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Case report

Dramatic tumor response of bulky liver metastases following treatment with CPT-11 and a chronomodulated 4-day infusion of 5-fluorouracil, folinic acid and oxaliplatin every 2 weeks in a colorectal cancer patient

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Three active antitumor agents, i.e. 5-fluorouracil (5-FU), oxaliplatin and CPT-11, are available for the treatment of advanced colorectal cancer (CRC) patients and have been successfully combined in two-drug regimens. Hence, CRC has become a chemosensitive disease, but the optimal combination of these agents in first-line treatment remains to be determined. We report the first case of the combination of CPT-11 with oxaliplatin, 5-FU and folinic acid (FA) as first-line chemotherapy for a patient with a pre-occlusive sigmoid adenocarcinoma and synchronous bulky liver metastases. CPT-11 was given at 125 mg/m^2, prior to the start of a chronomodulated 4-day infusion of oxaliplatin 25 mg/m^2/day, 5-FU 800 mg/m^2/day and FA 300 mg/m^2/day repeated every 2 weeks. The doses could be escalated to 150 mg/m^2 for CPT-11 and 900 mg/m^2/day for 5-FU. After six cycles of chemotherapy 70% reduction in tumor size was documented in the liver. The primary tumor was no longer detectable by barium enema. The toxicity included three episodes of grade 4 neutropenic fever, and two episodes of severe diarrhea and vomiting with dehydration. A cumulative grade 2 neurosensory toxicity was observed after six cycles. Following surgery of the primary tumor, because of the major hepatic tumor response and of the absence of extra-hepatic metastases, the patient might be registered for a liver transplantation program. This first report of combining the three active agents in CRC every 2 weeks led to a high dose intensity of each agent and was associated with a dramatic tumor response of a very advanced disease in a patient with already altered performance status. The antitumor activity in this patient suggests that a three-drug intensified regimen might be feasible and active. A prospective study appears warranted to further examine the efficacy and toxicity of this therapeutic approach, and to determine whether it may increase the fraction of advanced CRC patients becoming resectable. This aggressive chemotherapy program may contribute to a re-examination of the usefulness of liver transplantation in patients with metastatic CRC confined to the liver. [© 2000 Lippincott Williams & Wilkins.]

Key words: Chronomodulation, colorectal cancer, CPT-11, liver metastases, oxaliplatin.

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Introduction

During the last 10 years, we have enriched our chemotherapy armamentorium with two new active antitumor agents in colorectal cancer (CRC), CPT-11 (irinotecan) and oxaliplatin. These two agents have a mechanism of action independent of thymidylate synthase (TS)[1,2] and may be active after failure of 5-fluorouracil (5-FU)-based treatments.[3–7] CPT-11, a DNA topoisomerase I inhibitor, has been proven an effective antitumor agent for patients whose tumors no longer respond to 5-FU treatment.[3–5] Two phase III clinical trials demonstrated that its addition to 5-FU/folinic acid (FA) is superior to 5-FU/FA as first-line treatment of metastatic CRC patients.[8,9] The combination of oxaliplatin, a diaminocyclohexane platinum, 5-FU and FA exhibited response rates consistently superior to 20% in CRC patients with disease progression under 5-FU/FA.[8,10,11] The addition of oxaliplatin to 5-FU/FA as first-line treatment of metastatic CRC patients resulted in more than a 2-fold increase in response rate and significant increase of time-related parameters in two phase III randomized trials.[12,13] Since both CPT-11 and oxaliplatin are cytotoxic through a TS-independent mechanism, the combination of oxaliplatin with CPT-11 appeared as an

attractive therapeutic option as salvage therapy in patients who had failed 5-FU and its toxicity has been evaluated using either an every 3[14] or an every 2[15–17] week schedule.

The availability of these two agents in first-line regimens for advanced disease has rapidly changed the natural history and the therapeutic results in advanced CRC patients. To increase the fraction of patients eligible for surgery to have metastases removed is a new therapeutical goal.[18,19] The addition of oxaliplatin to 5-FU/FA allowed approximately 50% of the patients with initially unoperable liver metastases to have surgical resection.[20] To improve the results obtained with the two-drug regimens, we combined the three active agents active in CRC as first-line therapy in a young CRC patient with tumoral sigmoid stenosis, pre-occlusive symptoms and synchrone bulky liver metastases. We present here the first results available concerning the toxicity and efficacy of this approach, which appears very promising in patients with initially unresectable and even immediately life-threatening CRC.

