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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Hepatic arterial chemotherapy with raltitrexed and oxaliplatin versus standard chemotherapy in unresectable liver metastases from colorectal cancer after conventional chemotherapy failure (HEARTO): a randomized phase-II study

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Abstract

Background Hepatic arterial infusion (HAI) of chemotherapy could be used in patients with liver-only metastatic colorectal cancer (mCRC) to fight against chemoresistance. We previously reported the efficacy of raltitrexed plus oxaliplatin (HAI) in a retrospective series. We performed a randomized two-stage phase-II study to evaluate the efficacy of HAI of the combination of raltitrexed and oxaliplatin in refractory mCRC with only liver metastases in comparison with standard of care.

Patients and methods Eligible patients had unresectable mCRC and were refractory or intolerant to fluoropyrimidine, irinotecan, oxaliplatin, anti-VEGF therapy, and anti-EGFR therapy (for tumors with wild-type *KRAS*). Patients were randomized between HAI raltitrexed (3 mg/m^2 over 1 h) followed by oxaliplatin (130 mg/m^2 over 2 h) every 3 weeks and standard of care in a 2:1 ratio. A total of 57 patients (38 in the experimental arm and 19 in the standard of care arm) were to be included. The main objective was to demonstrate 6-month PFS of 45% by intention-to-treat analysis in the experimental arm, compared to theoretical PFS of 20%, with a unilateral alpha risk of 5% and beta risk of 10%.

Results After inclusion of 27 patients, the trial was terminated due to insufficient accrual. In the experimental arm, 11 and 4 patients experienced grade 3 and 4 toxicities, respectively. The most frequent grade 3–4 toxicities were neutropenia, liver toxicity, and abdominal pain. Median progression-free survival was 6.7 months (95% Confidence Interval; 3.9–7.2) in the HAI group and 2.2 months (95% CI 1.2–4.3) with standard of care [HR 0.32 (95% CI 0.14–0.76), $p = 0.01$]. Median overall survival did not differ between the two groups, at 11.2 months (95% CI 4.8–17.6) for the HAI group and 11.9 months (95% CI 2.8–14.3) for standard of care [HR 0.86 (95% CI 0.36–2.04), $p = 0.73$].

Conclusion Although stopped prematurely, this randomized trial provides evidence for the benefit and safety of HAI of a combination of raltitrexed and oxaliplatin in liver-only mCRC with chemoresistant disease.

Keywords Colorectal cancer · Liver metastasis · Hepatic arterial infusion · Oxaliplatin · Raltitrexed

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Introduction

Colorectal cancer (CRC) is one of the most common cancers and a leading cause of cancer death worldwide (Ferlay et al. 2013, 2015). Liver metastasis is the most frequent metastatic site in CRC and is a major cause of CRC mortality (Folprecht et al. 2005; Adam et al. 2009). An association of chemotherapy and surgery is the standard of care for liver metastasis when all metastatic site can be removed. However, when metastatic sites and primary tumor cannot be removed, chemotherapy remains the cornerstone treatment for metastatic colorectal cancer (mCRC). In such conditions,

