

Hepatic Arterial Chemotherapy with Oxaliplatin, Folinic Acid and 5-Fluorouracil in Pre-treated Patients with Liver Metastases from Colorectal Cancer

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Abstract. *Background:* Hepatic arterial chemotherapy (HAC) is an effective treatment of liver metastases from colorectal cancer (CRC). Phase I and II studies have already shown the feasibility and efficacy of intra-arterial oxaliplatin (OXA). *Patients and Methods:* Twenty-one pre-treated patients with liver metastases who received HAC with OXA/folinic acid (FA)/5-fluorouracil (5-FU) at our Division between March 2000 and November 2003, were clinically examined. Most patients were heavily pre-treated with two or more systemic chemotherapeutic regimes. All patients received a percutaneously implanted catheter into the hepatic artery through femoral or transaxillary access. Treatment was administered every 14 days: OXA 100 mg/m² as a 12-hour infusion on day 1; FA 100 mg/m² as a 2-hour infusion on days 2 and 3; 5-FU 2600 mg/m² as a continuous infusion on days 2 and 3. *Results:* Grade 3-4 toxicities were: asthenia (2 out of 21), transaminase elevation (2 out of 21) and pain (2 out of 21), nausea and vomiting (1 out of 21), neutropenia (1 out of 21), thrombocytopenia (1 out of 21) and neurotoxicity (1 out of 21). Main dose limiting toxicity was right upper quadrant pain. Response rates were: 5% complete response, 19% partial response, 28% stable disease and 48% progressive disease. Two patients became operable and underwent complete resection of liver disease. The median overall survival was 36.1 months. Two-year and 3-year survival rates were 62% and 52%, respectively. *Conclusion:* This regimen is feasible with low toxicity and with an encouraging overall tumor growth control (52%) in a subset of heavily pre-treated

patients. Intra-arterial OXA/FA/5-FU should be considered for the treatment of patients pre-treated with systemic chemotherapies with liver metastases from CRC.

Liver metastases from colorectal cancer (CRC) are present at diagnosis in 15-20% of patients or developed during disease progression in about another 50% of patients. Radical surgery remains the only curative treatment, while systemic chemotherapy is offered to the unresectable patients (1). Because of the poor outcome associated with metastatic CRC, alternative strategies have been explored.

One such strategy is hepatic arterial chemotherapy (HAC) for patients with liver-only metastases (2). Multiple trials over the past decades have shown that HAC is an effective treatment for liver metastases with superior response rates (RR) compared to systemic chemotherapy even if there is no significant improvement in survival (3). Thus, clinical use of this regimen has not been recommended. Recently, in a randomised trial, HAC with floxuridine, FA and dexamethasone has been compared with an intravenous (i.v.) bolus regimen with 5-fluorouracil (5-FU) and folinic acid (FA) in patients with metastases confined to the liver, and a significant advantage in overall survival (OS) was shown for HAC versus systemic treatment (24.4 vs. 20 months) and time to hepatic progression (9.8 vs. 7.3 months) (4).

Oxaliplatin (OXA) is a new platinum compound with significant activity in CRC. For patients with unresectable and/or extrahepatic disease, systemic chemotherapy with OXA combined with FA and 5-FU has produced RR greater than 50% and OS of more than 20 months. Two-year survival rate, however, remained poor (25-30%) and long-term survivors were rare (5-7). In a rabbit tumor model intra-arterial (*i.a.*) hepatic OXA has shown a significant pharmacokinetic advantage compared with *i.v.* infusion (8). Several phase I and II studies of HAC with OXA have been published to date. Tolerability and efficacy in heavily pre-

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Table I. Patient characteristics.

Total patients	21
Male/Female	12/9
Median age	63 (42-78)
Colon/rectum location	15/6
Synchronous / metachronous	8/13
Liver involvement	<25% = 4 <50% = 14 >50% = 3
PS 0-1/PS>1	17/4
Adjuvant/no adjuvant CT	10/11
3 line metastatic CT	11
4 line metastatic CT	10

PS: performance status; CT: computed tomography.

Table II. Toxicities.

Toxicity	Grade	
	1-2	3-4
Nausea/vomiting	17/21	1/21
Hepatic toxicity	15/21	2/21
Fatigue	10/21	2/21
Anemia	11/21	0
Neutropenia	9/21	1/21
Diarrhoea	10/21	0
Thrombocytopenia	5/21	1/21
Neuropathy	7/21	1/21
Pain	5/21	2/21
Anaphylaxis	2/21	0

treated patients have been demonstrated; in particular a liver extraction of OXA above 50% with reduced systemic bioavailability has been reported (9-12).

The aim of this study was to determine the feasibility, toxicity and efficacy of OXA/FA/5-FU given *i.a.* in patients with unresectable liver metastases (ULM) from CRC heavily pre-treated with two or three regimens of systemic chemotherapy.

Materials and Methods

Between March 2000 and November 2003, 21 patients with ULM who received HAC with OXA, FA, 5-FU in a prospective phase II study were evaluated.

Main inclusion criteria. The main inclusion criteria for the study were: histologically verified adenocarcinoma of the colon or the rectum, metastatic disease localized to the liver with bidimensionally measurable lesions, performance status (PS) Eastern Cooperative Oncology Group (ECOG) 0-2, liver replacement by tumor <70%, modest hepatic insufficiency with total bilirubin <2.0, aspartate transaminase (AST) / alanine transaminase (ALT) <4 times the upper limit of normal, absence of portal vein thrombosis, adequate bone marrow and renal function and years of age 18 to 75. Written informed consent was obtained from all patients.

