# Cetuximab with Hepatic Arterial Infusion of Chemotherapy for the Treatment of Colorectal Cancer Liver Metastases

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**Abstract.** *Background: Both hepatic arterial infusion (HAI) of chemotherapy and cetuximab (CET) have interesting activity for the treatment of colorectal cancer liver metastases (CRC-LM). Patients and Methods: Intravenous CET with HAI oxaliplatin (OXA) or i.v. Irinotecan (IRI) followed by HAI of infusion of folic acid modulated 5-fluorouracil 5-FU/l-FA was administered to patients (pts) with CRC-LM who had failed at least one line of prior chemotherapy. Results: Eight pts received i.v. CET with HAI-OXA (5 pts) and i.v.-IRI (3 pts) and HAI-5-FU/l-FA. Adverse events: repeated grade 3 skin toxicity (1 pt), abdominal pain with elevated liver enzymes and asthenia (2 pts), duodenal ulcer (2 pts) with catheter migration and intestinal bleeding (1 pt), reversible interstitial pneumonitis (1 pt), and cystic bile duct dilatation (2 pts) with arterio-biliary fistulisation (1 pt). A partial response was documented in 5 pts (62%). The median time to progression was 8.7 months (95% confidence interval 8-14 months). Conclusion: Intravenous administration of CET with HAI of chemotherapy is feasible and has promising activity but is associated with specific toxicity.*

Colorectal cancer (CRC) has an annual incidence of about 372,000 cases in the European Union and over 200,000 patients will die each year from this disease (1). About half of all patients with CRC are cured by surgery, radiotherapy and adjuvant chemotherapy. Patients with resectable liver metastases have a 25-30% chance of 5-year survival following hepatectomy (2). Systemic cytotoxic therapy is considered the standard treatment for patients with inoperable metastatic disease because it is more effective than best supportive care at prolonging survival and improving quality of life. The most active cytotoxic regimens available combine the topoisiomerase I inhibitor irinotecan (CPT-11) and/or the third-generation platinum analog oxaliplatin (OXA) with the folinic acid-modulated administration of infusional 5-fluorouracil (ci5-FU/FA) or an oral fluoropyrimine (so-called FOLFOX, FOLFIRI and FOLFOXIRI regimens) (3-6). Addition of the anti-VEGF monoclonal antibody bevacizumab to first-line and second-line chemotherapy further improves survival (7-9). The median survival of patients with metastatic CRC who are not candidates for curative intent surgery remains limited to 18-20 months. Patients with inoperable liver metastases only who experience regression of their metastases and subsequently become amenable for hepatactomy may experience long-term survival (10).

The epidermal growth factor receptor (EGFR) plays a key role in the growth of normal epithelial cells and is involved by mutation and/or amplification in a significant subset of epithelial tumors (11). Despite the absence of any mutations or frequent gene amplification of the *EGFR* gene in advanced CRC, inhibition by monoclonal antibodies has clinical activity in this disease. Cetuximab, a chimeric IgG1 monoclonal antibody, is active in the treatment of patients with irinotecan-refractory metastatic CRC (12-14). Cetuximab has been safely combined with the FOLFIRI and FOLFOX regimens and improved the response rate as opposed to FOLFIRI or FOLFOX alone in two randomized studies in the first-line setting (15, 16). Panitumumab, a fully human IgG2 monoclonal antibody, also demonstrated activity in patients with metastatic CRC with disease progression during or following fluoropyrimidine-, irinotecan (IRI)- and OXA-containing chemotherapy regimens (17, 18).

Colorectal cancer has a strong predisposition to metastasize to the liver. Colorectal liver metastases are characterized by

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neovascularisation that is dependent on the hepatic arterial blood flow. Hepatic arterial infusion (HAI) of the cytotoxic drugs fluorodeoxyuridine (FUDR), 5-FU, IRI and OXA allows local drug concentrations within liver metastases to be achieved that are above those achieved with conventional intravenous (*i.v.*) dosing (19). Although systemic administration of 5-FU, IRI and/or OXA-containing chemotherapy induces toxic changes in the liver, this has not been the treatment-limiting toxicity of standard combination regimens (20).

