Conversion to resection of liver metastases from colorectal cancer with hepatic artery infusion of combined chemotherapy and systemic cetuximab in multicenter trial OPTILIV

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Received 11 August 2015; revised 6 October 2015; accepted 28 October 2015

Background: Systemic chemotherapy typically converts previously unresectable liver metastases (LM) from colorectal cancer to curative intent resection in ~15% of patients. This European multicenter phase II trial tested whether hepatic artery infusion (HAI) with triplet chemotherapy and systemic cetuximab could increase this rate to 30% in previously treated patients.

Patients and methods: Participants had unresectable LM from wt KRAS colorectal cancer. Main non-inclusion criteria were advanced extra hepatic disease, prior HAI and grade 3 neuropathy. Irinotecan (180 mg/m²), oxaliplatin (85 mg/m²) and 5-fluorouracil (2800 mg/m²) were delivered via an implanted HAI access port and combined with i.v. cetuximab (500 mg/m²) every 14 days. Multidisciplinary decisions to resect LM were taken after every three courses. The rate of macroscopic complete resections (R0 + R1) of LM, progression-free survival (PFS) and overall survival (OS) were computed according to intent to treat.

Results: The patient population consisted of 42 men and 22 women, aged 33–76 years, with a median of 10 LM involving a median of six segments. Up to 3 extrahepatic lesions of <1 cm were found in 41% of the patients. A median of six courses was delivered. The primary end point was met, with R0–R1 hepatectomy for 19 of the 64 previously treated patients, 29.7% (95% confidence interval 18.5–40.9). Grade 3–4 neutropenia (42.6%), abdominal pain (26.2%), fatigue (18%) and diarrhea (16.4%) were frequent. Objective response rate was 40.6% (28.6–52.3). Median PFS and OS reached 9.3 (7.8–10.9) and 25.5 months (18.8–32.1) respectively. Those with R0–R1 hepatectomy had a median OS of 35.2 months (32.6–37.8), with 37.4% (23.6–51.2) alive at 4 years.

Conclusion: The coordination of liver-specific intensive chemotherapy and surgery had a high curative intent potential that deserves upfront randomized testing.


Key words: colorectal cancer, liver metastases, hepatic artery infusion, hepatectomy, cetuximab, chronotherapy

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Liver metastases (LM) affect nearly half of the 1.4 million patients who present with colorectal cancer worldwide each year [1], and represent the main cause of colorectal cancer mortality [2]. Aggressive liver-specific medico-surgical strategies however can shrink LM and enable macroscopically complete liver resection (R0–R1) resulting in consistent long-term survival [3–5]. However, hepatectomies with curative intent could typically be performed in only 15% of all patients with initially unresectable LM, following downsizing through systemic conventional or chronomodulated chemotherapy [5]. Thus, there is a need to further reinforce the targeting of current treatment strategies toward the liver, possibly through hepatic artery infusions of chemotherapy in order to attempt improve long-term survival in colorectal cancer patients [6–10].

The OPTILIV trial readily integrates hepatic artery infusion (HAI) chemotherapy into a curative intent medico-surgical strategy, with (R0–R1) hepatectomy being the primary end point, in patients who have received one to three prior systemic chemotherapy protocols. To maximize efficacy, OPTILIV combines irinotecan, 5-fluorouracil (5-FU) and oxaliplatin being given into the hepatic artery and cetuximab intravenously. The systemic administration of such triplet cytostatic combination therapy has been shown to be highly effective in downsizing LM and enabling surgical resection, as first-line treatment for metastatic disease [11–13]. The addition of cetuximab to systemic doublet or triplet chemotherapy could further enhance tumor response and resection rates and prolong survival, although this issue remains controversial [14–19]. Chronomodulated HAI of irinotecan–5-FU–oxaliplatin further enabled macroscopically complete (R0–R1) liver resection in 14% of 29 patients with unresectable LM following failure of a median of four prior systemic chemotherapy protocols [20]. Despite this very advanced setting, median OS was 18 months [20]. We reasoned that the combination of systemic cetuximab and triplet HAI could both represent the most effective regimen for LM downsizing, and enable adequate systemic treatment for controlling or preventing extrahepatic dissemination in previously treated patients with wt KRAS colorectal cancer. This hypothesis was tested in the prospective multicenter phase II trial OPTILIV.