treatment remains palliative and requires different chemotherapeutic protocols. Systemic chemotherapy dramatically enhances progression-free survival (PFS) and overall survival (OS) of mCRC patients. Treatment is currently based on the use of three cytotoxic chemotherapy drugs—fluoropyrimidine, oxaliplatin, and irinotecan—combined with targeted therapies [anti-EGFR (panitumumab and cetuximab) or anti-VEGF (bevacizumab or aflibercept) monoclonal antibodies]. Regorafenib and TAS-102 have recently been added to the therapeutic arsenal as the third line of therapy (Van Cutsem et al. 2016). In patients who present metastatic disease with extension limited to the liver, hepatic arterial infusion (HAI) of chemotherapy is a possible option. Once they exceed 2 mm in size, hepatic metastases derive their blood supply from the hepatic artery, while normal hepatocytes are perfused mostly from the portal circulation (Ridge et al. 1987; Ackerman 1974). In the setting of liver metastases resistant to conventional chemotherapy, HAI of floxuridine gives higher response rates in multitreated patients than conventional systemic chemotherapies. However, prolonged perfusions were required with an increased risk of catheter thrombosis and a high risk of biliary and hepatic side effects (Kemeny et al. 2006; Rougier et al. 1992). Oxaliplatin can also be given by intra-arterial perfusion in combination with systemic fluorouracil perfusion and demonstrated considerable efficacy in association with intravenous perfusion of fluoropyrimidine (Boige et al. 2008). 5-Fluorouracil is not used in arterial infusion, because it requires prolonged perfusion. Another thymidylate synthase inhibitor called raltitrexed is currently approved for the treatment of metastatic colorectal cancer alone or in association with oxaliplatin (Cocconi et al. 1998; Feliu et al. 2005). Due to its capacity to induce definitive inhibition of thymidylate synthase, this treatment could be used in short perfusion. We previously reported in a retrospective series the safety and efficacy of raltitrexed plus oxaliplatin HAI infusion (Khouri et al. 2010). Based on our previous results, we initiated the HEARTO study (HEpatic ARterial chemotherapy with RalTitrexed and Oxaliplatiin versus standard of care) randomized phase-II trial, which aimed to investigate the efficacy of raltitrexed and oxaliplatin HAI combination in chemorefractory CRC patients with disease limited to the liver.

Methods

Ethics

The study was approved by the Burgundy Committee for the Protection of Persons participating in clinical research. The trial was registered on ClinicalTrials.gov (NCT NCT01348412). The trial was conducted in three centers in France in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Design and population

We performed an open-label, randomized, two-stage (Simon's design) phase-II study. We aimed to investigate the effects of combined raltitrexed and oxaliplatin versus standard of care in patients with pathologically confirmed mCRC disease refractory to the standard treatment (fluoropyrimidine, oxaliplatin irinotecan, anti-angiogenic, and anti-EGFR therapies) and with metastatic disease limited to the liver. Patients were screened at Georges Francois Leclerc Cancer Center (Dijon, France), Dijon University Hospital (Dijon, France), and Besancon University Hospital (Besancon, France). The main criteria for eligibility were minimum age 18 years; Eastern Cooperative Oncology Group (ECOG) scores of 0, 1, or 2; and adequate hematological profile, renal function and hepatic function, previous failure of irinotecan and oxaliplatin-based chemotherapy, absence of extrahepatic metastatic disease with the exception of lung micronodules; previous HAI treatment; absence of previous oxaliplatin allergies; and absence of grade 3 peripheral neuropathy. After inclusion of 27 patients, the interim statistical analysis was performed as scheduled in the statistical analysis plan. The study was stopped because of low recruitment.

Treatment protocol

Experimental arm

Patients had surgical or radiological placement of a totally implanted HAI catheter (Celsite Implantable Access Port with Celsite T202F catheter or Celsite Interventional with Anthron arterial Catheter, BBraun, Velizy, France) and access port in the common hepatic artery after hepatic arteriography via the femoral route. The access port was implanted subcutaneously in the inguinal area. 1 week after implantation, CT arteriography, and dynamic contrast-enhanced CT (DCE-CT) scan with injection of 1 ml/s of iodine contrast medium (350 mg I/ml) through the port were performed to verify the absence of misperfusion and to assess tumor perfusion before starting hepatic arterial chemotherapy. In case of misperfusion, the radiologist performed additional embolization of arteries with non-liver destination. Patients were prescribed HAI Raltitrexed (3 mg/m^2 given over 1 h) followed by oxaliplatin (130 mg/m^2 given over 2 h). Treatment was repeated until disease progression or unacceptable toxicity, technical problem, or patient refusal was observed.

