Hepatic Arterial Infusion for Biliary Tract Carcinoma: Single-center Experience

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Abstract. Aim: The aim of the present study was to evaluate a single-center experience in hepatic arterial infusion (HAI) of patients with biliary tract carcinomas. Patients and Methods: A retrospective analysis of 60 patients treated between 1997 and 2011 was performed. Results: Most patients were treated with HAI of a combination of 5-fluorouracil, folinic acid and cisplatin. The response was not evaluable in most patients, predominantly because of prior surgical procedures. The median survival of all patients was 15.1 months (5-year survival=13%). The survival was significantly better in patients treated with radical surgery (median=50.1 months, 5-year survival=45%) or palliative surgery (median=22.5 months, 5-year survival=13%) compared to no surgery (median=7.6 months, 5-year survival=3%). Conclusion: The current data demonstrate the efficacy of HAI in patients with biliary tract carcinoma. HAI is a therapeutic method to be considered in patients with inoperable biliary tract carcinoma and no extrahepatic spread.

Biliary tract carcinomas, including gallbladder carcinoma and cholangiocarcinoma, represent less common malignant tumors that are usually diagnosed at an advanced stage and, consequently, generally have a poor prognosis (1). The poor prognosis of biliary tract carcinoma is partly due to the fact that because of their anatomical location, these tumors compromise liver function. The location of these tumors also represents a limitation with regard to radical surgical treatment, and radical surgery, the only curative treatment in patients with biliary tract carcinoma, can be performed only for a minority of patients. Moreover, the disease ultimately recurs in most patients undergoing resection (2, 3).

Although, in the Western world, primary liver tumors are relatively rare, the liver is frequently involved by metastatic spread of tumors of different primary locations. In fact, the liver represents the most common site of metastatic disease. Some aspects of the management of liver tumors are similar, irrespective of the primary site. One therapeutic approach that has been investigated in patients with both primary and metastatic liver carcinomas is hepatic arterial infusion (HAI), which utilizes anatomical targeting of cytotoxic agents to obtain higher intratumoral drug concentrations with less systemic toxicity (4). HAI has been best studied in patients with colorectal cancer metastatic to the liver. It has been demonstrated in patients with colorectal cancer metastatic to the liver that the postulated theoretical advantage of higher intratumoral drug concentration and lower toxicity indeed translates into a superior response rate. However, it was more difficult to demonstrate an overall survival benefit. Consequently, the use of HAI for colorectal cancer metastatic to the liver remains controversial (4). The role of HAI in patients with other primary tumors involving the liver is even less clear. Promising results were reported in patients with liver metastases of uveal melanoma (5) or biliary tract carcinoma (6-14). In the present article we present a retrospective analysis of a single-center experience with HAI in patients with biliary tract carcinoma.

Patients and Methods

A retrospective analysis was performed of all consecutive patients with histologically-verified biliary tract carcinoma treated at the Charles University Medical School and Teaching Hospital, Hradec Králové, Czech Republic, between June 1997 and April 2011, with at least one course of HAI. The patients’ charts were searched for relevant information. Survival was evaluated from the start of the first HAI course to the death or last follow-up in 2012. No patients
were lost to follow-up. Pilot results in patients included early in this cohort have been previously reported (6).

The staging classification of biliary tract carcinoma changed repeatedly over the time during which the patients in the present cohort were treated. To ensure comparability of the results for individual patients, all cases were re-staged according to the American Joint Committee on Cancer 7th edition staging manual (15, 16).

HAI was administered through catheters with a subcutaneous port system implanted either surgically during an open procedure or percutaneously, or through catheters introduced via the femoral artery by the Seldinger technique (17). Before the surgical implantation, an angiography of the arteries supplying the liver was usually performed, and the catheter introduced was used to deliver the first course of HAI. During the subsequent open surgery, the extent of disease was assessed. If the extent of the disease (including the absence of extrahepatic spread) was judged favorable for subsequent HAI, a catheter with a subcutaneous port system was implanted as described earlier (17). Percutaneous catheter with a subcutaneous port system was introduced by an interventional radiologist via the standard femoral approach (17).