methods

Study approval was obtained from the regulatory authorities in France, Belgium, Portugal and Italy between May 2008 and June 2010. The trial was conducted at nine centers in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

patients

Patients had histological or cytological proof of colorectal adenocarcinoma, with wild-type exon 2 KRAS. LM resection with curative intent had to be deferred at medico-surgical multidisciplinary review meetings involving an experienced hepatobiliary surgeon. Trial inclusion required at least one of the following criteria: (i) less than 30% residual liver expected after resection, (ii) malignant disease in contact with either three hepatic veins, both portal veins or the retrohepatic vena cava, (iii) documented progressive disease (PD) on imaging or doubling of serum levels of carcinoembryonic antigen (CEA) or CA19.9 over the prior 90 days or less [21]. At least one LM had to be measurable according to RECIST. Up to three extrahepatic resectable lesions of ≤10 mm were allowed. Eligible patients had received one to three prior systemic chemotherapy protocols. Other main inclusion criteria were World Health Organization (WHO) performance status (PS) of 0 or 1, absolute neutrophil count ≥10^9/L, platelet count ≥75×10^9/L and hemoglobin ≥8.5 g/dL, adequate liver and renal function tests. The main exclusion criteria included advanced extrahepatic disease, prior triplet HAI and grade 3 sensory neuropathy (NCIC CTCAE v.3.0). Prior exposure to oxaliplatin, irinotecan, 5-FU and/or cetuximab or prior surgery for LM was not exclusion criteria.

treatment scheme and modalities

Patients had surgical or radiological placement of a totally implanted HAI catheter and access port 1 week or more before protocol treatment (Celsite Implantable Access Port with Celsite T202F catheter or Celsite Interventional with Anthron arterial Catheter, BBraun, Velizy, France). Each protocol treatment course involved the i.v. administration of cetuximab (500 mg/m² over 2.30 h in the morning) followed with triplet HAI, jointly with usual intravenous supportive medications, every 2 weeks. Irinotecan (180 mg/m²), oxaliplatin (85 mg/m²) and 5-fluorouracil (2800 mg/m²) were administered into the hepatic artery catheter as a conventional or a chronomodulated delivery scheme, according to institutional choice and expertise (supplementary Figure S1, available at Annals of Oncology online). The radiological patency of the arterial catheter and the isolated perfusion of the whole liver were checked with contrast angiography before each course. The intravenous delivery of the same cetuximab–triplet combination protocol was planned in case of HAI interruption for causes other than PD or severe toxicity. Cetuximab–triplet was recommended after liver surgery for up to eight postoperative courses.

toxicity and response assessments

Blood cell counts, renal and liver serum biochemistry and plasma CEA and CA19.9 were determined before each course. PS and adverse events were graded according to WHO and NCI-CTCAE v.3.0, respectively, before each course. A thoraco-abdomino-pelvic computed tomography (CT) scan was performed within at least 1 month of inclusion, and after every third treatment course subsequently. The sum of the largest diameters of the target lesions was computed on the inclusion CT scan and used as baseline for the quantification of centrally reviewed tumor downsizing and response categorization according to RECIST. Maximum tumor response, as achieved while on triplet HAI or within the month following its cessation, was classified as complete, partial, stable or PD.

liver surgery

Decision for indication to undertake liver surgery was made at systematic multidisciplinary evaluations after every three courses. Partial hepatectomies were undertaken whenever a complete macroscopic resection of all the detected LM was foreseen, occasionally involving intraoperative radiofrequency ablation of ill-located lesions. In such cases, hepatectomy was rated as R0–R1. Further histopathology analysis was performed in the resected liver specimen for counting LM, estimating necrosis and fibrosis, assessing resection margins and any toxic lesion in the nonmalignant liver.

statistical consideration

OPTILIV aimed to increase the rate of macroscopic complete resection (R0 + R1) from a historical control rate of 15% (P0 = 0.15) on currently available systemic neoadjuvant chemotherapy [5–8] up to 30% (P1 = 0.30), with α = 5% and β = 20%, according to the exact single-stage phase II design method [22]. This required the inclusion of 48 assessable patients for the primary outcome. A 30% rate of nonassessable patients was expected for
technical reasons such as arterial complications, which could lead to HAI withdrawal within the first 2 months. As a result, the inclusion of 64 patients was planned (supplementary Text S1, available at Annals of Oncology online). All analyses were carried out with intent-to-treat using SPSS® v18.0 software (Chicago, IL). A P value <0.05 was considered statistically significant using bilateral tests.