Systemic underexposure and treatment failure outside the liver have impaired the potential of HAI with FUDR to improve survival (21). However, the systemic exposure to 5-FU and OXA, as opposed to (FUDR), is comparable following HAI as compared to *i.v.* administration at the same dose (22). Consequently, extrahepatic progression is not expected to abrogate the potential advantage of more active liver-directed treatment (23, 24). Promising activity has been reported with the use of OXA by HAI in phase I/II studies (25-33). Newer, less invasive techniques for the insertion of a hepatic artery catheter, such as the placement by laparoscopy or percutaneous procedure, have made the use of HAI more accessible (34, 35).

We have recently reported our experiences with HAI of OXA and 5-FU (29). In this pilot study, we investigated the safety and activity of adding *i.v.* cetuximab to HAI of 5-FU in combination with HAI of OXA, or *i.v.* administration of IRI in patients with pretreated stage IV CRC with predominant liver metastases.

## Patients and Methods

*Study plan, objectives and patient numbers*. The primary objective of this study was to demonstrate the feasibility and document the toxicity of *i.v.* cetuximab in combination with HAI of 5-FU and HAI of OXA or *i.v.* IRI. Recruiting patients in cohorts of 3 was planned. If >1 out of 3 patients experienced unacceptable toxicity at the initial dose level, the next 3 patients would be treated at a reduced dose level. This dose adjustment was to be decided upon the observed toxicity in the prior cohort of patients. A maximal recruitment period of 24 months was foreseen. The secondary objective of this study was to document the antitumor activity and survival.

*Patient selection criteria*. Patients were eligible for study participation if they had a histologically or cytologically documented colorectal adenocarcinoma with predominant metastasis to the liver that could not be resected with curative intent, or patients who refused such surgery. Asymptomatic extrahepatic disease localizations were allowed on the condition that the extent of the metastatic disease in the liver represented the bulk of the metastatic disease. Patients were required to have measurable disease in the liver, defined as lesions measuring >1 cm in largest diameter on spiral-computed tomography (CT) or magnetic resonance imaging (MRI); a performance status according to the WHO criteria of <2 and a life expectancy of >3 months. Up to two prior chemotherapy regimens for metastatic CRC were allowed. The anatomy of the hepatic arteries had to allow for the placement of one catheter in such a way that the liver was selectively perfused. In case of aberrant collateral arterial branches, these had to be obliterated prior to the first HAI of chemotherapy. Required laboratory values were: absolute neutrophil count (ANC) >1,500/mm$^3$, platelets >100,000/mm$^3$, partial thromboplastin time (PTT) >60% , serum creatinine <2.0 mg/dl with creatinine clearance >60 ml/min (as calculated by the Cockroft-Gault formula) and serum bilirubin <2.0 mg/dl.

Exclusion criteria were as follows: prior treatment with an EGFR-blocking agent, prior radiotherapy to all areas of measurable disease, other concurrent malignant disease, previous malignancies except for adequately treated *in situ* carcinoma of the cervix uteri, basal or squamous cell carcinoma of the skin or any other malignancy given potentially curative treatment more than 5 years before study entry, the presence of known metastatic disease in the central nervous system, pre-existing polyneuropathy with a severity of >grade 1 on the CTCAEv3.0 scale, patients at poor medical risk because of non-malignant systemic disease, as well as those with active uncontrolled infection and the concomitant use of other investigational drugs. The patients were not allowed to participate concurrently in any other clinical trial. Female patients of childbearing age not using contraceptives and nursing mothers were not allowed to participate in this study.

Patients had to be at least 18 years old and be able to perform regular visits for adequate follow-up. The Medical Ethical Committee of the UZ Brussel, Belgium approved the study protocol and all patients gave written informed consent before study entry.

*Baseline evaluation*. Baseline evaluation included a complete medical history, physical examination and laboratory studies (including complete blood count, urea, creatinine, ionogram, total bilirubin, lactate dehydrogenase, alkaline phosphatase, gamma-GT, alanine aminotransferase (AST) / aspartate aminotransferase (ALT), carcinoembryonic antigen (CEA), hepatitis B, hepatits C and HIV serology), contrast-enhanced CT or gadolinium-enhanced MRI of the abdomen and pelvis and an X-ray of the thorax. All patients underwent arteriography or angio-CT to evaluate hepatic arterial blood supply before placement of the hepatic artery catheter.

