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Intraarterial Hepatic Chemoembolization of Liver Metastases from Colorectal Cancer Adopting Irinotecan-eluting Beads: Results of a Phase II Clinical Study

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Abstract. *Since November 2005 a clinical trial of intraarterial hepatic chemoembolization (TACE) with irinotecan-eluting beads has been ongoing in 20 patients affected by liver metastases from colorectal cancer in a palliative setting. A high response rate (80%), with reduction of lesional contrast enhancement in all responding patients was found. The procedure was well tolerated by most patients, with a median duration of hospitalization of 3 days (range 1-10 days). The most important adverse event was abdominal pain during the injection. Adequate supportive treatment with antibiotic and antiemetic prophylaxis, dexamethasone, and intravenous hydration is strictly necessary until the serum levels of transaminases are stabilized and in order to prevent infections. Major analgesics such as morphine must be used before and after the procedure. Our results suggest that TACE using irinotecan-eluting beads is feasible and active in pretreated patients with liver metastases from CRC.*

The development of liver metastases from any solid tumour heralds a poor prognosis, unless the metastases are surgically resectable. For patients diagnosed with colorectal carcinoma (CRC), the vast majority of deaths are due to hepatic metastases with the liver being the second most common site of spreading disease after the lymph nodes (1). In approximately 35% of patients with CRC, metastases are confined to the liver (2). Surgery is the standard treatment in patients with isolated or limited liver disease. However less than 20% of the patients are suitable candidates for radical resection (1, 3). Nevertheless, approximately 70% of these patients have a disease relapse.

Evidence of regression of initially unresectable liver metastases after neoadjuvant chemotherapy offers new potential in improving long-term outcome for these patients (4-6). In a non-randomized study enrolling patients with CRC and liver involvement, treated with surgery after neoadjuvant chemotherapy, Adam *et al.*, report a 5-year survival of 34% (4, 5). After this report, the first attempt of oncologists has been the down staging of the disease to reach a level adequate for liver resection (2, 4, 5).

As regards patients with extra-hepatic metastatic disease or unresectable liver involvement, systemic 5-fluorouracil (5-FU)-based chemotherapy with combination of oxaliplatin and/or irinotecan (FOLFOX, FOLFIRI) offers higher response rates (RR) (35-50%) and longer median survival (15-20 months) *versus* observation or 5-fluorouracil (7-9).

The introduction into the clinical practice of bevacizumab, a recombinant humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), in combination with chemotherapy (irinotecan and 5-FU-leucovorin) in patients with previously untreated advanced CRC, produced an improvement in response rates (50%), progression-free (PFS) (10.6 months) and overall survival (20.3 months) (10). On the other hand, bevacizumab plus 5-FU-based systemic chemotherapy for patients refractory to oxaliplatin or irinotecan is rarely associated with response (11). Cetuximab, a humanized monoclonal antibody against epidermal growth factor receptor (EGFR), combined with irinotecan in refractory patients, produced a response rate of 23% and PFS of 4.1 months (12). Finally, Saltz *et al.*, reported interesting preliminary results using a combination of bevacizumab, cetuximab and irinotecan in advanced colorectal cancer, refractory to first-line irinotecan-based chemotherapy (13).

