Raltitrexed and oxaliplatin hepatic arterial infusion for advanced colorectal cancer: a retrospective study

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The aim of this study was to evaluate the efficacy and safety of combined hepatic arterial infusion (HAI), which is a combination of raltitrexed and oxaliplatin, in refractory colorectal carcinoma with only liver metastases. Seventeen consecutive patients with unresectable metastatic colorectal cancer, after the failure of two lines of systemic chemotherapy, were treated with HAI raltitrexed (3 mg/m^2 over 1 h) followed by oxaliplatin (130 mg/m^2 over 2 h) every 3 weeks between January 2006 and January 2009. All patients presented with the metastatic disease limited to the liver and had failed at least two lines of chemotherapy, which contained oxaliplatin, irinotecan and a fluoropyrimidine. The median number of cycles was six (range 1–15). We observed three complete responses and eight partial responses among assessable patients (overall response rate in intention to treat, 65%; 95% confidence interval, 44.3–87.7%). The median time to progression was 10.5 months and the median survival time was 27.5 months. Toxicity included grade 3–4 neutropenia (in 17%), grade 3–4 thrombopenia (in 17%), and grade 2 abdominal pain (in 47%). In conclusion, the combination regimen of HAI raltitrexed and oxaliplatin is feasible and promising in patients who presented isolated hepatic metastases of colorectal cancer after failure of irinotecan and oxaliplatin treatment. Further evaluation of this combination is required. *Anti-Cancer Drugs* **21:656–661 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Colorectal cancer is the third most common cancer worldwide [1]. Approximately 30% of patients with colorectal cancer present with overt metastatic disease; and metastatic disease develops in 40–50% of newly diagnosed patients. Approximately 30% of these patients present exclusively hepatic metastases. For these categories of patients prolonged survival can be obtained if complete resection of liver metastases is performed. However, only 10% of these patients are operable, and for inoperable patients only palliative chemotherapy can be proposed [2,3].

Standard first-line treatments include fluorouracil (5-FU) with leucovorin and irinotecan [4,5] or oxaliplatine [6], alone or combined with bevacizumab [7]. If the tumor expresses wild-type K-RAS and B-RAF [8,9], patients could benefit from cetuximab, a chimeric IgG1 monoclonal antibody against epidermal growth factor receptor (EGFR) [10]. In mutant K-RAS and B-RAF patients, there are no accepted treatment options after the failure of the oxaliplatin and irinotecan regimen. Indeed, after the failure of fluoropyrimidin, irinotecan, oxaliplatin, and biotherapies, the historical estimation of progression-free survival (PFS) and overall survival (OS) are about 2 and 4 months, respectively [11].

In patients that present metastases extension limited to the liver, hepatic arterial infusion (HAI) chemotherapy is a logical treatment. Indeed, when hepatic metastases once reach above 2–3 mm in size, they derive their blood supply from the hepatic artery, whereas normal hepatocytes are perfused mostly from portal circulation [12]. Floxuridine administered by intra-arterial perfusion gives a higher response rate than that of conventional systemic chemotherapies , in multitreated patients (50 vs. 10% in a recent meta-analysis) [13]. However, prolonged perfusions are required with an increased risk of catheter thrombosis and a high risk of biliary and hepatic side effects [14,15]. Moreover, floxuridine is available only in USA and Canada. Prolonged perfusions are also required for the optimal administration of fluorouracil. Oxaliplatin can also be given by intra-arterial perfusion combined with systemic fluorouracil perfusion, and this has shown a response rate even after the failure of multiple systemic therapies [16]. Until now, only a few trials have tested the combination of intra-arterial administration of oxaliplatin and fluoropyrimidine because of the complexity of fluoropyrimidine administration using the intra-arterial route [17]. Another thymidylate synthase inhibitor called raltitrexed is currently approved for the treatment of metastatic colorectal cancer, alone or in association with oxaliplatin [18,19]. Owing to its capacity to induce

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definitive inhibition of thymidylate synthase, this treatment can be used in short perfusion. Thus, this treatment can be a good candidate for HAI.

Therefore, we hypothesized that in multitreated colorectal patients, with metastases extension limited to the liver, HAI with raltitrexed and oxaliplatin can have an additive therapeutic effect. In our center, the protocol used for HAI in patients with colorectal cancer is the combination of raltitrexed and oxaliplatin.

The goal of this retrospective study was to evaluate the safety and efficacy of HAI raltitrexed and oxaliplatin in patients with unresectable liver metastases colorectal cancer, which had progressed after two lines of chemotherapy that included fluoropyrimidine, oxaliplatin, and irinotecan.