*Study treatment*. The patients were premedicated with 10 mg of oral cetirizine, 10 mg of *i.v.* dexamethasone, a setron antiemetic and in the case of OXA 1 g $CaCl_2$ plus 1 g $MgCl_2$ (in 250 ml of glucose 5% ) before and after OXA, and in the case of IRI half an ampoule of 0.25 mg/ml scopolamine. Cetuximab (Erbitux®, Merck, Overijse, Belgium) was administered by *i.v.* infusion at a dose of 400 mg/m$^2$/2 h *i.v.* on day (d) 1 and 250 mg/m$^2$/1 h *i.v.* on d 8 and for all subsequent weekly doses. Oxaliplatin (Eloxatin®; Sanofi-Aventis, Diegem, Belgium) was administered as a 6-h HAI or 2-h *i.v.* infusion at a dose of 100 mg/m$^2$. Irinotecan (Campto®; Pfizer, Brussels, Belgium) was administered as a 2-h *i.v.* infusion at a dose of 180 mg/m$^2$. L-FA (Elvorin®; Wyeth, Louvain-la-Neuve, Belgium) was administered as a 2-h *i.v.* infusion during the 2 final hours of OXA or IRI administration. After the end of OXA or IRI infusions and L-FA infusions, 5-FU was administered as a 42-h HAI by a portable pump. Treatment was repeated every 2 weeks.

*Evaluation of adverse events, dose modifications and treatment continuation*. All toxicities were graded according to the National Cancer Institute common toxicity criteria (CTCAEv3.0). Unless considered not be in the interest of the patient, retreatment and dose

modification of cetuximab and chemotherapy agents were considered independently.

In the case of ANC<1,500/mm$^3$ and/or platelets <100,000/mm$^3$ or any nonhematological toxicity (other than alopecia) that had not recovered to <grade 2 or to baseline toxicity levels on d 15 (=the planned day 1 of the following cycle), treatment had to be delayed until recovery to grade <2 or baseline. A maximum treatment delay of 2 weeks was allowed.

In the case of grade 4 neutropenia (symptomatic or not), febrile neutropenia, grade 4 thrombocytopenia or grade 3/4 thrombocytopenia accompanied by hemorrhage of grade >2 during a treatment cycle, three consecutive dose reductions were allowed (1=dose reduction of OXA or IRI by 20%; 2=dose reduction of OXA or IRI by 20% and 5-FU by 20%; 3=dose reduction of OXA or IRI by 40% and 5-FU by 20%).

In the case of grade 3 or 4 nonhematological toxicity (other than alopecia), two dose reductions (to level 2 and 3) were allowed. In the case of oxaliplatin-related isolated dysesthesia associated with pain and unrelated to cold exposure lasting more than 3 days or provoking functional impairment, two dose reductions of oxaliplatin by 20 and 50% were allowed. If, at the allowed maximal dose reduction, repeat unacceptable toxicity was seen, the patient had to stop the study treatment. In cases of severe abdominal pain during HAI treatment, treatment had to be stopped and an angiography of the hepatic artery port and hepatic artery were required to rule out extrahepatic perfusion.

In cases of treatment-limiting toxicity related to the administration of oxaliplatin or irinotecan, the patient was allowed to continue treatment with cetuximab and HAI of 5-FU/l-FA.

The dose of cetuximab was adjusted for cetuximab-related grade 3 skin toxicities only. If a patient experienced a grade 3 skin toxicity (as defined in the NCI-CTCAEv3 criteria), cetuximab therapy was delayed for up to two consecutive weeks without changing the dose level. If the toxicity resolved to grade 2 or less by the following treatment period, treatment was resumed. With the second and third occurrences of grade 3 skin toxicity, cetuximab therapy was again delayed for up to two consecutive weeks with concomitant dose reductions to 200 mg/m$^2$ and 150 mg/m$^2$, respectively. Cetuximab dose reductions were considered permanent.