**results**

**patient characteristics**

Sixty-four patients were registered from May 2008 to March 2012. Initial nonindication to LM resection was specified for 58 patients (90.6%), and was based on an estimated residual liver of <30% after curative intent surgery (56.3% of the patients), tight disease contact with liver main vessels (55.2%) and/or PD (73.4%). The majority of patients had bilobar LM, high number of LM and segments involved and large LM (Table 1). Extrahepatic disease was documented for 40.6% of the patients. All the patients had received prior chemotherapy (supplementary Table S1, available at Annals of Oncology online). The majority of patients had received two or more chemotherapy protocols for metastatic disease. HAI catheter placement was through interventional radiology for 49 patients (77%) or surgery for 15 patients (23%) for whom LM resection was deferred at laparotomy. The 61 treated patients received a total of 363 protocol courses, resulting in a median number of six courses per patient (1–20) for a median protocol treatment duration of 2.8 months (1st to 3rd quartiles, 1.5–4.1) (Figure 1).

**surgery of liver metastases (R0–R1), disease-free survival and patterns of relapse**

The main end point was reached, with 19/64 patients undergoing secondary R0–R1 liver resection, including 13 R0, after a median of six protocol treatment courses. Thus, in the intent to treat population (ITTP) rate of macroscopically complete tumor resections was 29.7% [95% confidence limits (CL) 18.5–40.9] (supplementary Table S2, available at Annals of Oncology online). The majority of patients had received two or more chemotherapy protocols for metastatic disease. HAI catheter placement was through interventional radiology for 49 patients (77%) or surgery for 15 patients (23%) for whom LM resection was deferred at laparotomy. The 61 treated patients received a total of 363 protocol courses, resulting in a median number of six courses per patient (1–20) for a median protocol treatment duration of 2.8 months (1st to 3rd quartiles, 1.5–4.1) (Figure 1).

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<th>Table 1. Main characteristics of the overall study population and according to the number of prior chemotherapy protocols</th>
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All the patients were previously treated with chemotherapy protocols including 5-fluorouracil (93.3% of the patients), irinotecan (78.1%), oxaliplatin (62.5% median cumulative dose, 510 mg/m²), bevacizumab (62.5%) and cetuximab (32.8%). Both irinotecan and oxaliplatin had been given to 40.6% of the patients.

*Primary tumor, lung micromodules, lymph nodes, ascites.
*bThe last systemic chemotherapy protocol was completed within a median of 1.8 months (25%–75% quartiles, 1.2–3.0 months) before inclusion.

(N = 6), steatosis (N = 6), fibrosis (N = 5), segmental cholangitis (N = 3) or regeneration nodules (N = 2). Multivariate logistic regression revealed that an age below the median of 58 years (P = 0.006), a single prior chemotherapy protocol (P = 0.006) and 10 or fewer LM (P = 0.001) were the main independent predictive factors for achieving R0–R1 resection (supplementary Table S3, available at Annals of Oncology online). The median disease-free
**Figure 1.** CONSORT diagram. ITTP, intent to treat population.

**Figure 2.** Case report in a 33-year-old patient illustrating exceptional outcome on OPTILIV as second-line treatment. (A and B) Abdominal CT illustrating occurrence of multiple nonresectable synchronous liver-only metastases from sigmoid cancer; (C and D) Minor response with partial calcification of metastases after nine courses of first-line FOLFIRI; nonresectable at laparotomy; sigmoidectomy and surgical placement of HAI catheter; (E and F) Major response after four courses of i.v. cetuximab and HAI of chronomodulated triplet; three-stage hepatectomy; only a few possibly active remaining cancer cells in a single metastasis; (G and H) Liver CT scan 3 years after third stage of hepatectomy; as of March 2015, patient is disease-free and treatment-free, with PS = 0 and no residual toxicity 6.5 years after initial presentation and 4.5 years after last treatment.
survival was 8.9 months (5.9–12.8). Relapses occurred only in the liver for six patients (31.6%), in extrhepatic sites for three patients (15.8%) and in both for six patients (31.6%), 2–50 months after protocol withdrawal, despite 15 of 19 patients received post-operative chemotherapy (supplementary Table S4, available at Annals of Oncology online).

**toxicities and dose intensities**

The initial protocol doses were effectively delivered to 76.5% of the patients receiving six courses. Grade 3–4 toxicity of any type was encountered by 47 patients (77%), and mainly consisted of neutropenia, abdominal pain, fatigue and diarrhea (supplementary Table S2, available at Annals of Oncology online). HAI was substituted by IV delivery because of HAI catheter-related issues in 38 patients. Median time to catheter occlusion was 3.3 months (2.4–8.2). The occurrence of hepatic artery thrombosis or arteritis did not affect the rate of R0 + R1 resections (10/32, 31.2% versus 9/32, 28.1%).