Materials and methods

Eligibility criteria

The eligibility and exclusion criteria, and pretreatment characteristics of the patients are presented in Table 1. For all patients, a multidisciplinary team composed of oncologists, radiologists, and surgeons decided to propose an HAI procedure. Informed consent was required before the intra-arterial catheter implantation procedure and chemotherapy.

Treatment plan

An intrahepatic arterial catheter was implanted in the common hepatic artery after hepatic arteriography through the femoral route. The catheter was then connected to a subcutaneous implantable port system, located in the inguinal area. After implantation, a computed tomography (CT) arteriography and a dynamic contrast-enhanced CT scan with the injection of 1 ml/s of iodine contrast material (350 mg/ml) through the port were performed, to check the absence of misperfusion and to assess the tumor perfusion, before starting hepatic arterial chemotherapy. Patients were prescribed HAI raltitrexed (3 mg/m^2 given over 1 h) followed by oxaliplatin (130 mg/m^2 given over 2 h). The pumps for the HAI injection were external ambulatory pumps (GemstarR, Company Abott, France). The treatment was repeated every 3 weeks until disease progression, limiting toxicity, technical problems or patient refusal. Dose modifications of oxaliplatin or raltitrexed were done for hematological or nonhematological toxicity, based on the most severe grade of adverse effects (National Cancer Institute Common Toxicity Criteria grade 3 or 4) that occurred during the earlier cycle. Treatment was delayed until the absolute number of neutrophils was greater than 1000/µl, platelets were greater than 100 000/µl, and mucositis and diarrhea had recovered to grade 1 or less. In particular, in the case of grade 3 or higher thrombopenia or mild permanent paresthesia, the oxaliplatin dose was reduced to 80%. In the case of grade 3 or higher neutropenia or diarrhea, the raltitrexed dose was reduced to 80%. Creatinine clearance was measured before each cycle for all patients. Recommended dose modifications for reduced creatinine clearance included cessation of raltitrexed for those with creatinine clearance of 25 ml/min or less, 75% reduction for clearance of 25–54 ml/min, and 50% reduction for clearance of 55–65 ml/min. For other toxicities of grade 3 or higher, a 20% dose reduction for both raltitrexed and oxaliplatin was prescribed by the protocol.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Histologically confirmed colorectal adenocarcinoma	Extraliver metastases (two to three lung nodules <1 cm could be included)
Disease limited to the liver	Central nervous system metastasis
Unresectable disease by surgery or other local therapies	The presence of the primary tumor with occlusive or hemorrhagic symptoms
Age >18 years	Cardiovascular disease
ECOG performance status 0–2	Pregnant or lactating women
Adequate hematological, hepatic, and renal function	
Failure of at least two lines of chemotherapy, including oxaliplatin and irinotecan-based treatment	
Failure caused by significant intolerance to either drug was allowed	
No secondary malignancy	

ECOG, Eastern Cooperative Oncology Group.

Pretreatment and follow-up evaluation

Pretreatment evaluation included physical examination, complete blood cell counts, blood chemistry, tumor marker level (carcinoembryonic antigen; CEA), and thorax, abdominal, and pelvic CT within 15 days of starting chemotherapy. Tumor responses were determined by Response Evaluation Criteria In Solid Tumors (RECIST) criteria [20]. Complete blood cell counts, serum chemistry, including liver and renal function, were performed at least every 3 weeks, and tumor assessment by thorax, abdominal, and pelvic CT and CEA dosage was performed every three cycles (9 weeks). Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0, except for peripheral neuropathy, which was graded according to the modified Levi Scale.

Statistical analysis

In the analysis of survival and subsequent treatment, all patients were followed up until death, loss to follow-up, or termination of the study. PFS and OS were calculated using the Kaplan–Meier method. PFS was calculated from the date the therapy started to the date of disease progression, and OS was calculated from the date the therapy started to the date of death.

Table 2 Patient characteristics

Characteristics	No. of patients
Median age (range) (years)	62 (42–71)
Sex	
Male	10
Female	7
ECOG performance status	
0	9
1	7
2	1
CEA level (range) (ng/ml)	548 (3–1838)
Previous chemotherapy	
Oxaliplatin (Folfox or Xelox)	17
Irinotecan (Folfiri or Xeliri)	17
Fluoropyrimidine (5-FU or capecitabine)	17
Bevacizumab (with bichemotherapy)	14
Cetuximab (always with irinotecan)	8
Number of hepatic metastases	
1–3	4
4–10	8
>10	5
K-RAS status	
Wild-type	10
Mutated	7

CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; 5-FU, fluorouracil.