*Evaluation of response and survival*. Patients underwent blood analysis (including liver tests and CEA) every 2 weeks and contrast-enhanced CT of the abdomen every 8 weeks during study treatment. The objective tumor response was assessed according to the RECIST criteria (36). Progression-free and overall survival were calculated from the date of recruitment until disease progression, death, or last follow-up (for censored cases) according to the Kaplan-Meier method using SPSS statistical software (release 7.5, 1996; SPSS Inc., Chicago, IL, USA).

## Results

*Patient characteristics*. Eight patients were recruited in this study. The patient demographics, prior history and disease characteristics are summarized in Table I. In all patients, the permanent hepatic artery port was inserted by a laparoscopic procedure during which a cholecystectomy was performed (34). In four patients (50%), a hepatic arterial port was already available because of prior treatment by the hepatic arterial route.

Table I. *Patient demographics and disease characteristics*.

| | No. | % |
|---|---|---|
| Number of patients (male/female) | 8 (7/1) | 87.5/12.5 |
| Median age in years (range) | 60 (38-68) | |
| WHO-PS 0/1/2 | 5/1/2 | 62.5/12.5/25 |
| Localization of primary | | |
| Rectum | 5 | 62.5 |
| Colon | 3 | 37.5 |
| Sites of metastasis | | |
| Liver only | 5 | 62.5 |
| Liver and lung | 3 | 37.5 |
| Surgery for primary CRC | 8 | 100 |
| Preoperative RT for rectal tumor | 2 | 25 |
| Adjuvant chemotherapy | 0 | 0 |
| Prior chemotherapy for metastatic CRC | | |
| FOLFIRI | 2 | 25 |
| FOLFOX & FOLFIRI | 3 | 37.5 |
| IV & HAI Oxaliplatin + HAI 5-FU/L-FA | 2 | 25 |
| IV & HAI Oxaliplatin + HAI 5-FU/L-FA & FOLFIRI | 1 | 12.5 |
| Hepatectomy | 1 | 12.5 |

*Treatment disposition and adverse events*. Five patients initiated treatment with the combination of *i.v.* cetuximab/HAI-OXA/HAI-5-FU/l-FA (OXA/5-FU/l-FA) and three patients were treated with *i.v.* cetuximab/*i.v.* IRI/HAI-5-FU/l-FA (IRI/5-FU/l-FA). Three patients received additional cycles of cetuximab and HAI 5-FU/l-FA (respectively 1, 3 and 10 cycles) after stopping the administration of OXA (2 patients), and IRI (1 patient). A total of 215 weeks of study treatment were analyzed (median 23 weeks, range 11-55 weeks in individual patients). Treatment is summarized in Table II and treatment-related adverse events in Table III.

A total of 178 administrations of cetuximab were performed (with a median number of 20 and a range of 8-50). The large majority (86%) of cetuximab treatments were administered at the 100% dose level. All patients experienced cetuximab-related skin toxicity. Initially this toxicity presented as acneiform dermatitis on the face, scalp and upper parts of the thorax. Two patients experienced grade 3 skin toxicity and one patient required a dose reduction following 2 consecutive treatment interruptions. The acneiform dermatitis was managed with local treatment (topical antibiotic and hydrating creams) and by courses of oral antibiotics (minocycline or flucloxacillin). The intensity of this acneiform dermatitis diminished after the 8th week of treatment in all patients. Manifestations of xerodermia with exfoliation, skin fissures and paronichia were more frequent beyond week 8 of treatment.

A total of 85 bi-weekly chemotherapy cycles were administered. Among the first three patients treated with OXA/5FU/l-FA, two experienced dose-limiting toxicity

Table II. *Study treatment*.

| | Dose level | | | | | |
|---|---|---|---|---|---|---|
| | No. pts | Total no. administered (median range) | 100% | 80-60% | DLT <8 wks (No. pts) | DLT >8 wks (No. pts) |
| Cetuximab | 8 | 178 (20, 8-50) | 154 (86%) | 24 (14%) | 1 | 0 |
| Oxaliplatin + 5-FU/l-FA | 5 | | | | | |
| Oxaliplatin 100 mg/m$^2$ | 3 | 30 | 10 (33%) | 20 (66%) | 2 | 0 |
| Oxaliplatin 80 mg/m$^2$ | 2 | 11 | 8 (72%) | 3 (28%) | 0 | 0 |
| Irinotecan + 5-FU/l-FA | 3 | | | | | |
| Irinotecan 180 mg/m$^2$ | 2 | 12 | 12 (100%) | 0 | 0 | 2 |
| Irinotecan 135 mg/m$^2$ | 1 | 18 | 8 (44%) | 10 (56%) | 0 | 0 |

DLT: dose-limiting toxicity.

