2$/week, respectively (Table 6). In XELIRINOX combination, dose intensity reached 8,750 for capecitabine, 90 for irinotecan, and 42.5 mg/m$^2$/week for oxaliplatin (Table 7).

Consequently, as suggested by Scheithauer, these regimens might offer enhanced antitumor activity without inducing more toxicity thanks to minimized exposure of healthy tissues to cytotoxic agents. When detailing tolerance profile, no unexpected toxicity was noted (Table 3). Furthermore, these results seem better than those reported in different phase I–II trials testing capecitabine and irinotecan combination, with oxaliplatin or not, independently the type of delivery (Tables 11 and 12). XELIRI findings comply with the results of a recent phase II trial evaluating biweekly regimen (irinotecan 175 mg/m$^2$ D1 and capecitabine 2,000 mg/m$^2$ D2–D8) as first-line treatment in metastatic colorectal cancer [26]. In our trial, neutropenia was the most severe adverse event observed (42 and 54% of grade 3–4 neutropenia, respectively) which led to the death in one patient. This chemotherapy-induced toxicity could appear to be more frequent than with other regimens previously described [27–31], but this merits discussion. Patients in our study presented with advanced tumors, and most of them had been heavily pretreated.

**Table 6** Dose intensity of capecitabine and irinotecan in various combination regimens

| Author | Regimen | Nb of patients | Dose intensity (mg/m$^2$/week) | |
|---|---|---|---|---|
| | | | Capecitabine | Irinotecan |
| Bajetta [27] | XELIRI | 140 | 9,333 | 80 |
| Borner [28] | XELIRI weekly | 75 | 9,333 | 70 |
| Kim [29] | CAPIRI | 47 | 9,333 | 66.7 |
| Fuschs [30] | CAPERI | 144 | 9,333 | 83.3 |
| Our trial | XELIRI biweekly | 17 | 10,500 | 90 |

CAPIRI = capecitabine 1,000 mg/m$^2$ on days 2–15 + irinotecan 100 mg/m$^2$ on days 1 and 8

XELIRI = capecitabine 2,000 mg/m$^2$ on days 1–14 + irinotecan 240 mg/m$^2$ on day 1 every 3 weeks

XELIRI weekly = capecitabine 2,000 mg/m$^2$ on days 1–14 + irinotecan 70 mg/m$^2$ on days 1, 8, and 15 every 3 weeks

CAPERI = irinotecan 250 mg/m2 on D1, capecitabine 2,000 mg/m2 D1 to D14 (D1 = D21)

XELIRI biweekly = capecitabine 3,000 mg/m2 D1 to D8, Irinotecan à 180 mg/m2 (D1 = D14)

**Table 7** Dose intensity of capecitabine, irinotecan, and oxaliplatin in various tritherapy combinations

| Author | Regimen | Nb of patients | Dose intensity (mg/m$^2$/week) | | |
|---|---|---|---|---|---|
| | | | Capecitabine | Irinotecan | Oxaliplatin |
| Bajetta [24] | COI | 38 | 5,000 | 90 | 42.5 |
| Fornaro [25] | XELOXIRI | 15 | 7,000 | 82.5 | 42.5 |
| Our trial | XELIRINOX | 11 | 8,750 | 90 | 42.5 |

COI = capecitabine 2,000 mg/m$^2$/day D2 to D6, Irinotecan 180 mg/m$^2$ on D1, Oxaliplatin 85 mg/m$^2$ on D2, every 2 weeks

XELOXIRI = capecitabine 2,000 mg/m$^2$/day D1 to D7, Irinotecan 165 mg/m$^2$ on D1, Oxaliplatin 85 mg/m$^2$ on D1, every 2 weeks

XELIRINOX = capecitabine 2,500 mg/m$^2$/day D1 to D7, Irinotecan 180 mg/m$^2$ on D1, Oxaliplatin 85 mg/m$^2$ on D1, every 2 weeks

Moreover, neutropenia rate may be explained by the high dose intensity seen in these protocols. This severe neutropenia rate is higher than that observed in the Souglakos et al.'s study [32] but using lower doses of chemotherapies. It remains inferior to that observed in tritherapy with IV 5-FU [15, 18] for comparable dose intensity for oxaliplatin and irinotecan. Even though neutropenia needs to be closely monitored, it currently can be prevented by the use of G-CSF. Primary prophylaxis with G-CSF is therefore recommended for this regimen, as already mentioned for the IV tritherapy. Importantly, increased dose intensity of capecitabine did not make the skin-related toxicity worse, particularly the typical hand-foot syndrome. In both stages, no patient experienced any grade 3 capecitabine-induced hand-foot syndrome, and only 30% had grade 2 toxicity. This trend was also confirmed in other trials [24–26] exploring biweekly scheduling, suggesting the positive effect of the weekly alternation of capecitabine administration.

Pharmacokinetic parameters are consistent with those described in the literature. As expected, interindividual variability was found for irinotecan and its metabolites [33, 34]. This could not be correlated with mutation in the UGT1A1 gene promoter, whose prevalence was slightly lower than usually encountered in the global population. As demonstrated by Chabot et al. [35], high irinotecan or SN38 concentrations can explain the occurrence of chemotherapy-related toxicity. Due to small cohort and reduced number of events, no direct correlation was established between PK parameters and toxicity. Same findings were applicable for capecitabine and its metabolites regarding the relative small number of toxic events and the dose level variations. In this work, the heterogeneity in tumor histology, the number of prior chemotherapy courses, and the small sample size made difficult the interpretation of response rate analysis according to RECIST criteria. Nevertheless, XELIRINOX regimen showed promising results since 5/11 patients were still controlled at the end of treatment. This tritherapy may provide valuable therapeutic alternative, especially in patients with gastrointestinal cancer. Interestingly, Bajetta et al. [36] reported an overall RR of 58% in a cohort of 12 patients with metastatic gastric cancer treated by biweekly capecitabine with oxaliplatin and irinotecan. Likewise, the Prodige ACCORD 11 trial recently showed that first-line FOLFIRINOX tritherapy significantly improved RR, PFS, and OS compared to gemcitabine monotherapy among 342 patients with metastatic pancreatic adenocarcinoma [37]. Lastly, tritherapy with FOLFOXIRI or FOLFIRINOX is being developed in metastatic colorectal cancer to optimize RR and secondary resection of metastases [38].

In conclusion, both XELIRI and XELIRINOX regimens have been demonstrated to be feasible but with a need to use prophylactic G-CSF. In the move toward targeted therapy, these regimens warrant further investigations in combination with targeted agents, particularly in gastrointestinal cancers.

**Conflict of interest** Pr Marc YCHOU: ROCHE, PFIZER.

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