Results

Patients' characteristics

Between January 2006 and January 2009, a total of 17 patients were treated by the HAI procedure using this drug combination at the Department of Medical Oncology, Georges-Francois Leclerc Cancer Center, Dijon, France. Demographic details of the patients included in the study are shown in Table 2. There were 10 male and seven female patients, median age 62 years (range 42–71). Ten patients had wild-type K-RASas tumor. All patients had received at least two systemic chemotherapy lines earlier, which included fluoropyrimidine, oxaliplatin, and irinotecan (median 2; range 2–5). All patients were assessed as progressive, based on the RECIST criteria, by their oncologist and a radiologist on their last CT scan before inclusion in the protocol. Twelve patients had received becacizumab 14 (82%) and eight patients (47%) had received cetuximab and underwent radiological progression. Importantly, all patients had been treated earlier with fluoroprymidine and oxaliplatin systemic chemotherapy, and had experienced progression according to the RECIST criteria, after this treatment.

Toxicity and feasibility

A total of 102 cycles of chemotherapy were administered (median 6; range 1–15). All patients received at least one cycle of HAI chemotherapy. Dose modifications or interruptions were necessary in three patients. Specific complications of HAI occurred in five patients, but only one required discontinuation of the treatment. In detail, we observed one case of chemical cholangitis that needed discontinuation of the treatment. In one patient, catheter occlusion necessitated its change. Two local infections of the catheter required changing them. One patient presented an extrahepatic perfusion on the angiographic CT scan that needed an embolization of the gastroduodenal artery. The incidence of hematological and nonhematological toxicity is summarized in Table 3. The major grade 3 or 4 hematological toxicity included neutropenia in three patients (17%) and thrombocytopenia in three patients (17%) that resulted in raltitrexed and oxaliplatin dose modification. One neutropenic fever with septic shock was observed. Two other patients had to discontinue the treatment because of an episode of intercurrent *Clostridium difficile* colitis and an episode of grade 4 oxaliplatin allergy. Grade 2 asthenia occurred in eight patients (47%). Grade 1/2 nausea, vomiting, and diarrhea developed in five patients; however, this toxicity was mild and manageable. Eight patients (47%) described hepatic pain during HAI perfusion that was treated by opiates. Only two patients developed worsening symptoms of peripheral neuropathy. There was one treatment-related death because of a grade 4 neutropenia and septic shock. Four deaths occurred by disease progression.

Table 3 Observed toxicity according NCI-CTC grading ($n=17$)

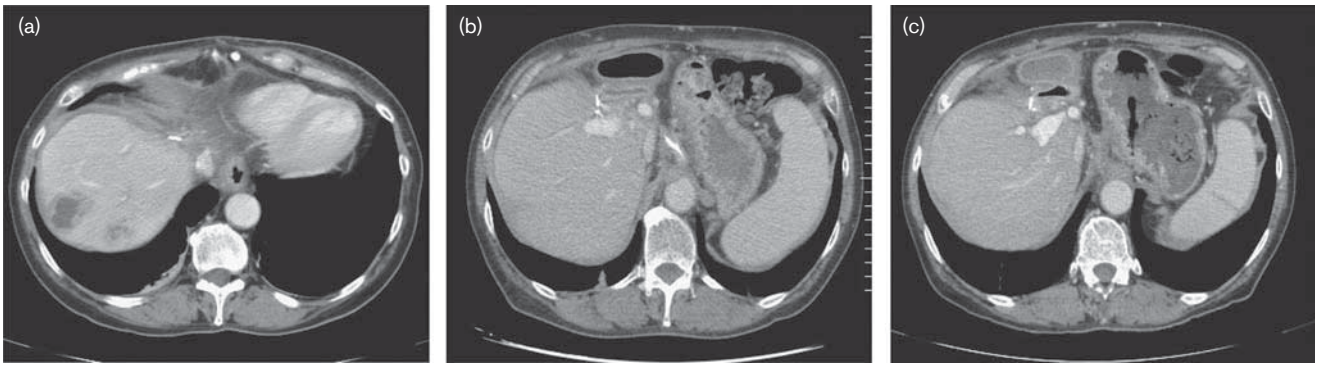
	NCI-CTC grade		
	1	All grades (%)	Severe (%)[a]
Hematological			
Anemia	4 (23)		
Leucopenia	6 (36)		3 (17)
Neutropenia	6 (36)		3 (17)
Thrombocytopenia	5 (30)		3 (17)
Nonhematological			
Nausea/vomiting	5 (30)		
Oxaliplatin allergia	1 (6)		1 (6)
Mucositis	3 (17)		
Diarrhea	3 (17)		
Infection	3 (17)		1 (6)
Asthenia	8 (47)		
Neuropathy	9 (53)		2 (12)