(DLT) within the first 8 weeks of therapy. It was decided the dose of OXA would be lowered to 80 mg/m$^2$ in the next three patients. Two patients treated at this dose level did not experience chemo-related DLT in the first 8 weeks.

Among the first two patients treated with IRI/5F-U/l-FA, no acute DLT was observed. Both patients however needed to stop treatment after 5 and 10 cycles respectively. One patient experienced an acute upper gastro-intestinal bleeding. At gastroscopy, a duodenal ulcer was diagnosed as well as a migration of the hepatic artery catheter through the duodenal wall. The patient was hospitalized and managed conservatively with *i.v.* sandostatin, transfusion of packed cells, total parenteral nutrition and a proton pump inhibitor (first *i.v.* later *p.o.*). Evolution was uneventful and the hepatic artery catheter was removed after healing of the duodenal ulcer.

A second patient treated with IRI/5-FU/l-FA experienced an increase in upper abdominal pain that was accentuated during the administration of the ninth and tenth cycle of chemotherapy. A CT scan of the liver had indicated the appearance of hypodense, FDG-PET-negative cystic lesions throughout the liver. Besides mild HAI-related pain that was initially managed with pain medication, the patient had evolved favorably with both declining CEA levels and regression of liver metastases on CT scan. However, manual injection of contrast through the hepatic artery port demonstrated a shunt of contrast from the hepatic artery to the intra- and extrahepatic bile ducts. There was no observation of spontaneous internal bleeding and there was no associated increase in bilirubin, transaminases or alkaline phosphatases above grade 2. The hepatic artery port was removed and the catheter clipped. Further evolution was uneventful but the hypodense cystic lesions (presumably representing cyctic dilatations of the bile ducts) remained unchanged up to the latest follow-up (12 months after the initiation of HAI). This patient however resumed treatment with cetuximab and IRI because of disease progression.

Table III. *Treatment-related adverse events (worse toxicity per patient)*.

| | CTCAEv3.0 - Grade, No. (%) | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Acneiform dermatitis | 0 (0) | 6 (75) | 2 (25) | 0 (0) |
| Dry skin, exfoliation & skin fissures | 0 (0) | 8 (100) | 0 (0) | 0 (0) |
| Diarrhea | 0 (0) | 2 (25) | 0 (0) | 0 (0) |
| Nausea/Vomiting | 4 (50) | 0 (0) | 1 (12.5) | 0 (0) |
| AST | 6 (75) | 0 (0) | 1 (12.5) | 0 (0) |
| ALT | 4 (50) | 1 (12.5) | 0 (0) | 0 (0) |
| G-Glutamyl transferase | 2 (25) | 1 (12.5) | 5 (62.5) | 0 (0) |
| Alkaline phosphatase | 4 (50) | 2 (25) | 2 (25) | 0 (0) |
| Bilirubin | 4 (50) | 1 (12.5) | 0 (0) | 0 (0) |
| Asthenia | 3 (37.5) | 0 (0) | 2 (25) | 0 (0) |
| Anorexia | 7 (87.5) | 1 (12.5) | 0 (0) | 0 (0) |
| Abdominal pain | 1 (12.5) | 3 (37.5) | 3 (37.5) | 0 (0) |
| Sensorial PNP* | 0 (0) | 4 (50) | 1 (12.5) | 0 (0) |
| Leucopenia | 0 (0) | 4 (50) | 0 (0) | 0 (0) |
| Neutropenia | 0 (0) | 2 (25) | 0 (0) | 0 (0) |
| Thrombocytopenia | 7 (87.5) | 1 (12.5) | 0 (0) | 0 (0) |
| Lymphopenia | 1 (12.5) | 2 (25) | 4 (50) | 1 (12.5) |
| Hemoglobin | 7 (87.5) | 1 (12.5) | 0 (0) | 0 (0) |
| *Streptococcus bovis* septicemia (non-neutropenic) | 0 (0) | 0 (0) | 1 (12.5) | 0 (0) |
| Duodenal ulcer | 0 (0) | 1 (12.5) | 0 (0) | 0 (0) |
| Catheter migration, duodenal ulcer, upper GI bleeding | 0 (0) | 0 (0) | 1 (12.5) | 0 (0) |
| Toxic interstitial pneumonitis | 0 (0) | 1 (12.5) | 0 (0) | 0 (0) |
| Cystic bile duct dilatation | 2 (25) | 0 (0) | 0 (0) | 0 (0) |
| Arterio-biliary shunt | 1 (12.5) | 0 (0) | 0 (0) | 0 (0) |