**tumor response, progression-free survival and overall survival**

The rates of objective responses and disease control were 40.6% [95% confidence limit (CL) 28.6–52.3] and 84.4% (75.5–93.3) respectively, with a median time to response of 1.6 months (supplementary Table S2, available at Annals of Oncology online). Most objective responses occurred after three courses on chronomodulated (7/18, 87.5%) when compared with conventional delivery (9/18, 50%). As a result, the rate of early responses was twice as large on chronomodulated when compared with conventional delivery (38.9% versus 19.6%). After a median follow-up of 41 months, median ITTP PFS and OS were 9.3 months (7.7–10.9) and 25.7 months (19.2–32.2) respectively (Figure 3A and B). The successful conversion to R0–R1 resection resulted in a median PFS of 15.7 months (12.7–18.7), while median PFS was 8.6 months (6.4–10.9) in the nonresected patients (P < 0.001) (Figure 3C). The median OS of the 19 LM resected patients reached 35.2 months (32.6–37.8), when compared with 18.7 months (12.1–25.3) for the nonresected ones (P < 0.001) (Figure 3D). These results were supported by landmark analysis, involving 11 patients with R0–R1 resection before the prespecified landmark of 6 months. The median OS of these patients was 35.2 months (23.6–48.8), when compared with 21.9 (14.0–9.8) for the 53 other patients including 8 who had liver surgery afterwards (P = 0.036). Multivariate Cox model analysis identified R0–R1 resection, initial liver replacement by tumor and sex as independent prognostic factors for both PFS and OS (with best outcomes for female patients), while the number of prior chemotherapy lines was prognostic for OS only (supplementary Table S3, available at Annals of Oncology online).

**impact of medico-surgical strategy as second-line treatment**

The medico-surgical strategy conducted here achieved secondary R0–R1 resection in 13 of the 28 patients enrolled in OPTILIV for second-line treatment (46.4%), when compared with 6 of the 36 patients recruited for third to fourth line (16.7%) (P = 0.014). Respective median PFS were 10.1 months (7.8–12.3) and 8.5 months (5.8–11.2) (P = 0.088). OS was twice as large for the patients completing the OPTILIV medico-surgical strategy as second rather than third to fourth treatment protocol, despite similar other characteristics (data not shown). Thus, the respective median survival times were 31.8 months (26.0–37.6) when compared with 15.7 months (10.1–21.2) (P = 0.001) (Figure 3E and F).

**discussion**

This is the first prospective international trial, whose primary end point is the conversion of initially uncontrolled and/or unresectable LM from colorectal cancer to resection, employing an aggressive liver-specific medico-surgical strategy. The main end point was met, achieving a complete macroscopic resection rate of LM in nearly 30% of all included patients with initially unresectable LM, as defined by the high number of LM, the bilaterality of the metastases, the high number of segments involved, the large size of the largest lesion, the ill-location of the metastases and ‘oncological’ non indication for surgery based on disease progression [5, 21].

The incidence and type of adverse events seen were in line with those encountered with systemic combinations of first-line cetuximab and triplet chemotherapy [18, 23]. The only specific adverse event was abdominal pain, an effect that was likely related to the vascular toxicity of the drugs, particularly oxaliplatin [6, 8]. However, pain was well controlled with analgesics. The major complications of the protocol treatments were hepatic artery thrombosis or arteritis, which led to the interruption of HAI delivery for nearly half of patients after a median number of six courses. This rate was 34% in our previous monocentric study using the same triplet HAI with a 3-weekly schedule, no cetuximab and no contrast liver angiography before each course [20]. The shorter interval for allowing recovery between courses, the addition of cetuximab [24] and the thorough assessment of liver artery permeability, could account for this apparent increase [25]. A prophylaxis scheme involving the HAI of dexamethasone (8 mg) and heparin 3000 IU both before and after each HAI course, was gradually implemented based on similar work using continuous HAI of floxuridine (FUDR) [7]. Nevertheless, the catheter-related events had no clinical significance as collateral arterial vascularization developed quickly. No biliary toxicity was observed, in contrast to what is known for the HAI of FUDR [6].

The OPTILIV strategy met highest expectations in this advanced disease population involving patients receiving treatment as median third-line chemotherapy, and overcoming clinical resistance to the same agents. Indeed, the 40.6% rate of objective responses and the 9.3 and 25.5 months found for median PFS and OS, respectively compare very favorably with the most effective recent systemic second or third-line chemotherapy protocols [25–28].