Case report

A 36-year-old woman without medical history was admitted to the Department of Oncology of the Paul Brousse hospital (Villejuif, France) in July 1999 for the treatment of a sigmoid cancer with synchronous hepatic metastases. General status was altered (WHO performance status of 2) with a 12 kg weight loss from 75 to 63 kg over the previous 3 months. The patient had abdominal pain. The physical examination revealed a major hepatomegaly measuring 18 cm on the medio-clavicular line with evident abdominal deformation.

Colonoscopic examination showed a circumferential obstructive sigmoid tumor. The tumor biopsies revealed a well-differentiated infiltrative adenocarcinoma.

Abdominal CT scan showed a massive liver involvement of more than 75% of the hepatic parenchyma (see Figure 1A). The thoracic CT scan was within normal limits. The liver was the only detected metastatic site.

Blood cell counts were normal. Hepatic biology showed moderate elevation of transaminases with ALAT at 1.5 N , ASAT at 2.7 N and anicteric cholestasis with γ-GT at 6 N, alkaline phosphatases at 2.5 N, bilirubin at 12 μmol/l with unconjugated bilirubin at 4.

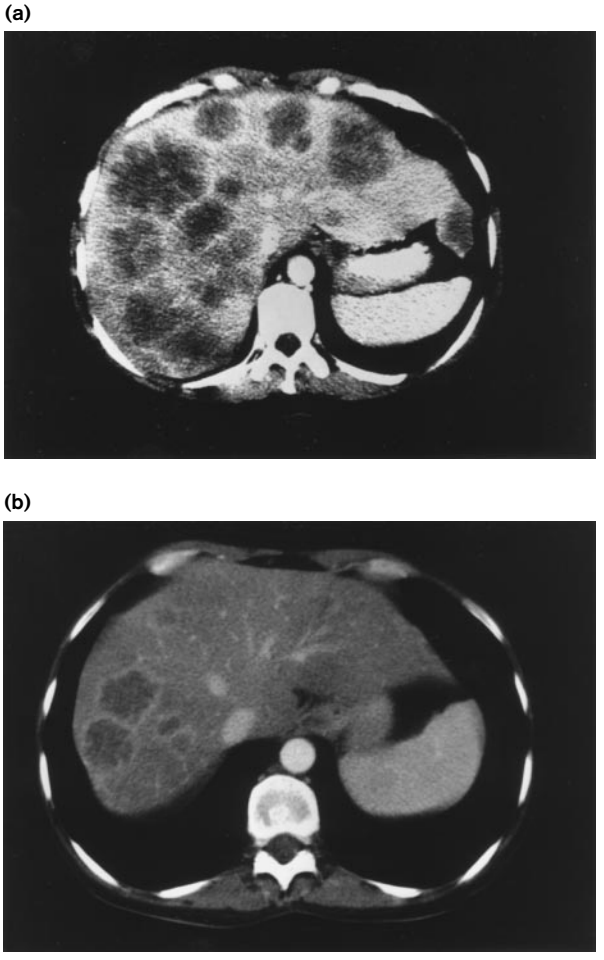

Figure 1. Liver metastases (a) prior to the first treatment cycle of chemotherapy and (b) after the sixth treatment cycle of chemotherapy.

Table 1. Toxicity following the six treatment cycles with the combination of CPT-11, FA, 5-FU and oxaliplatin

Treatment (mg/m^2) CPT-11 (day 1)/ 5-FU (days 1–4)	Grade 3–4 diarrhea	Grade 4 neutropenia	Febrile neutropenia	Treatment delay (days)
125/800 1 cycle	no	no	no	no
125/900 1 cycle	no	no	no	no
150/900 4 cycles	2/4 (cycles 3 and 4)	3/4 (cycles 3, 4, 6)	3/4 (cycles 3, 4, 6)	4, 3, 0, 6

For all the six cycles, the dose of FA was 300 mg/m^2/day and the dose of oxaliplatin was 25 mg/m^2/day, given for 4 days every 2 weeks. The doses of 5-FU and CPT-11 were varied as indicated (first column).