NCI-CTC, National Cancer Institute Common Toxicity Criteria.
[a]Grade 3–4 according to the NCI-CTC version 2.0 scale, except for neuropathy grade 3 according the Levi Scale.

Objective tumor responses and survival

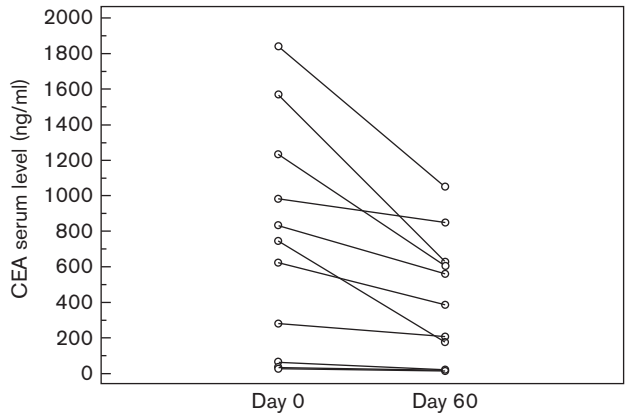
A median of six cycles (range 1–15) of chemotherapy was administered. Chemotherapy was stopped because of disease progression (in eight patients), complete remission (in three patients), local therapy (surgery or radiofrequency in two patients), or toxicity (in four patients). Only one patient received fewer three cycles of chemotherapy because of the occurrence of a fatal septic shock and was not assessed for tumor response. Among the 16 assessable patients, according to the RECIST criteria, three (17%) complete responses, eight (53%) partial responses, four (23%) stable diseases for at least 3 months, and one (6%) progression were observed. In the seven K-RAS mutated patients, we observed one complete response, four partial responses, and two stable diseases. Among the whole population, an intention-to-treat overall response rate was 65% [95% confidence

Fig. 1



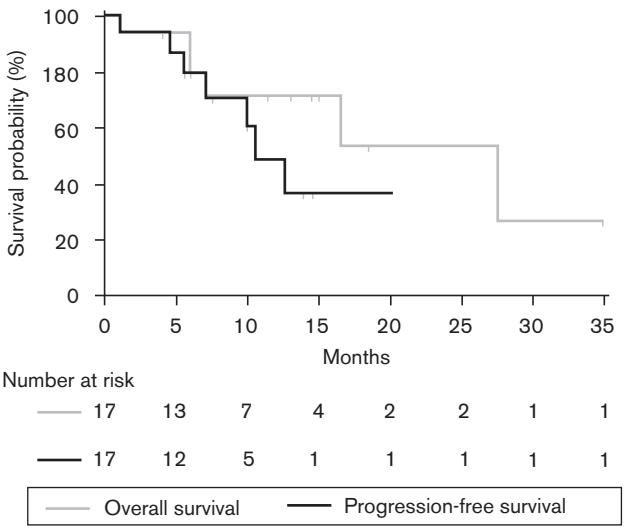
Example of tumor response. Complete response after 4 months (six cycles) of combined raltitrexed and oxaliplatin hepatic arterial infusion regimen. Here are the computed tomography scans before the beginning of the treatment (a) and after three cycles (b) and after six cycles (c). CT, computed tomography; HAI, hepatic arterial infusion.

Fig. 2



Carcinoembryonic antigen serum level before and 2 months after the beginning of the treatment.

Fig. 3



Kaplan–Meier curves of progression-free survival and overall survival.

interval (CI): 44.3–87.7], resulting in tumor control in 88% (95% CI: 72.5–100) (Fig. 1). Partial tumor response allowed radio-frequency ablation in one patient and R0 surgical resection in another. The three patients with complete responses stopped the therapy and are still alive without treatment. CEA level was informative in 13 patients, and at 2 months the CEA level decreased in all patients (mean level 837 ± 672 vs. 441 ± 386; $P = 0.0005$ Wilcoxon's test; Fig. 2). During the follow-up, five patients stopped therapy because of extrahepatic evolution, two patients stopped therapy because of liver evolution, and three because of a toxic event.