Standard of care arm

At the beginning of the trial, standard of care proposed was an association of capecitabine and mitomycin C. After approval of regorafenib, the standard of care arm treatment was at the physician's discretion. After progression, crossover to HAI injection was authorized.

A chest–abdomen–pelvis CT scan was performed every 9 weeks to assess tumor progression. Patients had to have received at least three cycles of therapy to be evaluable. Tumor response was evaluated using the RECIST 1.1 criteria by computed tomography (CT)-scan (Therasse et al. 2000). Patients were followed until tumor progression.

Outcomes

The primary endpoint was 6-month progression-free survival using the RECIST criteria. Secondary endpoints were response rate according to RECIST criteria and overall survival rates at 6 and 12 months. The incidence of all adverse events (AE) or serious AEs (SAE), irrespective of the link with treatment, was also analyzed.

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTC AE) v 4.0.

Sample size and statistical analysis

We proposed a non-comparative randomized phase-II trial with a randomization ratio of 2:1. In this clinical condition, an estimated 10% of patients is expected to have 6-month PFS with standard of care. A 6-month PFS of less than 20% was considered futile (P0 = 20%). A 6-month PFS of 45% was expected (P1 = 45%).

Using Simon's two-stage design, with a unilateral alpha risk of 5% and a beta risk of 10%, 16 patients at the first stage and 22 patients at the second stage for a total of 38 patients were calculated to be necessary in the experimental arm. Using an imbalanced 2:1 randomization ratio, 19 patients were thus to be included in the standard of care arm.

Analyses were performed on the intention-to-treat population. Descriptive analysis was performed using median and range for quantitative variables and number (percentage) for qualitative variables. Median follow-up was determined using the reverse Kaplan–Meier method. Survival curves were plotted using the Kaplan–Meier method. Comparisons between PFS curves in the 2 arms were performed in an exploratory manner using the log-rank test. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient population

Recruitment started in December 2010 and was stopped in July 2016 because of low recruitment. At that time, 27 patients had been included in three centers; 16 in the experimental arm and 11 in the standard arm. Median follow-up was 9.5 months (CI 1.1–26.5). In the experimental arm, median age was 65.6 (44.5–82.4) years, eight patients had RAS mutated tumor and four had right colon tumor. In the Standard arm, median age was 54.7 (39.9–81.9) years. Five patients had RAS mutated tumor and four had right colon tumor. All patients had received at least two lines of therapy. Eight patients received three lines of therapy in the experimental arm and three in the standard arm. No patients with MSI tumors were included in this clinical trial. All patients previous received anti-angiogenic therapies and received both oxaliplatin and irinotecan and experienced progression under this treatment. Six patients received anti-EGFR in the experimental arm and two in the standard arm. The baseline characteristics of the study population are listed in Table 1. HAI catheter placement was performed by interventional radiology in 12 patients and by surgery in 3 patients. HAI catheter placement was impossible in one patient. The 16 patients included in the experimental arm received a total of 84 protocol courses, resulting in a median number of 6 courses per patient (0–8).

Safety

Grade 3–4 toxicity occurred in 11/16 (69%) patients in the experimental arm and in 2/11 (18%) patients in the standard arm ($p = 0.018$). In the experimental arm, 15 patients received at least 1 cycle of HAI chemotherapy. Specific complications of HAI occurred in three patients, requiring dose modification or interruption in two patients. One patient could not receive HAI chemotherapy because of technical problems. Two patients required implantation of a second arterial catheter because of dysfunction or catheter occlusion due to arterial thrombosis. One patient presented severe abdominal pain during chemotherapy perfusion, requiring prolonged intravenous injection of morphine derivative. The incidence of hematological and non-hematological toxicity is summarized in Table 2. In the experimental arm, grade 3 toxicity occurred in 11 patients and grade 4 toxicity in four patients. The most frequent grade 3/4 toxicities were hematological (anemia and thrombopenia mostly) and digestive, with mostly abdominal pain (eight patients) and abnormal liver enzymes in