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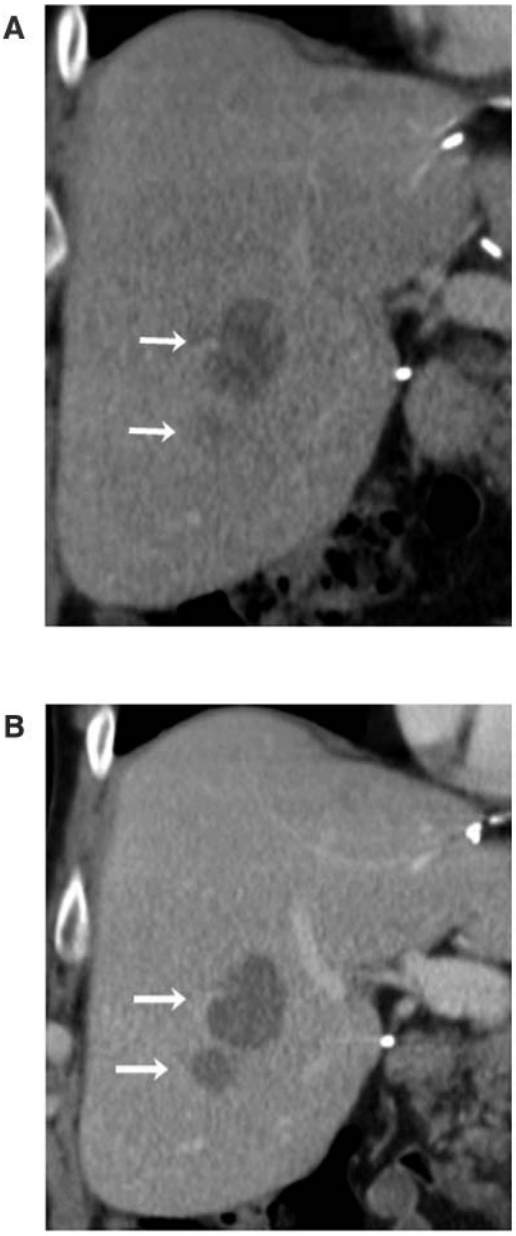

Figure 1. *A) CT scan with MPR reconstructions showed two metastases in the right hepatic lobe (arrows). B) CT scan at 1 month after TACE, hepatic lesions showed homogeneous ipodensity. C) CT scan at 3 months: one lesion decreased in size, the other one disappeared.*

These authors reported a response rate of 37% and a PFS of 7.9 months with the three-drug treatment, and an RR of 20% and PFS of 5.6 months (13).

The addition of new drugs for the treatment of CRC has extended the median survival beyond 21 months, but all treatments remain clearly palliative and yet there is no evidence that the new therapies increase the cure rates (14).

Nevertheless, the doubling of the median survival has been accompanied by a 340-fold increase in therapy costs. While the monthly Mayo Clinic regimen costs $63, the FOLFOX regimen costs $11,889 and $21,033 when combined with bevacizumab (14). Similarly, the combination of irinotecan and cetuximab for patients whith advanced and metastatic pre-treated CRC increases the median survival by 1.7 months, but an 8-week course costs more than $30,000 (14). Considering the poor outcome of these patients and the high costs of specific therapies, alternative strategies should be evaluated, particularly after a second or third-line chemotherapy.

Intraarterial hepatic chemotherapy combined with vascular occlusion agents (TACE) or single vascular occlusion (TAE) has a potential in a palliative or symptomatic setting (1). TACE is a combination of local drug infusion with selective embolization of the feeding arteries of the liver metastases. The advantage of delivering chemotherapy by hepatic arterial infusion is the administration of a high-dose of the drug to the target. The aim of this therapeutic technique is to reduce the tumor size by ischemic necrosis and direct drug effects. Largely used for the treatment of hepatocellular carcinoma, it is also used in a neoadjuvant or palliative setting in patients with isolated liver metastases from CRC (1, 17). Radiofrequency (RF) can be considered another valid therapeutic choice (15, 16). Different types and caliber of microspheres, as well as collagen and gelatin sponges are used to produce a temporary arterial hepatic occlusion and polyvinyl alcohol is used to obtain permanent embolization (1, 17-27). Mitomycin-C (MMC), melphalan, cisplatin, epirubicin and irinotecan have been the most used chemotherapeutic agents in such procedures (17-22).

The most common complication experienced by almost all patients undergoing chemoembolization is post-