*Oxaliplatin-treated patients only. AST: alanine aminotransferase; ALT: aspartate aminotransferase; PNP: polyneuropathy.

A third patient received the IRI/5-FU/l-FA combination at a dose of 135 mg/m$^2$ of IRI. As for the former patient, the incidence of cystic hypodense lesions was observed throughout the liver (although at a lesser extend) without clinical

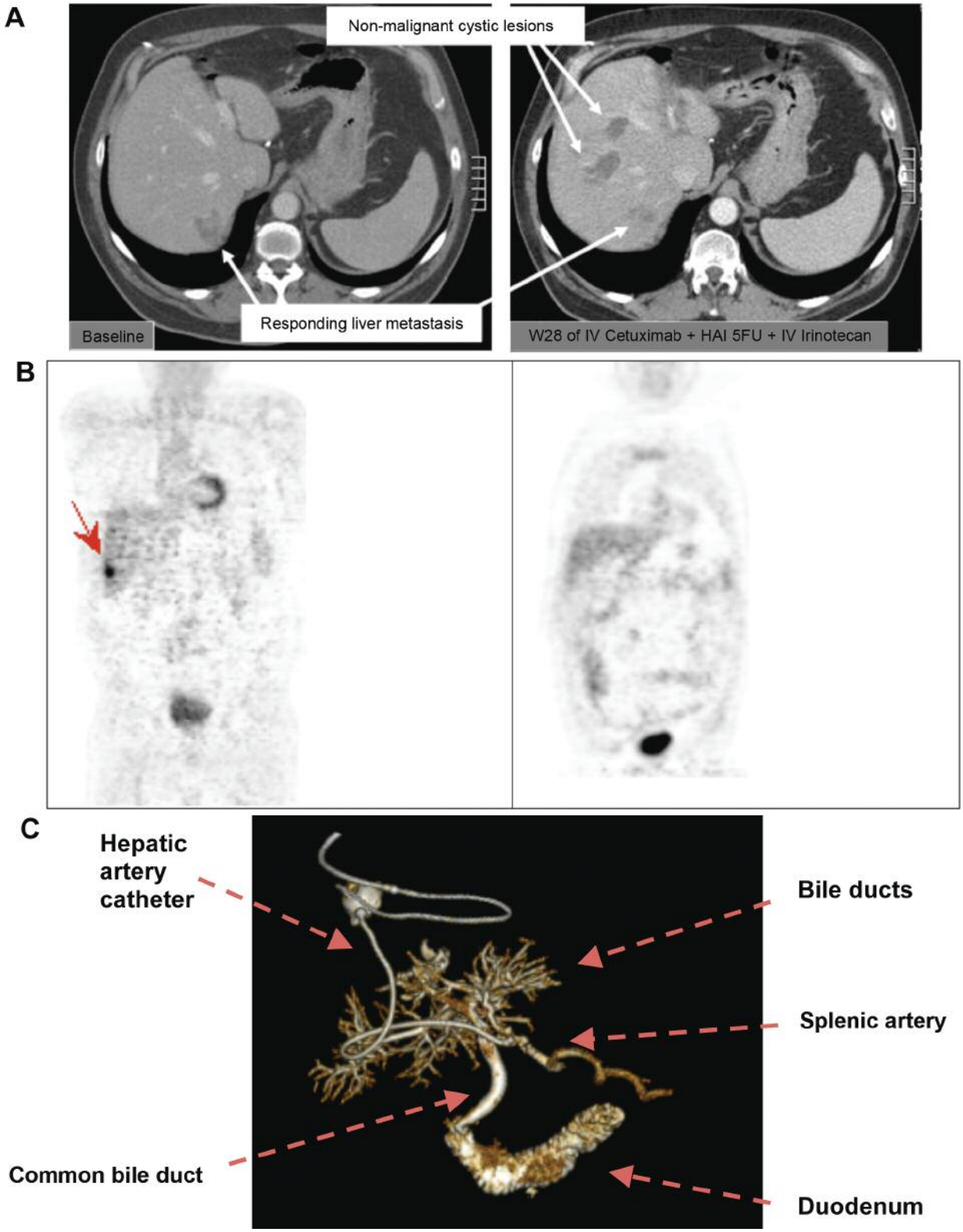


Figure 1. *Intrahepatic cystic dilatations related to treatment with i.v. cetuximab in combination with i.v. irinotecan and HAI 5-FU/l-FA. (A) Computed tomography of the liver after i.v. injection of contrast medium shows regression of hypovascular CRC liver metastases and formation of cysts in the liver. (B) Corresponding FDG-PET images show FDG-positive liver metastases at baseline and complete metabolic response following treatment. (C) Arterio-hepatic shunt phenomenon following manual injection of contrast fluid into the hepatic artery catheter (3-dimensional CT-image).*

symptoms or increase of liver enzymes and bilirubin in the blood. No arterio-biliary shunt was observed in this patient at repeated examination and the patient remained on study treatment for 40 weeks with a near-complete regression of his liver metastases and normalization of CEA levels. Treatment was discontinued because of a thrombosis of the hepatic artery.

All except one patient experienced mild to severe upper abdominal pain related to the administration of chemotherapy by HAI. This pain typically increased with subsequent cycles of chemotherapy. Pain was managed with the use of opioid pain medication (*e.g.* oral tradonal, or transdermal buprenorphine). Concomitant with the increase of HAI-related pain three patients also experienced severe asthenia and elevated cholestatic enzymes. This syndrome of toxic hepatic injury was reversible upon treatment interruption and patients resumed treatment thereafter.

One patient developed a toxic interstitial pneumonia that was reversible after discontinuation of the study treatment and one patient experienced a *Streptococcus bovis* septicemia (non-neutropenic).