Table 1 Summary of baseline patient characteristics

	Experimental arm $N=16$ (%)	Standard arm $N=11$ (%)
Age at diagnosis, in years		
Median	65.6	54.7
Range	44.5–82.4	39.9 – 81.9
Sex—no. (%)		
Male	9 (56)	7 (63.5)
Female	7 (44)	4 (36.5)
ECOG-no. (%)		
0	14 (87.5)	8 (73)
1	2 (12.5)	3 (27)
Primary site—no. (%)		
Colon right side	4 (25)	4 (36)
Colon left side	6 (37.5)	5 (45)
Rectum	6 (37.5)	2 (19)
Mutational status—no. (%)		
Wild type	8 (50)	6 (54.5)
RAS mutated	8 (50)	5 (45.5)
Number of prior metastatic treatments—no. (%)		
2	8 (50)	8 (73)
3 or more	8 (50)	3 (27)
Prior systemic anticancer agents—no. (%)		
Fluropyrimidine	16 (100)	11 (100)
Oxaliplatin	16 (100)	11 (100)
Irinotecan	16 (100)	11 (100)
Bevacizumab	15 (94)	11 (100)
Aflibercept	3 (19)	0 (0)
Anti-EGFR	6 (37.5)	2 (18)
Primary tumor in place—no. (%)		
Yes	5 (31)	0 (0)
No	11 (69)	11 (100)

ten patients. We observed one episode of grade 4 allergic reaction to oxaliplatin. In the standard arm, two patients experienced grade 3 or more toxicity, namely, increased liver enzymes in one patient, and fatal lung infection in one patient.

Efficacy

Based on RECIST criteria at the first evaluation after 9 weeks of therapy in the experimental arm, we observed seven patients (43.8%) with partial response, 5 patients (31.2%) with stable disease, and four patients (25%) with progression, yielding a disease control rate of 75%. In the standard arm, no RECIST response was observed and only three patients had stable disease (33.3%) after 9 weeks of therapy. The primary endpoint was the rate of patients with more than 6-month PFS, with a target rate of 45%. We observed that 58.7% (29.9–79.1%) of patients in the experimental arm had more than 6-month PFS. In contrast, only 9.1% (0.5–33.3%) had more than 6-month PFS in the control arm, thus validating our hypotheses for the sample size calculation. Median progression-free survival was 6.7 (95% CI 3.9–7.2) months in the HAI group and 2.2 (95% CI 1.2–4.3) months in the standard of care group [HR = 0.32 (95% CI 0.14–0.76), $p=0.01$]. Median overall survival did not differ between the two groups, at 11.2 months (95% CI 4.8–17.6) in the HAI group and 11.9 months (95% CI 2.8–14.3) in the standard of care group [HR = 0.86 (95% CI 0.36–2.04), $p=0.73$] (Fig. 1a, b). However, six patients from the standard of care arm received HAI after experiencing progression.

Discussion

This randomized trial is the first trial, which tests HAI of a combination of raltitrexed and oxaliplatin. We provides evidence for the benefit and safety of this HAI combination in liver-only mCRC with chemoresistant disease.

Table 2 Observed toxicity in experimental arm, according NCI–CTC grading ($N=16$)

	NCI–CTC grade	
	All grades (%)	Grade 3–4 (%)
Hematological		
Anemia	11 (69)	4 (25)
Leucopenia	10 (62.5)	1 (6)
Neutropenia	6 (37.5)	2 (12)
Thrombocytopenia	11 (69)	2 (12)
Non-hematological		
Nausea/vomiting	3 (19)	1 (6)
Oxaliplatin allergy	1 (6)	1 (6)
Mucositis	2 (12)	0 (0)
Liver enzymes	15 (94)	10 (62.5)
Diarrhea	5 (31)	1 (6)
Infection	3 (19)	1 (6)
Asthenia	13 (81)	1 (6)
Neuropathy	7 (44)	1 (6)
Toxicity related to HAI procedure		
Catheter thrombosis	2 (12)	2 (12)
Pain during injection	9 (56)	6 (37.5)