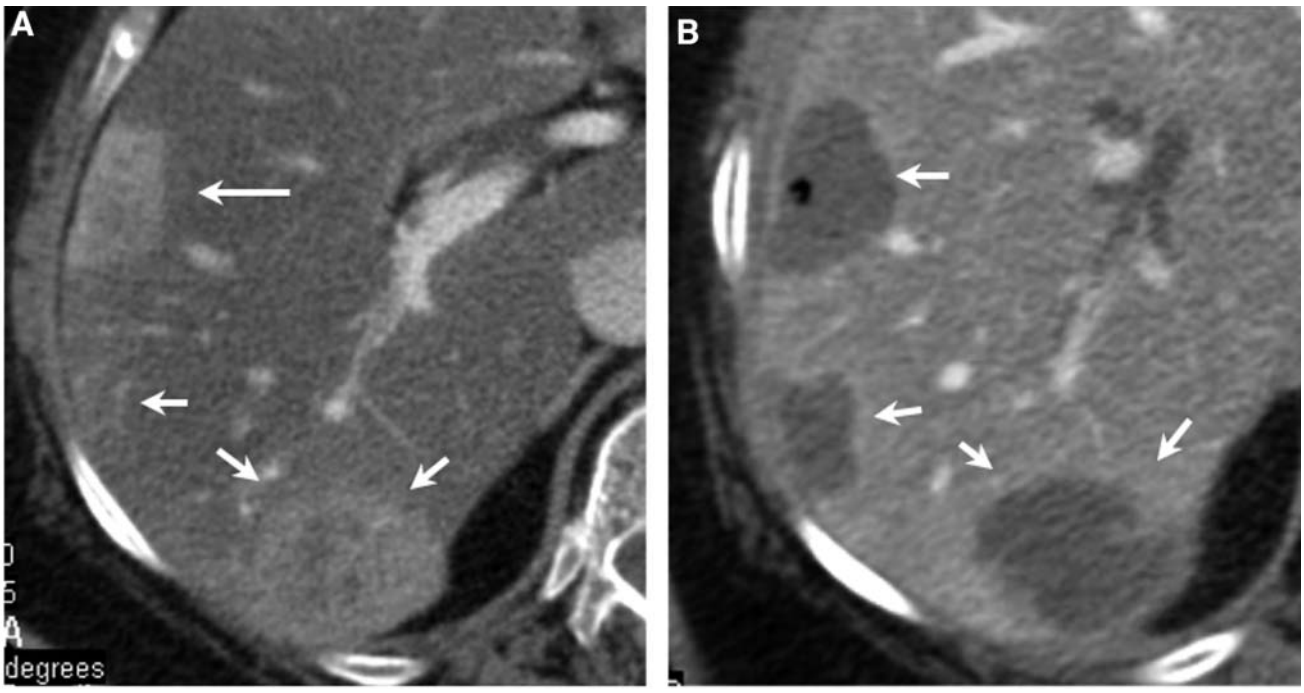

Figure 2. *A) CT scan showed three hypervascularized hepatic nodules (arrows). B) CT scan after 1 month showed absence of intra-lesional contrast enhancement.*

embolization syndrome, with pain in the right upper quadrant, nausea, vomiting, fever and elevation of liver enzymes (1). These adverse events are less pronounced when temporary vascular occlusive agents are used (1, 17). Less common complications are liver abscess, tumor rupture, acute liver failure and infarction (17-29).

Over the last few years, many efforts have been made to provide a more accurate dosage of drugs delivery to the liver for a more prolonged period, and new agents, more active and efficacious *via* systemic administration, have been tested *via* intraarterial infusion. Hepatic infusion of irinotecan has been demonstrated to be safe and feasible, with a favorable activity in patients with liver metastases from colorectal cancer (30, 31, 32). DC beads are new embolic microsphere products that can be loaded with irinotecan before administration. The use of irinotecan drug-eluting beads seems active and feasible from previous studies (27, 34).

Since November 2005 we have carried out a study with irinotecan drug-eluting beads in order to better assess the safety, feasibility, tolerability, response rate and duration of response, as well as to define the modifications of the contrast enhancement ratio evaluated by computed tomography in liver metastases. We have also studied the impact on survival rate and quality of life of treated patients (35, 36).

Patients and Methods

Patient enrolment. Thirty-one patients were evaluated for recruitment, 11 of which refused, preferring palliative care or complementary medicine. Twenty patients were enrolled into the clinical study.

All patients had CRC, not resectable, nor treatable with further chemotherapy histologically confirmed liver metastases >1 cm in size. The measurable liver tumour burden was of no more than 75% of the total liver volume. The presence of extra-target sites of disease was allowed only if the bulk was in the liver. A performance status of 0-2 (WHO criteria) and a life expectancy of at least 3 months, with age <85 years were required. Previous chemotherapy had to be discontinued at least 4 weeks prior to study entry. All patients had multiple lesions with liver substitution: 8 patients grade I (<25% involvement), 7 patients grade II (<50%) and 5 patients grade III (up to 75% of substitution).