For most patients, a regimen combining HAI of folinic acid (50-200 mg bolus or short infusion), 5-fluorouracil (850 mg/m²) and cisplatin (25 mg/m²) for 3-24 hours on days 1-3 was used (for some patients, the regimen was extended for four days). Pre-medication that included intravenous injection of a setrone antiemetic (usually granisetron), short infusion of dexamethasone (16 mg), and adequate intravenous hydration were also administered. Continuous 24-h HAI was possible only during hospital stay, and for patients treated on an outpatient basis, HAI of shorter duration (3-6 hours) was administered. To the 5-fluorouracil, folinic acid and cisplatin chemotherapy backbone, HAI of doxorubicin (10 mg/m² for 24 h on days 1-3 or 45 mg/m² for 24 hour on day 1), etoposide (110 mg/m² for 24 hour on days 1-3) and/or gemcitabine (1000 mg/m² for 30 min days 8 and 15) were added for individual patients. In a few patients, only HAI of 5-fluorouracil (600-1000 mg/m² for 24 h) and short bolus of 50 mg of folinic acid (FUFa) were administered. HAI of gemcitabine (1000 mg/m² administered for 30 min as weekly courses), doxorubicin (20 mg/m² for 2-3 h weekly), weekly doxorubicin (20 mg/m² for 2 hours) plus 5-fluorouracil (500 mg/m² for 2 hours), or interferon-alpha (9 MU for 1 h 3 times weekly) were used as second- or third-line therapy.

The response was evaluated by imaging studies of liver lesions using World Health Organization criteria (18). Standard descriptive statistical analyses were performed to characterize the present retrospective cohort of patients. Overall survival was evaluated using the Kaplan–Meier method, and the differences between patient subgroups were studied by log-rank tests. The decision on statistical significance was based on the p=0.05 level. The statistical analyses were performed using NCSS software (Number Cruncher Statistical Systems, Kaysville, UT, USA).

Results

Sixty patients, 38 females and 22 males, aged (mean±standard deviation) 58±12 (range 26-85) years, with histologically-verified biliary tract cancer, including 28 patients with carcinoma of the gallbladder, 28 patients with cholangiocarcinoma, and four patients with carcinoma of the ampulla of Vater were treated with at least one cycle of HAI. The location of cholangiocarcinoma was perihilar in 16 patients and intrahepatic in 12 patients. The stage distribution at the start of therapy was as follows: stage I in two patients, stage IA in one, stage IB in one, stage II in nine, stage III in one, stage IIIA in five, stage IIIB in six, stage IVA in nine, stage IVB in 16, and recurrent disease in 10 patients. Twenty-six patients had a surgical procedure immediately prior to or shortly after the start of HAI, including 11 patients in whom the surgery was considered radical and 15 patients who had palliative surgery. Ten patients had recurrent disease after prior surgery, and seven patients had prior systemic chemotherapy. The percentage of patients with stage I or II disease was similar in cholangiocarcinoma (five patients; 18%) and carcinoma of the gallbladder (six patients; 21%).

Thirty-three patients had HAI administered via implanted catheters. The catheters with a subcutaneous port system were implanted surgically in 23 cases and percutaneously by an interventional radiologist in 10 cases. Twenty-seven patients had HAI administered only through single-use catheters inserted using the Seldinger method. In nine of these patients, the findings during subsequent laparotomy performed with intent to implant a catheter with a port system, contraindicated the insertion of a port system. Only one course of therapy was administered to 17 patients treated via single-use catheter, and to three patients who had a permanently implanted catheter.

The median time from diagnosis to the start of HAI was 1.3 (range=0.3-53) months. The HAI of cisplatin/FUFA combination was administered to 57 patients, including one patient treated with doxorubicin plus cisplatin/FUFA, one patient treated with etoposide and doxorubicin plus cisplatin/FUFA, and one patient treated with gemcitabine plus cisplatin/FUFA. HAI of FUFA was administered to the remaining three patients. The median number of cycles administered was 3 (range=1-18). The actual daily doses of 5-fluorouracil and cisplatin were (mean±standard deviation) 840±183 mg/m² and 24±7 mg/m², respectively.