The five patients on OXA-containing chemotherapy all developed sensorial grade 2 sensorial polyneuropathy (PNP). One patient who had a grade 1 residual PNP due to prior OXA treatment needed to stop OXA following the 5th cycle of chemotherapy due to worsening of the PNP to grade 3.

Nausea, vomiting and hematological tolerance were mild with the exception of noncomplicated lymphopenia (grade 3/4 in 5 patients).

*Antitumor activity (CEA and tumor response according to RECIST criteria)*. All patients had an elevated CEA level at the time of treatment (median 99 kU/l, range 6-374 kU/l). Normalization (<laboratory) upper normal limit of the CEA level that persisted for more than 4 weeks was documented in two patients. In an additional five patients, the CEA decreased more than 50% for more than 4 weeks.

Regression of the hepatic metastases was seen in all patients (the maximal reduction of the sum of the longest diameter of the ≤5 target lesions in individual patients was between 23% and 48%). A partial tumor response (PR) according to the RECIST criteria was observed in five out of eight patients (62%, the PR was confirmed in 4/8 patients). In two patients, regression of the liver metastases was documented at the first evaluation on week 8 but new metastases to the lungs (despite further regression of liver metastases) were documented at the second evaluation in both patients (at week 12 and week 16 respectively). No correlation was found between the response characteristics and the results of EGFR immunohistochemistry (IHC).

*Time to progression and overall survival*. Four patients stopped study treatment because of and have died due to disease progression. In three patients, progression was restricted to the lung (2) or the lung and the brain (1). Four patients stopped study treatment because of treatment-related adverse events. Three of these patients are being followed up with progression of disease and one patient is alive without progressive disease 30 months after the initiation of study therapy.

According to Kaplan-Meier survival estimates, the median time to progression of our study population is 8.7 months (95% CI 8-14 months). The median overall survival from the initiation of study treatment and from diagnosis of metastatic disease has not been reached (respectively over 18 and 40 months).