Exclusion criteria were history of inflammatory bowel disease, significant diseases of cardiac, renal, bone marrow or pulmonary apparatus, central nervous system involvement, uncontrolled infection, liver function tests and bilirubin 3-folds or more the normal value, history of other cancer except adequately treated *in situ* carcinoma of the cervix or basal or squamous carcinoma of the skin, not understanding or not acceptance of written consent.

All patients had a CT scan of the abdomen and pelvis, baseline complete blood cell count, carcinoembryonic antigen (CEA), lactate dehydrogenase (LDH), alkaline phosphatase, AST, total bilirubin, albumin and creatinine determinations. CT was used to determine the percentage of liver involvement and assess response.

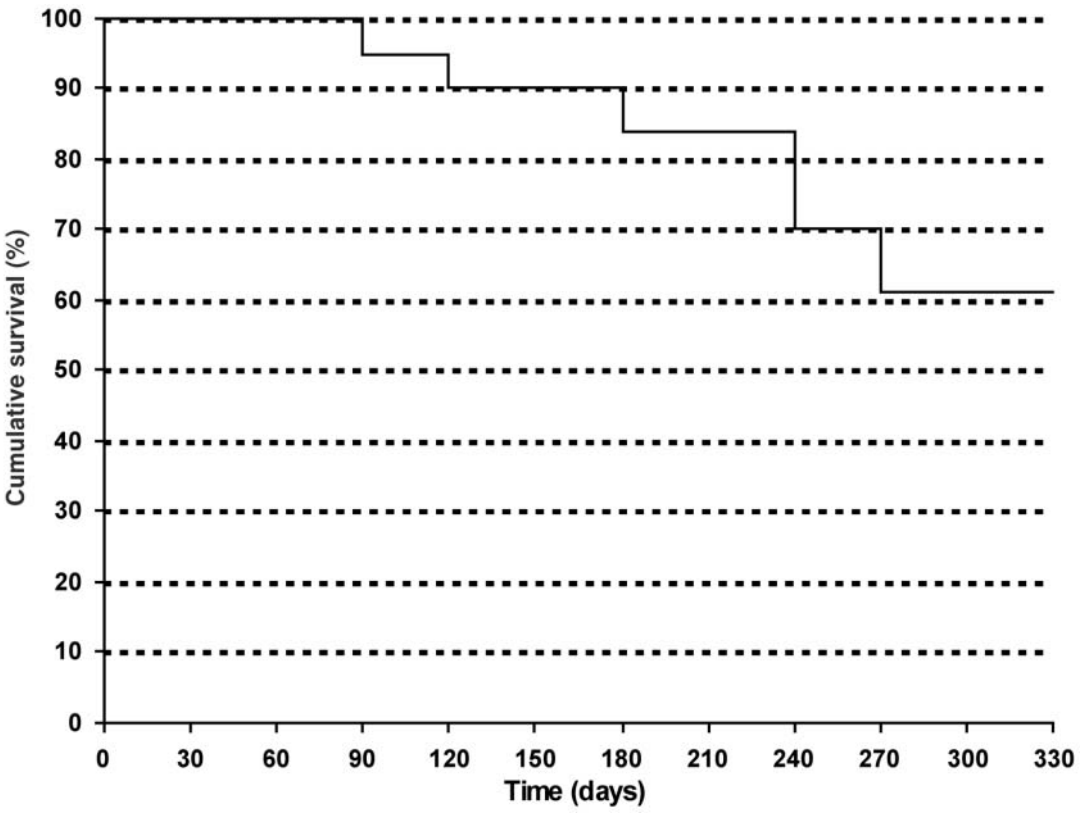

Figure 3. *Survival curve (Kaplan-Meier method).*

Twenty patients were enrolled into the study: one of them had one metastatic lesion, one presented four lesions. Eight patients presented multiple lesions with a median liver substitution of 40% (range 20-70%). All patients had undergone prior chemotherapy for metastatic colorectal cancer, eight patients progressed after a partial response due to FOLFOX and two after a partial response induced by FOLFIRI.