Second-line HAI was administered to 16 patients, including FUFA to six patients, gemcitabine to five, gemcitabine/FUFA to one, interferon-alpha for one, cisplatin/FUFA to one, doxorubicin plus 5-fluorouracil to one, and doxorubicin plus cisplatin/FUFA to one patient. Third-line HAI was administered to three patients, two patients were treated with doxorubicin and one patient with cisplatin/FUFA. The median number of courses of second-line HAI was 6 (range=2-26) and the median number of courses of third-line HAI was 5 (range=3-12). Twenty-six patients received subsequent systemic therapy.

The response rate was analyzed only for the first-line therapy. Partial response was observed in two patients, stable disease in three and progressive disease in six. The response was not evaluated in 49 patients, mostly because of prior surgical procedure (26 patients), or because only one course of HAI was administered (14 additional patients).
Serious adverse events that required hospitalization were observed in 15 patients (25%). Arterial thrombosis requiring hospitalization was recorded in four patients (7%); two patients had thrombosis of the hepatic artery, which was in one case complicated by liver abscess and fatal sepsis; one patient with percutaneous catheter had peripheral embolization of the lower extremity, and one patient had thrombosis of the celiac axis with fatal vascular ileus. Three patients had venous thrombembolic disease, including two patients who had lung embolism and one patient who had deep-vein thrombosis. Two patients had febrile neutropenia. One additional patient had bacterial sepsis resulting from port system infection, and one patient had grade 4 diarrhea. Two patients died of early symptomatic progression thought to be the result of tumor progression, one patient had fatal pneumonia (not associated with neutropenia), and one patient who also had had prior brachythrapy died of fatal tumor bleeding. With the exception of the six fatal cases described above, all patients affected by serious adverse events recovered. Thrombosis of the hepatic artery that did not require hospitalization was noted in another six patients, including a patient who also had venous thrombembolic disease manifesting with lung embolism. Thus, the total number of patients with arterial thrombotic events was 10 (17%).

The median survival of all patients was 15.1 months (1-year survival 57%, 2-year survival 33%, 3-year survival 23%, 4-year survival 18% and 5-year survival 13%). The median survival of patients treated with radical surgery was 50.1 months (5-year survival 45%) compared to 11.9 months in patients without radical surgery (5-year survival 6%; \( p<0.0001 \); Figure 1). The median survival of patients treated with palliative surgery was 22.5 months (5-year survival 13%; \( p=0.038 \) compared to radical surgery). The median survival of patients with no surgery (radical or palliative) was 7.6 months (5-year survival 3%; \( p<0.0001 \) compared to radical surgery and \( p=0.020 \) compared to palliative surgery). Among 49 patients with no radical surgery, the median survival was significantly shorter in 20 patients who had only one cycle of therapy or had laparotomy without port system implantation (median 4.8 vs. 21.7 months, \( p=0.005 \); Figure 2). Similar differences in the survival of patients who had only one cycle of therapy or had laparotomy without port system implantation were observed in 34 patients with no radical or palliative surgery (median 3.7 vs. 11.9, \( p=0.044 \)). No statistically significant differences in survival were observed between patients with cholangiocarcinoma and gallbladder carcinoma (median survival 18.0 months and 5-year survival rate 13% vs. median survival 13.3 months and 5-year survival rate 11%, respectively; \( p=0.910 \)). Six patients were alive at the time of the analysis. Five patients treated with radical surgery were without evidence of recurrence 53.8, 118.5, 120.3, 167.1 and 174 months after the start of therapy, while one patient originally treated with palliative surgery, who underwent repeated procedures for progressive disease, was alive after 104.8 months.

