in vivo *20*: 707-710 (2006)

Hepatic Arterial Chemotherapy in Combination with Systemic Chemotherapy Compared with Hepatic Arterial Chemotherapy Alone for Liver Metastases from Colorectal Cancer: Results of a Multi-centric Randomized Study

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Abstract. *Hepatic arterial infusion (HAI) chemotherapy is accepted to be an option in patients with non-resectable metastases from colorectal cancer confined to the liver. In a multi-istitutional trial, 76 patients were randomly assigned to receive HAI versus HAI plus systemic bolus 5-fluorouracil and leucovorin. The primary end-point was survival, followed by response, recurrence and toxicity. Survival was longer for HAI plus systemic chemotherapy (HAI+SYC) than HAI (median, 20 vs. 14 months; p=0.0033), as were responses (47.5% and 41.7%; p=0.09) and time to hepatic progression (12 vs. 8 months; p=0.039). Side effects included haematological toxicity that was mostly mild and reversible in 432 cases. Neutropenia grade 3 occurred in four patients in the HAI+SYC arm and one in the HAI arm. Diarrhoea occurred in 20% and 7% of patients and stomatitis occurred in 18% and 2%, respectively. On the contrary biliary toxicity was significant; twelve patients had evidence of bilirubin elevations of more than 3 mg/dl (six in each arm), and two had asymptomatic arterial biliary-tree fistulae: one in the HAI+SYC arm and one in the HAI arm. Grade 3 elevation in alkaline phosphatase and aminotransferase levels occurred in 26% and 24%, respectively. In conclusion, the combination of HAI+SYC is active and safe showing a clinical advantage with respect to simple HAI, increasing overall survival, response rate and time to progression.*

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Key Words: Intra-arterial hepatic chemotherapy, liver metastases, colorectal cancer.

Colorectal cancer (CRC) is one of most prevalent cancers worldwide (1). In Europe, it has an incidence of about 150,000 new cases per year. With worldwide 500,000 related deaths yearly, it is ranked near the top of the leading causes of cancer death. Its prognosis is primarily determined by the stage of disease. Overall 5-year survival is estimated to be about 60%, whereas in the presence of distant metastases, 5-year survival rates are less than 10%. Liver metastases are the most frequent sites of advanced disease in CRC; about 50% of the cases are limited to the liver and not resectable at diagnosis. More than half of all patients develop hepatic metastases, and in one third of these patients the liver is the only metastatic site discovered. If these metastases are resectable, radical resection offers the best chance of long-term survival, otherwise palliative systemic chemotherapy is the treatment (2). In patients with non-resectable metastases confined to the liver, hepatic arterial infusion (HAI) chemotherapy has been considered to be an option (3, 4).

In view of the high incidence and frequent hepatic localization of metastases from colorectal cancer, studies involving HAI chemotherapy have been initiated. HAI was proposed as a treatment option for non-resectable hepatic metastases larger than 3 mm because they derive their blood supply mainly from the hepatic artery (4-8).

HAI is intended to result in a high exposure of the tumor tissue to the administered chemotherapy, whereas normal liver parenchyma, which is mainly supplied by the portal circulation, is relatively spared (5, 6). However, this is only the case if the active drug is eliminated rapidly by hepatic extraction (first-pass effect). Because this also results in low systemic concentrations, compared to intravenous (*i.v.*) administration, less systemic toxicity may be expected. HAI of 5-fluorouracil

(FU), and especially of fluorodeoxyuridine (FUDR), approximates to this ideal pharmacokinetic profile, in the sense that 95% of the FUDR is extracted by the liver, resulting in 16-fold higher concentrations in the hepatic metastases, compared to *i.v.* administration (5-8). Usually, hepatic arterial chemotherapy is infused slowly for a longer period, because prolonged exposure of tumor cells to the drug is assumed to result in higher therapeutic effects as well. Compared to *i.v.* schedules, HAI chemotherapy strategies based on FUDR have failed to show significant differences in median survival, although HAI of FUDR has seemed to be correlated with higher response rates (8). Compared to the response and survival rates with current combination schemes including oxaliplatin and/or irinotecan, these single HAI-strategies appear to be equal or inferior, even though comparative clinical trials have not been done (2, 8). The present randomized study was designed to determine if FUDR given as HAI and combined with systemic chemotherapy (SYC) is superior to FUDR given as HAI alone. In other words, whether the double route of administration is more effective than HAI alone in patients with liver metastases from CRC.

Materials and Methods

In May 1993 a randomized multi-centric phase III trial was started comparing HAI plus SYC *versus* HAI alone.

All patients were previously untreated and presented non-resectable liver metastases from CRC with less than 50% liver involvement following Pettavel's classification.

All patients had histologically confirmed CRC tumors and measurable hepatic lesions. Entry requirements included a Karnofsky performance status of 80% or better, a serum bilirubin level of 1.8 mg/dl or lower, and no evidence of extra-liver disease. Pre-operative evaluation included a complete history, a physical examination, chest roentgenography, computed tomography (CT) of the abdomen, accurate ultrasonography, a complete blood count, measurement of carcinoembryonic antigen (CEA) levels and a serum biochemical screening profile. After informed consent had been obtained, the patients underwent laparotomy to evaluate the absence of extrahepatic lesion and to position a hepatic artery implantable port.

The port was placed in a prepared pocket in the abdominal wall, with the tip of the catheter inserted into the common hepatic artery. A methylene blue test was performed to confirm the complete perfusion of the liver. An external pump for HAI was adopted in all patients.