When metastases cannot be removed, systemic chemotherapy remains a palliative strategy. When disease is limited to the liver, HAI can be used to bypass resistance to systemic chemotherapies. The aim of HAI is to deliver chemotherapies directly into the liver, to obtain a high drug concentration in the tumor. While FUDR was developed in the USA (D'Angelica et al. 2015; Kemeny et al. 2009), oxaliplatin-based HAI procedures were developed in European countries (Boige et al. 2008). Many trials have tested oxaliplatin HAI procedures, or the concomitant use of systemic chemotherapy with systemic LV5-FU and HAI oxaliplatin in selected patients, and these combinations have led to impressive response rates, reaching 80% in some clinical trials in first-line therapy. In second line, such therapies yield response rates in 30–50% of patients (Boige et al. 2008; Fiorentini et al. 2004, 2006; Kern et al. 2001; Mancuso et al. 2003; Del Freo et al. 2006; Bouchahda et al. 2009; Levi et al. 2016; Lim et al. 2017). In these trials, progression-free survival was around 4–5 months. Recently, we reported a retrospective study testing the association of raltitrexed and oxaliplatin during HAI procedures (Khouri et al. 2010). Raltitrexed is a definitive thymidylate synthase inhibitor that can be used in association with oxaliplatin for systemic chemotherapy. Raltitrexed is a good candidate for HAI, because it requires only a short infusion and in vitro raltitrexed demonstrated a higher dose dependence that 5-fluorouracil (Gunasekara NS, Faulds D. Raltitrexed. A review of its pharmacological properties and clinical efficacy in the management of advanced colorectal cancer. Drugs 1998; Levasseur et al. 1998). Our retrospective study in selected patients gave impressive results, with an overall response rate of 65%, and 88% tumor control. We observed median OS and PFS of 10.5 and 27.5 months, respectively (Khouri et al. 2010). Based on these results, we designed the current randomized phase-II study to test the efficacy of raltitrexed plus oxaliplatin versus standard of care in patients with liver-only metastatic CRC and previous failure of oxaliplatin and irinotecan-based chemotherapy. Treatment was well tolerated. No grade 5 toxicities were observed in the experimental arm. Only two patients required interruption of therapy due to catheter dysfunction. The toxicity profile of HAI in our study is comparable to studies testing HAI