## Discussion

Despite the advances made in the medical treatment of advanced colorectal cancer, the life expectancy for patients with metastatic disease who cannot undergo resection with curative intent remains poor. Contemporary medical treatment rarely succeeds in the complete cure of individual metastatic sites, even if a complete radiological remission is obtained (37). Complete cytoreduction, as achieved by surgical removal of metastases from the liver and/or the lung remains the only therapeutic option that can offer a significant percentage of 5- and 10-year survival. Even in the case of inoperable patients rendered operable following chemotherapy, survival is substantially improved (10). New modalities that can substantially increase the complete pathological response of liver metastases might impact significantly on survival. Hepatic arterial administration of 5-FU-based combination chemotherapy might achieve this as higher concentrations of cytotoxic drugs can be delivered to the hepatic metastases without compromising systemic exposure to the cytotoxic drugs. In addition, systemic administration of new targeted agents against the EGFR, such as cetuximab, might further increase the antitumor activity.

In this single institution pilot study, we tested the feasibility of the combination of cetuximab with the administration of combination chemotherapy by HAI in pretreated colorectal cancer patients with predominant metastases to the liver. Our observations indicate that such therapy is feasible and active but at the cost of increased treatment complexity and associated morbidity. Some of the treatment-related adverse events we encountered are well known to be associated with the drugs that were used and the use of HAI and can be managed. These include the cetuximab-related skin toxicity, the upper abdominal pain syndrome related to the infusion of cytotoxic agents (this was seen with both the OXA and IRI combinations), the reversible hepatic toxicity in some patients and the OXA-related sensorial PNP. All other systemic adverse events (such as nausea, vomiting and hematological toxicity) were not more frequent than what would have been expected. The high incidence of lymphopenia is most likely related to the extensive prior treatment of most patients and was not of clinical relevance.

The patients with toxic interstitial pneumonitis and non-neutropenic *Streptococcus bovis* septicemia (an infectious agent that has been associated with CRC) are most likely due to coincidence than being specifically related to the study treatment. Interstitial pneumonitis has been associated with the use of small molecule tyrosine kinase inhibitors and most frequently in Asian patients. The EGFR monoclonal antibodies cetuximab and panitumumab have not been associated with this toxicity. It is therefore more likely that this case of interstitial pneumonitis was related to a non-EGFR-mediated toxic injury of the lungs. The fact that it was reversible upon withdrawal of the study treatment supports this hypothesis as cases related to the use of gefitinib or erlotinib have typically been irreversible and life threatening.

Of interest is our observation of two cases of intrahepatic cystic dilatation of the bile ducts. These represent, to our knowledge, the first two cases that are described in the literature. The bile ducts are dependent on the hepatic artery and are therefore more susceptible to toxicity using HAI of cytotoxic agents as compared to the hepatic parenchyma that derives most of its blood supply from the portal vein. The use of FUDR without co-infusion of dexamethasone results in an unacceptable incidence of sclerosating cholangitis. This toxicity has not been observed with HAI of 5-FU. Intravenous administration of IRI (as was the case in our study) has been related to the occurrence of steatohepatitis rather than cholangitis. The combination of cetuximab, IRI and 5-FU by HAI is however most likely to have induced the cystic intrahepatic lesions we observed. These lesions were hypometabolic (as assessed by FDG-PET), were asymptomatic and were not accompanied by an important rise in liver enzymes or bilirubin. Histopathological examination of these lesions is not available at present but would be required to determine the exact nature of this toxicity. Not withstanding their seemingly absent repercussion on the patient's health, they should be regarded as a sign of potentially dangerous and irreversible toxicity. However, both these patients had received prior treatment with HAI of OXA and 5-FU which could have predisposed their liver for this unexpected toxicity.

We conclude that the observed antitumor activity and survival in our patient population are encouraging. Further study of these regimens in a phase II protocol restricted to patients who had no prior HAI treatment and have CRC liver metastases that cannot be resected (even after response to *i.v.* treatment) is justified and two such protocols have been initiated in France. New insights into the use of predictive biomarkers for the sensitivity towards OXA, IRI and cetuximab (such as *KRAS* mutation status, *EGFR* gene copy number and *PTEN* mutation status) should aid the decision-making on which kind of combination therapy is likely to benefit which patient most (38-42).

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