WHO standard criteria were used for the evaluation of results and toxicity. Complete response (CR) was defined as the disappearance of all disease as assessed by clinical evaluation, CT, biochemical profile and CEA level. Partial response (PR) was defined as a reduction of more than 50% in the sum of the product of the largest perpendicular diameters of all lesions as measured by either CT or ultrasound.

Drug doses and schedule. The HAI consisted of FUDR at the dose of 0.25 mg/kg/day for 14 days every four weeks, and the combination was HAI (as above but every five weeks) plus SYC which consisted of *i.v.* leucovorin 100 mg/m^2 followed immediately by FU 400 mg/m^2 for four consecutive days every five weeks.

All patients received a fixed dose of heparin 30,000 U added to saline at each pump filling and dexametasone 20 mg during every cycle of HAI in order to prevent or reduce biliary toxicity and vascular occlusions.

Statistical considerations. The study was designed with a high statistical power of 80% to find an increase of the median overall survival (OS). The statistical goal was to detect a gain of OS, from 10 to 16 months comparing patients receiving only HAI and patients receiving HAI and SYC, respectively. It was planned taking into account the previous clinical phase II-III studies which suggested that the effects of the HAI and SYC combination could be relevant (3, 4). A multicentric study was organized for the evaluation of OS. As the question to be answered was a one-sided hypothesis, the use of a one-sided test of significance was appropriate. Since survival comparisons were performed using the long-rank test at a 0.05 (one side) level of significance, approximately 75 deaths occurred. The study was initiated with an accrual goal of 210 patients and it was later reduced to 76 due to the slower than expected accrual rate related to the complexity of the administration route and the appearances of new active drugs in CRC. In spite of the decrease in the total number of accrued patients, the power of the study was not affected because it was a function depending on the number of deaths. OS was defined as the time between randomization and death. OS, time to progression (TTP), time to hepatic progression (THP) and time to extra-hepatic progression (TEP), were calculated from the time of random assignment using the Kaplan-Meier method and compared using the long-rank test (9, 10).

Eighty-two patients were randomly ascribed to the treatment, and the final results of 76 evaluable cases are presented. The two arms were well balanced for gender, age, site, site of primary, grading, performance status and liver involvement.

Of the evaluable patients, 40 received the double route treatment and 36 patients received HAI alone.

Results

Between May 1993 and May 1999, 82 chemo-naïve patients were randomly assigned: 42 to HAI+SYC and 40 to HAI alone. In the HAI+SYC group two patients had port catheter occlusions, in the HAI group two withdrew consent and two underwent resection. The entire population of 76 patients received the full treatment and remained evaluable for response and toxicity. The median number of cycles received was eight for HAI+SYC and 8.5 for HAI, respectively. The responses are summarized in Table I.

Survival. OS was significantly longer in the HAI+SYC group than the HAI group: 20 months and 14 months ($p=0.0033$), respectively. Two-year survival estimates were 48% and 31%, and the median duration of response was 12 and 8 months, respectively.

Haematological toxicity was mostly mild and reversible in 432 instances. Neutropenia grade 3 occurred in four patients in the HAI+SYC arm and one in the HAI arm. Diarrhoea occurred in 20% and 7% of patients, and stomatitis occurred in 18% and 2%, respectively.

Table I. *Responses to HAI+SYC and HAI treatments in patients with non-resectable hepatic metastases from CRC.*

	HAI + SYC	HAI
CR	8 (20%)	3 (8.4%)
PR	11 (27.5%)	12 (33.3%)
SD	13 (32.5%)	9 (25%)
PD	8 (20%)	12 (33.3%)
Total	40 (100%)	36 (100%)
MDR	12	8
OS	20	14

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; MDR=median duration response (months); OS=overall survival (months).

In contrast, biliary toxicity was significant, twelve patients had evidence of bilirubin elevations of more than 3 mg/dl (six in each arm), and two had asymptomatic arterial biliary-tree fistulae: one in the HAI+SYC arm and one in the HAI arm. Grade 3 elevation in alkaline phosphatase and amino-transferase levels occurred in 16 patients (40%) and 15 patients (41.7%), respectively.

Response. Among the 76 registered patients 11 were recorded as CR: eight in the HAI+SYC arm and three in the HAI arm.

Twenty three were recorded as PR: eleven in the HAI+SYC arm and twelve in the HAI arm. No differences between treatments in social functioning or general health perceptions were reported by the patients.

Discussion

A comparison of the results of HAI+SYC *versus* HAI in patients with non-respectable hepatic metastases from CRC indicated that HAI+SYC prolonged the OS (20 *vs.* 14 months), was linked to a greater likelihood of objective responses in the liver (47.5% *vs.* 41.7%), and enhanced time to hepatic progression (12 *vs.* 8 months).

In this study, the systemic chemotherapy used did not include irinotecan or oxaliplatin in addition to FU and leucovorin. This multi-center study was initiated in 1993, at which time FU and leucovorin was a treatment of choice. Recent studies have demonstrated that irinotecan, oxaliplatin, FU and leucovorin increase survival (11). These older drugs may still be considered active as shown by Kemeny *et al.,* who recently reported a survival advantage conferred by HAI over systemic chemotherapy using FUDR *versus* FU and leucovorin (12).

In conclusion, the combination of HAI+SYC is active and safe showing a clinical advantage in respect to HAI alone. The success is possibly due to the reduction of distant metastases and the prolongation of the duration of responses in the liver. Whether or not this double route strategy can be enhanced further through the addition of new systemic agents (irnotecan, oxaliplatin, bevacizumab or cetuximab) will be the focus of future investigations (13-15).

Acknowledgements

We are particularly grateful to Ms. Lidia Lamoglie who undertook the final preparation of the manuscript.

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Received July 10, 2006
Revised October 24, 2006
Accepted October 25, 2006