Treatment. The patients received a percutaneously implanted catheter into the hepatic artery through femoral or transaxillary access with a subcutaneous reservoir, which could then be accessed intermittently or continuously for treatment. Anatomical variants of the hepatic artery could preclude perfusion of the entire liver, in which case small vessels were tied off to allow complete and specific hepatic perfusion. The patients received treatment every 14 days: OXA given 100 mg/m² as a 12-hour infusion on day 1 followed by FA 100 mg/m² as a 2-hour infusion on days 2 and 3, and by 5-FU 2600 mg/m² as a 48-hour infusion on days 2 and 3; two such treatments consisted 1 cycle. Antiemetic prophylaxis with 5-HT3-receptor antagonist granisetron (8 mg) *i.v.* and dexamethasone (8 mg) *i.a.* prior to the application of OXA, as well

as dexamethasone (8 mg) *i.a.* during 5-FU-infusion were administered. Treatment was continued for six months in the case of clinical response or until disease progression, unacceptable toxicity or in accordance with patient's choice. Toxicity was assessed before starting each treatment using the National Cancer Institute (NCI)-Common Toxicity Criteria. In cases of grade 2 hematological or grade 3 non-hematological toxicity one rest week was allowed.

Evaluation criteria. Physical examinations and blood counts were performed in every treatment. Hepatic and renal function, carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19.9 tests, and computed tomographic (CT) scans of measurable lesions were assessed at baseline and repeated after three and six cycles. World Health Organization (WHO) criteria were used to assess tumour response. Liver surgical treatment was planned for 4 weeks after completion of chemotherapy. The primary objectives of the study were to evaluate the toxicity profile and the RR of OXA administered as HAC; the secondary objective was to increase the rate of liver resection.

Results

Twenty-one consecutive patients entered this study over 44 months. All patients were evaluable for toxicity and tumor response.

Patient characteristics. Patient characteristics are shown in Table I. Ten out of 21 patients received adjuvant chemotherapy with systemic regimens containing 5-FU. Eleven patients received HAC as a third chemotherapeutic regime (after systemic regimens containing 5-FU and OXA), and 10 as a fourth chemotherapeutic regime [after systemic regimens containing 5-FU, OXA and irinotecan (IRI)].

Toxicity. One hundred and twenty-nine treatments have been administered with a median number of 6 treatments per patient (range 1-12 treatments). The incidence of the main toxicities is summarised in Table II. In general, toxicity

mainly consisted of nausea/vomiting (18 out of 21 patients), hepatic toxicity (17 out of 21 patients), fatigue (12 out of 21 patients), anemia (11 out of 21 patients), neutropenia (10 out of 21 patients), diarrhoea (10 out of 21 patients), sensory neuropathy (8 out of 21 patients), thrombocytopenia (6 out of 21 patients), upper abdominal pain (7 out of 21 patients) and anaphylaxis to OXA (2 out of 21 patients). The main dose limiting toxicity was right upper quadrant pain which was observed in 7 out of 21 patients. Catheter thrombosis or displacement occurred in 3 out of 21 patients.

Response. One patient achieved a complete response (CR), four a partial response (PR), six a stable disease (SD) and ten a progressive disease (PD) for a RR of 24% and an overall tumor growth control (TGC) of 52%. The CR was observed by CT-scan in a patient with metachrone metastases and lasted 8 months. Three out of the four PR were observed in patients with synchrone metastases and one in a patient with metachrone metastases. Two PR and five SD were obtained in patients not responsive to systemic chemotherapy with OXA. Two patients became operable and underwent a complete resection (rate of liver resection of 10%). The median OS was 36.1 months and 2- and 3-year survival rates were 62% and 52%, respectively. The median OS from the diagnosis of liver metastasis was 23.7 months. The median OS from the start of HAC was 10.6 months. The median time to progression was 5.9 months.

Discussion

Untreated patients with ULM of CRC have a poor prognosis, with a median survival of 6-12 months and 5% 5-year survival. Surgical resection is the only effective treatment for liver metastases: in resected patients the 5-year survival rates are 25-37% and 10-year rates 20-22%, but, unfortunately, less than 20% of patients are candidates for resection. For the majority of patients systemic chemotherapy with new agents and 5-FU have shown interesting RR but long-term survivors are very few. HAC is an attractive therapeutic option because extraction of cytotoxic drugs from the hepatic arterial circulation *via* the first-pass effect can result in high local concentrations and minimal systemic toxicity. A recent trial has demonstrated that HAC improved RR with a positive trend on survival compared to systemic chemotherapy. The ideal agent should have a high dose-response curve, high extraction rate, and rapid total body clearance once infusion is discontinued. Preclinical studies are necessary to evaluate the best concentration- and time-dependent cytotoxic effects of the drugs used in hepatic arterial infusion, because the combination of more cytotoxic agents do not always result in synergistic anti-proliferative effects (13).

The feasibility and the low toxicity of *i.a.* OXA/FA/5-FU was confirmed in the present study. No complications related to angiographic technique occurred. The toxicity was similar to that for systemic delivery of OXA but most symptoms were not severe and manageable by the administration of supportive drugs; right upper abdominal pain and not sensory neuropathy was the main dose-limiting toxicity. The RR (24%), the overall TGC (52%) and the median OS (36.1 months) are interesting because a poor prognosis population was treated, including heavily pre-treated patients (48% treated with OXA and IRI), 38% with synchronous metastases and 81% with a liver involvement of more than 25%. Moreover, two PR and five SD were obtained in patients not responsive to systemic chemotherapy with OXA; this could be due to the prolonged exposure of tumor cells to the drug during *i.a.* therapy. Slow continuous infusion of the drug over 12 hours could have resulted in a higher proportion of tumor cytotoxicity and less overall toxicity. Intra-arterial OXA, FA, 5-FU should be considered as an integrated strategy in the treatment of ULM of CRC after failure of current systemic chemotherapies.

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