With a median follow-up of 14 months, five deaths occurred, PFS was 10.5 months (95% CI: 7–20), and the median OS was 27.5 months [95% CI: 16.5–not reached (NR)]. Figure 3 shows PFS and OS curves.

Discussion

This study suggests that the HAI combination of raltitrexed and oxaliplatin produced an intention-to-treat overall response rate of 65 and 88% of tumor control. We observed a median OS and PFS of 10.5 and 27.5 months, respectively. All patients had earlier received at least two lines of chemotherapy with fluoropyrimidine, irinotecan and oxaliplatin. In particular, three complete responses were obtained after HAI alone, and two patients benefited from radical local (surgery or radio-frequency) therapy after tumor shrinkage. Thus, HAI, using raltitrexed and oxaliplatin could bring five patients (30%) in complete remission with an arrest of cancer therapies, which is very rare in such heavily pretreated patients.

This treatment was favorable when compared with the third-line systemic chemotherapy that gave a response rate of about 10% [21] or with yttrium microsphere that gave a response rate in about 40% of the cases [22]. Compared with the fluoropyrimidine HAI regimen, which gave a 50% response rate in a recent meta-analysis [13], the response rate observed in this study seems very interesting.

The rationale to use HAI oxaliplatin was obtained from pharmacological studies that showed an extraction of oxaliplatin after HAI, and that it is concentrated in the tumor [23,24]. Although oxaliplatin alone has a very poor effect on colorectal cancer *in vitro* and *in vivo* [25–27], its combination with fluoropyrimidine or raltitrexed, which is another thymidylate synthase inhibitor, drastically enhances the efficacy of oxaliplatin. Raltitrexed is a better candidate for HAI compared with 5-fluorouracil or floxuridine, because it is a definitive thymidylate synthase inhibitor that can be administered by short infusion, and because in-vitro raltitrexed showed a higher dose dependence than 5-fluorouracil [28,29]. Moreover, in patients pretreated with fluoropyrimidine, an increase in thymidylate synthase expression was observed in liver metastases, thus rendering these cells more resistant to the conventional dosage of fluoropyrimidine and maybe more sensitive to a higher dosage of thymidylate synthase inhibitor, that are reached by HAI [30,31]. Importantly, this study is the first to test HAI raltitrexed and it clearly showed that association of raltitrexted and oxaliplatin is safe and effective.

The toxicity profile of HAI in this study is comparable with the study of testing HAI monotherapy of oxaliplatine [16,32,33]. We observed classical but manageable toxic effects of raltitrexed and oxaliplatin. Importantly, the most frequent side effect was hepatic pain that occurred during the 24 h after HAI. This side effect was managed by 24 h hospitalization and the administration of intravenous morphine PCA (patient control analgesia). Complications in the HAI procedure occurred in only five patients. Only one patient presented thrombosis of the catheter probably because we used only a short HAI procedure and a mechanical pump that could infuse chemotherapy with sufficient pressure. Moreover, the catheter was purged with isotonic NaCl immediately after the completion of chemotherapy infusion and the needle was removed. Technical problems and two cases of sepsis occurred in the patients included first. We then modified the procedure of catheter implantation. The catheter implantation was performed under prophylactic antibiotherapy (cefazolin 2 g 30 min before implantation, then 1 g every 8 h for 24 h). The first injection was administered 1 week after the implantation of the catheter (and not the day after) to obtain a good cicatrisation and only after CT arteriography and a dynamic contrast-enhanced CT. With this new procedure we did not observe further complications.

In conclusion, an HAI combination of raltitrexed and oxaliplatin is feasible, active and shows a good profile of tolerance in colorectal cancer patients with unresectable liver metastases after the failure of systemic chemotherapies containing fluoropyrimidine, oxaliplatin and irinotecan. This treatment induced a high response rate and interesting overall survival in this category of multitreated patients. Interestingly, this is the first report of HAI treatment that showed that HAI treatment could overcome resistance to modern systemic regimens using EGFR or anti-VEGF inhibitors. The use of a subcutaneous implantable catheter by a radiological procedure and a short schedule (every 3 weeks) make this treatment less invasive and more feasible than other intra-arterial procedures. A multicentric study is planned to confirm the results of this retrospective study. Although we must note the complexity of the actual setting in metastatic colorectal cancer, which requires a comprehensive multidisciplinary approach, it is of great importance to take into account the possible hurdles of locoregional therapies and to also test their utility in less advanced situations.

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