Treatment. Irinotecan drug-eluting beads were administered as TACE once every 3 weeks (range 1-3) at a dose of 100 mg. The dose was reduced by 50%, after the first cycle, if toxicity grade 4 occurred. Treatment was stopped in cases of progressive disease, toxicity persisting more than 5 weeks or patient refusal.

Drug administration. The irinotecan loaded microsphere solution was prepared 2 hours before TACE. Diagnostic angiography (DSA) was performed under fluoroscopic guidance. A solution of 2-4 ml of 100-300 μm and/or 300-500 μm irinotecan drug-eluting beads mixed with non-ionic contrast medium was injected into the artery feeding the metastases. A total of 40 individual TACE were performed with 100% technical success. We performed 25 TACE with Irinotecan 100 mg preloaded in 2 ml of 300-500 μm microsphers and 15 with irinotecan 100 mg preloaded in 2 ml of 100-300 μm and 2 ml of 300-500 μm microspheres.

Six patients received one TACE, 8 patients received two TACE and 6 received three TACE. In 16 procedures, treatment was administered following selective cannulation of the right branch of the hepatic artery, in 5 procedures of the left branch and in 19 procedures of both branches.

Program of supportive treatment and intra-arterial lidocaine. The prophylactic treatment to prevent renal failure was *i.v.* hydration which started on the day before TACE and continued on days 0, +1, +2 with a bag of 2000 ml (1000 ml of saline solution, 1000 ml of glucose 5%) with the addition of ranitidine 900 mgr, infused for 24 hours. Ranitidine was used to reduce the risk of gastric and pancreatic toxicity.

The prophylactic treatment against nausea and vomiting was based on tropisetron 5 mg, 1 vial before TACE and 1 vial after 6 hours on day 0 and dexamethasone 8 mgr at 08.00 am and 08.00 pm on days 0,+1,+2,+3,+4,+5.

The prophylactic treatment against pain was based on morphine 10 mg, 1 vial, 30 minutes before and 6 hours after TACE. Intra-arterial lidocaine 5 ml was infused immediately before TACE.

Prophylactic treatment against infection was based on cefazolin 2000 mg at 08.00 am and 08.00 pm on days 0,+1,+2. The supportive treatment went on if required on days +3,+4,+5.

Study end-points. The primary objective of this study was to determine the safety, feasibility and tolerance of TACE adopting irinotecan-loaded microspheres. The secondary objective was to evalue the response rate, quality of life and survival of patients.

Evaluation of response and toxicity. Pretreatment evaluation included a complete history and physical examination, a complete blood cell

count, blood chemistry tests including creatinine, alkaline phosphatase, γ-glutamyl-transferase, bilirubin, prothrombin time, CEA and CA19-9. Clinical evaluations were scheduled before the procedure at 1 and every 3 months. Each examination included: clinical status, complete serum biochemistry, dynamic computed tomography (DCT), positron emission thomography (PET) was considered optional.

The Edmonton Symptom Assessment System (ESAS) questionnaire seems one of the best methods to define anxiety and depressed mood related to physical symptom burden. The compilation of the ESAS questionnaire was carried out at every clinical examination (36).

The behaviour of tumor vascularity was evaluated by DCT 1 month after TACE to define the percentage reduction of the contrast enhancement in the liver metastases.

Complete response was defined as the complete disappearance of lesional contrast enhancement.

Results

All patients were evaluable for response and toxicity. A response rate of 16 out of 20, according to RECIST criteria, was observed. CT scans showed a reduction of the lesional contrast enhancement in all responding patients (Figures 1, 2). One month after TACE, a reduction of more than 50% of the CEA level was achieved in 12 of the treated patients. Fifteen out of 20 patients are still alive, with a median follow-up of 200 days (range 90-380 days). The median survival has not been reached (Figure 3). The mortality was due to: one heart stroke, three progressive disease, one pulmonary embolism. Regarding toxicity, all patients experienced grade 2 fever (WHO criteria) for 2 days (range 1-7 days), grade 2 and 3 right upper abdominal quadrant pain was observed in 10 and 5 patients, respectively, lasting 12 hours (range 3-30 hours). Finally, grade 2 nausea and vomiting was observed in all patients, for a median duration of 11 hours (range 2-48 hours). None of the patients experienced bone marrow toxicity. One patient developed a liver abscess two days after TACE. Prolonged antibiotic therapy was required to avoid a surgical approach. One grade 3 toxicity occurred as acute pancreatitis, with spontaneous resolution.