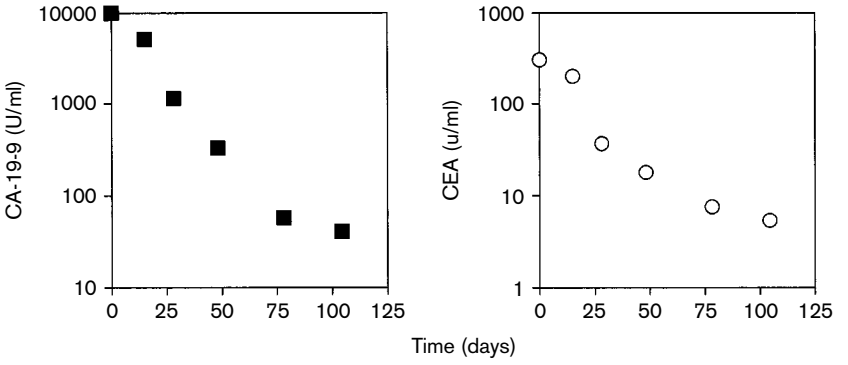

Figure 2. Kinetics of plasma tumor markers CEA and CA19-9 during chemotherapy. Day 0: levels immediately prior to the first administration of chemotherapy.

LDH were at 10.6 N. CEA and CA 19-9 plasma levels were elevated at 305.3 ng/ml (normal <5) and 9993 U/ml (normal <37), respectively. At the first cycle, CPT-11 was given at 125 mg/m^2 as a 30-min infusion prior to the start of a chronomodulated 4-day infusion with oxaliplatin 25 mg/m^2/day (peak at 16:00 h), 5-FU 800 mg/m^2/day (peak at 4:00 h) and FA 300 mg/m^2/day repeated every 2 weeks. The patient remained ambulatory and was treated at home except for the infusion of CPT-11 on day 1 which was done at the outpatient clinic. The dose of each agent and the resulting toxicity following each cycle is summarized in Table 1. Despite altered performance status and biological liver alterations, no severe toxicity was noted following the two initial courses. As a consequence, the dose of 5-FU was escalated to 900 mg/m^2/day from cycle 2 and the dose of CPT-11 was increased to 150 mg/m^2 from cycle 3.

Parenteral rehydration was necessary after cycles 3 and 4 because of severe diarrhea and vomiting. Both diarrhea and vomiting were less severe (grade 2 or less) following the fifth and sixth courses in the absence of dose reduction, possibly because of the major tumor response which resulted in less disease-related vomiting, improved intestinal transit and thus in a faster clearance of SN-38, the active metabolite of CPT-11, which undergoes entero-hepatic recirculation. Cumulative toxicities were anemia (grade 2 from cycle 5), thrombocytopenia (grade 2 from cycle 6) and neurosensory (grade 2 in the previously described Levi's scale[21]).

The abdominal pain had resolved after the first cycle of chemotherapy. The kinetics of the tumor markers is shown in Figure 2. A dramatic anti-tumor effect was seen on the liver metastases with reduction of the clinical hepatomegaly and objective partial response documented by CT scan (Figure 1A and B). The sigmoid tumor had disappeared on barium enema. Left colectomy was performed following the sixth cycle. A major anatomopathological tumor response was noted. The patient received post-surgical chemotherapy with CPT-11 combined with a chronomodulated 4-day infusion of 5-FU/FA every 2 weeks. She presently has normal CA19-9 and CEA plasma levels, and is being considered for liver transplantation.

Discussion

Although tritherapy preclinical models have not been assessed, the different mechanisms of action and resistance, the additivity or synergism observed with the three possible double combinations[22–24] and the different safety profiles give enough rational basis for its clinical investigation. Albeit very preliminary, this first experience with tritherapy suggests that the combination of the three drugs on the same day is feasible and results in a high dose intensity.

We have reported here our first experience of the combination of CPT-11 with 5-FU, FA and oxaliplatin every 2 weeks, as first-line therapy of metastatic CRC patients because we believe that it might be the most promising approach. We could maintain a high dose intensity of each agent, close to the one expected using a one- or two-agents regimen. The starting doses for this patient were based on the experience of our center of the combination of 5-FU/FA and oxaliplatin,[13,20,21,25] and of the combination of CPT-11 plus oxaliplatin,[14,15] which led us to consider a 2 weeks schedule as the best schedule for both 5-FU, oxaliplatin and CPT-11.