OPTILIV further shifted the concept of using single-agent FUDR or oxaliplatin HAI as an adjunct to systemic chemotherapy [6–8, 29] toward HAI of combination chemotherapy, and its modulation with systemic targeted agents in order to help convert LM to resection. This intensive liver-specific medico-surgical treatment strategy offered potential cures and long-term survival...
for patients with metastatic colorectal cancer in an international multicenter setting, despite the patients had prior chemotherapy and often prior liver surgery, prior progression on systemic chemotherapy and frequently concurrent extrahepatic disease. Patients on OPTILIV as second-line therapy clearly received the greatest benefit from this aggressive medico-surgical strategy. Nearly half of them had R0–R1 resection, and more than half of resected patients were alive at 4 years. However, the sample size of the patient subgroups is limited, so confirmatory studies are needed.

In conclusion, we claim that the OPTILIV strategic protocol offers patients with metastatic colorectal cancer a better chance of prolonged survival and possibly cure when compared with current standard practice. Indeed, the most recent first-line systemic chemotherapy protocols for colorectal cancer LM achieved a 5-year survival rate of 5%–15% at best [30, 31]. Application of the OPTILIV strategy could bring this figure up to 40%, a hypothesis that deserves randomized comparative trial assessment.
Acknowledgements

We sincerely acknowledge the contribution of the patients who participated in this trial and all our colleagues and staff at the participating institutions, as well as L. Proux and L. Aubrée (CRESGE, Lille, France) for the conduct of the administrative steps, trial monitoring and database management. We address sincere thanks to S. Giacchetti (Medical Oncology, Saint Louis Hospital, Paris), O. Soubrane (Hepato-Biliary Surgery, Beaujon hospital, Paris) and T. Moreau (Biostatistics, INSERM, Villejuif) for their participation in the Independent Review committee, which met periodically along the course of the trial.

Funding

This work was supported by ARTBC International, a nonprofit organization, which sponsored the trial, through obtaining support from private donators as well as Merck-Serono and Pfizer. None of them had any implication in study design, conduct, analysis or reporting. The study was supported by ARTBC International, Villejuif; Merck-Serono, Lyon; and Pfizer, Paris (France).

Disclosure

RA has honoraria to disclose from Merck Serono, Sanofi Aventis, Amgen and a consulting or advisory role for Merck Serono and Sanofi Aventis. PR has honoraria to disclose from Lilly for himself and from Ipsen, Sanofi, Celgene, Keoeyt for immediate family member; he has to disclose a consulting or advisory role for Lilly (himself) and Sanofi (his institution) and research funding from Novartis (for his institution). MD has honoraria to disclose from Roche, Celgene, Mercik Serono, Amgen, Novartis, Sanofi, Pfizer; he has to disclose grants from Roche, Chugai, Pfizer. All remaining authors have declared no conflicts of interest.

References

A randomized trial of intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma


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Background: Colorectal cancer is the third most common and the third most lethal cancer in both men and women in developed countries. About 75% of cases are first diagnosed when the disease is classified as localized or regional, undergo potentially curative treatment and enter a post-treatment surveillance program. Although such programs drain significant resources from health systems, empirical evidence of their efficacy is scanty.

Patients and methods: Dukes B2-C colorectal cancer patients who had no evidence of disease at the end of their front-line treatment (surgery and adjuvant radiochemotherapy, if indicated) were eligible for the trial and randomized to two different surveillance programs. These programs differed greatly in the frequency of diagnostic imaging. They had similar schedules of physical examinations and carcinoembryonic antigen (CEA) assessments. Patients received baseline and yearly health-related quality-of-life (HR-QoL) questionnaires. Primary outcomes were overall survival (OS) and QoL.

Results: From 1998 to 2006, 1228 assessable patients were randomized, 933 with colon cancer and 295 with rectal cancer. More than 90% of patients had the expected number of diagnostic procedures. Median follow-up duration was 62 months [interquartile range (IQR) 51–86] in the minimal surveillance group and 62 months (IQR 50–85) in the intensive group. At primary analysis, 250 patients had recurred and 218 had died. Intensive surveillance anticipated recurrence, as shown by a significant difference in mean disease-free survival of 5.9 months. Comparison of OS curves of the whole intention-to-treat population showed no statistically significant differences. HR-QoL of life scores did not differ between regimens.