Eighteen out of 20 patients declared an improvement in their quality of life. The median duration of hospitalization was 3 days (range 1-10 days).

The calculated cost of the whole TACE procedure, including angiographic hall, catheters, non-ionic medium contrast, DC beads and irinotecan 100 mg, was between €1.200 and €1.800.

Discussion

Despite the introduction of new chemotherapeutic agents and molecular target therapy for patients with liver metastases from CRC, the prognosis remains poor and the 1- and 3-year median survival is 31% and 2.6%, respectively (2-7). Systemic chemotherapy with or without biological target therapy produces a high response rate and an increase in resectable liver disease, progression free- and overall survival. But all patients experience hepatic and/or extra-hepatic progression of the disease. At the same time, a significant increase in the cost of chemotherapy which does not provide an increase in the cure rate has been observed. Despite only a limited benefit on overall survival and a considerable deterioration of the quality of life of the patients, high cost antineoplastic drugs are proposed (14). Nevertheless, according to the Outcomes Working Group of the American Society of Clinical Oncology (ASCO), the primary endpoint of any treatment should be survival and quality of life, giving a secondary relevance to cancer outcomes (response rate) and pharmacoeconomic evaluation (35). In a palliative setting and for patients with metastatic disease limited to the liver, regional approaches able to provide local control of the disease with less impact on quality of life and relatively low cost, regarding drug costs, hospitalization and technical procedures, are needed. Selected patients (CEA level <200 ng/ml, <3 lesions of diameter <5 cm, age <70 years, not heavily pretreated) could benefit from radio frequency ablation (RFA) (15, 16).

When RFA cannot be proposed for a patient, TACE is a suitable procedure able to offer effective hepatic control and prolonged survival. In recent decades, many efforts have been made to improve the outcome of TACE by integrating new chemotherapeutic agents and providing a more accurate dosage of drug delivery to the liver for a more prolonged period. Irinotecan was demonstrated to be a useful and safe drug when administered into the hepatic artery, and DC Bead™ embolic microspheres are able to load irinotecan and release the drug in a sustained way in the liver after injection in the hepatic artery.

Responses to TACE are reported for about 50% of the patients, although to date it has not been clearly demonstrated if the high response rate is correlated with increased overall survival or improved quality of life (17-27). Muller *et al.* in a study on a relatively large series of patients reported a high response rate with a 2-year survival of 66%, combining intraarterial 5-FU chemotherapy and granulocyte-macrophage colony-stimulating factor (Gm-CSF) with TACE using melphalan, lipiodol and gelfoam (20).

We performed this clinical trial of TACE with irinotecan-eluting beads in 20 patients affected by liver metastases from colorectal cancer in a palliative setting, observing a relevant response rate of 16 out of 20, with significant reduction of lesional contrast enhancement in all responding patients. The procedure was well tolerated by most patients with a median duration of hospitalization of 3 days (range 1-10 days). The most important adverse effect

was abdominal pain, especially during injection of irinotecan-DC beads. A major analgesic, such as morphine, must be used in the procedure. Adequate supportive treatment with antibiotic and antiemetic prophylaxis, dexamethasone and intravenous hydratation is strictly necessary until stabilization of transaminase serum levels and in order to prevent infections.

Our results suggest that TACE using irinotecan-eluting beads is feasible and active in pretreated patients with liver metastases from CRC. We are now planning an international multicentric phase III clinical trial of TACE with 100 mg irinotecan-eluting DC Beads™ *versus* FOLFIRI chemotherapy in second-line treatment of CRC patients with liver metastases in order to evaluate the efficacy and clinical utility of this therapeutic approach. The objectives of the phase III study will be overall survival and quality of life evaluation. We consider that irinotecan-eluting bead-TACE with 100 mg of irinotecan may be an appropriate palliative therapy for patients after chemotherapy failure.

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