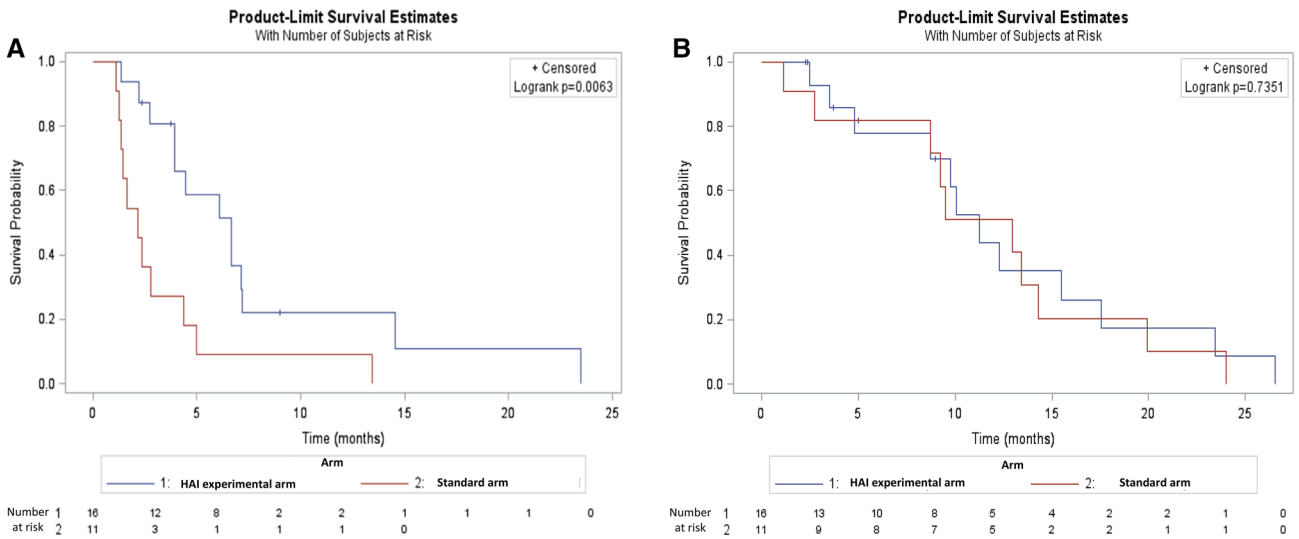

Fig. 1 Kaplan–Meier curve for progression-free survival (**a**) and overall survival (**b**)

monotherapy with oxaliplatin (Ducreux et al. 2005; Volovat et al. 2016). The main toxic effects were hematological toxicity, liver enzyme disturbances, and abdominal pain, and all adverse effects were manageable. Importantly, the most frequent side effect was hepatic pain that occurred during the 24 h following HAI. This side effect was managed by a 24-h hospitalization and administration of intravenous patient-controlled analgesia with morphine. The findings reported here confirm those of our previous retrospective study. In the present study, we observed 43.8% partial response and 31.2% stable disease, with median PFS of 6.7 months and median overall survival of 11.2 months. One of the limitations for the interpretation of these results is that the design of the study does not allow a blinded evaluation of response by the radiologist. The primary objective of the study was reached, with 6 months PFS achieved in 58.7% of patients, for an expected rate of 45%. Despite the small size of the cohort, we performed exploratory analysis and observed a significant advantage of HAI in comparison with standard of care, with a more than twofold increase in median PFS. Recently, another retrospective report compared the efficacy of raltitrexed and oxaliplatin (TOMOX) by HAI procedure versus FOLFOX HAI procedure (Guo et al. 2017). This population included 18 patients treated with TOMOX and 24 with FOLFOX. In this Asian population, OS was 15.4 and 20.6 months for the FOLFOX and TOMOX arms, respectively, while PFS was 6.6 and 4.0 months for the FOLFOX and TOMOX arms. Disease control was obtained in 87.5% and 72.2% of patients in the FOLFOX and TOMOX arms, respectively, thus suggesting similar efficacy of these two procedures (Ducreux et al. 2005).

In conclusion, our study reports the first prospective randomized trial testing HAI with a combination of raltitrexed and oxaliplatin. This procedure represents a feasible and effective approach with acceptable toxicity for patients with mCRC with liver-only metastatic disease, and who are refractory to two or more lines of chemotherapy. Additional studies with larger samples sizes are required to validate this result and compare this regimen to other HAI chemotherapeutic protocols. Currently, new local therapies could also be proposed to treat mCRC with liver-only metastatic disease such as liver transplantation (Toso et al. 2017) and radioembolization (Hendlisz et al. 2010). These new technics give new hope for patient and clinical trial that compare efficacy and safety of all these technics are awaited.

Author contributions FG and AB were the main authors of the manuscript. They were involved in the conception, design and coordination of the study as well as in data analysis, interpretation of results, and drafting of the manuscript. JV, LB, JLJ, CB, BG, and RL participated in the collection and analysis of data. JB performed statistical analysis. All authors contributed to the interpretation of data and critically revised the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval This study was prospective and approved by the Ethics Review Committee od Dijon (CCP EST 1).

Informed consent All participants provided written informed consent to participate.

Availability of data and materials The data sets generated and analyzed during the current study were not approved for public release by the Ethics Committee, but are available from the corresponding author on reasonable request.

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