The dose-limiting toxicities of CPT-11 are febrile neutropenia and delayed diarrhea,[26] and were also the acute limiting toxicities of the combination of CPT-11 with oxaliplatin when given every 3 weeks.[14] Incomplete recovery of neutrophils at day 15 was the limiting toxicity when these two agents were combined every 2

weeks.[15] These acute toxicities were 3-fold more severe in patients with altered nutritional status (PS 2) than PS 0–1 patients. As a consequence, the recommended dose of CPT-11 when given with oxaliplatin every 2 weeks was 175 mg/m^2 in PS 0–1 patients and 150 mg/m^2 in PS 2 patients[15] without granulocyte colony stimulating factor support. The treatment was feasible in an outpatient setting. No pharmacokinetic interaction was detected between oxaliplatin and CPT-11 or SN-38.[14] The addition of oxaliplatin to 5-FU/FA resulted in an increased frequency of diarrhea, mucocitis and neutropenia.[8–13,20,21,25] The oxaliplatin-induced neurosensory toxicity was the cumulative dose-limiting toxicity.[8–13,20,21,25] The adaptation of dose delivery to circadian rythms has improved tolerability and has enhanced antitumor efficacy against metastases from CRC.[21,25] Chronomodulation of the chemotherapy combining oxaliplatin, 5-FU and FA was found less toxic and more effective than constant-rate infusions.[21,25] The chronomodulated 4-day infusion of these agents allowed us to give a dose of 100 mg/m^2 of oxaliplatin every other week and to reduce the incidence of mucocitis. A first-line randomized trial to test intensive 5-FU/FA/oxaliplatin versus intensive 5-FU/FA as first-line therapy reported markedly improved response rates (50 versus 22%, $p = 0.0001$) and progression-free survival (median 8.7 versus 6.1 months, $p = 0.0001$).[13]

A large panel of 5-FU and CPT-11 schedules have been tested in combination.[27–31] Using infusional 5-FU, it was consistently possible to maintain a high dose intensity of both 5-FU and CPT-11. In contrast, concomitant bolus administration of 5-FU seemed associated with severe hematotoxicity (neutropenia as dose-limiting toxicity), required dose reduction and thus led to the reduced dose intensity of both agents.[28,29] Albeit conceptually interesting and effective, the alternative combinations[32,33] are now less attractive, given the good tolerability, the higher dose intensity and the antitumor activity of the schedules giving the two drugs at the same time. Two phase III studies, one in Europe and one in the US, evaluated the effect of the addition of CPT-11 to 5-FU/FA for the first-line treatment of advanced colorectal cancer patients.[6,7] In the European study, 387 patients were randomized to receive 5-FU/FA given with or without CPT-11. Two of the most common European modalities of administration of 5-FU/FA were used, either based on the LV5FU2 or on the 5-FU. The dose of CPT-11 was 80 mg/m^2 weekly in combination with the AIO FA/5-FU regimen and was 180 mg/m^2 every other week with LV5FU2. One toxic death (infection with neutropenia) was observed in the CPT-11 arm. Forty-two percent of the patients receiving CPT-11 experienced grade 3+4 neutropenia versus 11% in the FA/5-FU arm. The frequency of febrile neutropenia was also higher in the CPT-11 arm (5 versus 1%). Grade 3–4 diarrhea was observed in 22% of the patients receiving CPT-11 versus 10% of the patients treated with FA/5-FU. In the study of Saltz *et al.*, using CPT-11 125 mg/m^2 followed by 20 mg/m^2 FA, 5-FU 500 mg/m^2 bolus, weekly times 4, every 6 weeks, the combination arm was complicated with more diarrhea but less grade 4 neutropenia, less febrile neutropenia and less mucositis than the 5-FU/FA arm. This unexpected decreased toxicity in the combination using this weekly schedule might be due either to a reduced dose intensity by omission of the last infusions of the cycle or might enlighten the interaction between 5-FU and CPT-11 at the cellular level which led to antagonism when the antimetabolite was given *in vitro* prior to the topoisomerase I-mediated DNA damages.[24]

There is a relationship between 5-FU dose intensity and the objective tumor response rate in advanced CRC patients.[34] While bitherapy may allow a better dose intensity of both agents, the tritherapy might be beneficial despite dose reduction because of the enlarged spectrum of antitumor activity covering three different targets instead of two, without cross-resistance. Ongoing clinical trials will determine how beneficial is an initial agressive approach combining 5-FU, FA, oxaliplatin and CPT-11. In less than a decade, CRC has switched from the status of a chemotherapy-refractory disease to that of chemotherapy sensitive, due the more rational use of 5-FU and to the introduction of CPT-11 and oxaliplatin. Intensified chemotherapeutic cytoreduction may be warranted to increase the fraction of patients with metastatic disease capable of undergoing surgical resection of their metastases.

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