![Figure 1. Overall survival of the patients in the cohort. Kaplan–Meier curves are shown of the whole cohort (All), patients treated with radical surgery (RS), patients treated with palliative surgery (PS) and patients with no surgery (NS). Overall survival was significantly longer in patients who had radical surgery (median=50.1 months, 5-year survival=45%; \( p<0.0001 \)) or palliative surgery (median=22.5 months, 5-year survival=13%; \( p=0.020 \)) compared to patients who had no surgery (median=7.6 months, 5-year survival=3%).](image-url)
Discussion

The present series, constituting one of the largest cohorts of patients with biliary tract carcinomas treated with HAI, demonstrates the efficacy of this therapeutic method for patients with these relatively uncommon tumors. Survival, rather than objective response rate, was the principal parameter of efficacy evaluated in the present cohort. In fact, objective response could not be assessed in most patients in this cohort, mostly because of prior surgical procedures and/or because only a single course of HAI was administered. Given the fact that objective response could not be evaluated in a high proportion of patients, progression-free survival was not analyzed. However, objective response and progression-free survival, although frequently used in clinical trials, are only surrogates for survival. In addition, the standards of imaging have changed over the 14 years during which patients in the present series have been treated. Consequently, the data on objective response may not be as reliable as in prospective studies that have shorter duration of recruitment and stricter selection criteria. Given the long duration of follow-up, the survival data in this cohort are mature, and overall survival represents the best estimate of treatment efficacy in a patient population that was selected less strictly than in a prospective trial. The median survival from the start of therapy was 15.1 months. This compares favorably with reported survival of untreated patients, as well as of patients treated with systemic chemotherapy, HAI or surgery as single-modality treatment (19, 20). Importantly, the median survival of patients who had radical surgery was over four years, indicating that the combined modality treatment may achieve long-term response or even cure.

Because biliary tract carcinomas are relatively uncommon tumors, and disease complications, e.g. biliary obstruction, often preclude administration of chemotherapy, the data for the efficacy of anticancer agents, both administered systemically or as HAI, are relatively limited. In fact, many trials included patients with biliary tract carcinoma together with those with hepatocellular carcinoma and pancreatic carcinoma, i.e. tumors that have biological and clinical behavior distinct from that of biliary tract carcinoma. For example, an early trial that demonstrated survival advantage of systemic chemotherapy over best supportive care enrolled both patients with biliary tract carcinoma and patients with pancreatic carcinoma (21). Fluopyrimidines (22), cisplatin (23), combination of 5-fluorouracil with cisplatin (24), or combinations of fluoropyrimidines with anthracyclines (doxorubicin or epirubicin) and/or mitomycin C (25-28) have been studied in prospective trials. Promising results have been reported for gemcitabine administered as monotherapy or in combinations (29-31). However, none of the many regimens of systemic chemotherapy that have been investigated in patients with biliary tract carcinoma has
demonstrated a clear superiority, with the exception of a recently published trial that is outstanding for its size in this relatively rare group of tumors, and that demonstrated a 3.6-month overall survival benefit of the combination of gemcitabine with cisplatin over gemcitabine alone (20). Based on the results of this trial, the combination of gemcitabine and cisplatin is regarded as the current standard-of-care in systemic chemotherapy of advanced inoperable or metastatic biliary tract carcinoma.

Different cytotoxic agents have been used in HAI. Although across the spectrum of different primary tumors involving the liver 5-fluoro-2'-deoxyuridine (floxuridine) has been regarded as a standard agent for hepatic arterial infusion, a randomized trial in patients with metastatic colorectal carcinoma indicates that the activity of 5-fluorouracil is at least comparable with that of floxuridine (32). A number of studies reported the results of HAI in patients with biliary tract carcinoma. As these tumors are relatively rare, the trials were usually small and the number of patients studied ranged between 11 and 30. Early trials of HAI in patients with biliary tract carcinoma reported the results with 5-fluorouracil and/or mitomycin C (7, 8). In an early trial, patients with cholangiocarcinoma treated with HAI of floxuridine and mitomycin C responded (33). A response rate of 54% was obtained and median overall survival of more than two years was reported for HAI of floxuridine combined with dexamethasone (9). Using a regimen combining HAI of cisplatin and epirubicin with systemic administration of 5-fluorouracil, Cantore et al. (10) reported an objective response rate of 40% and a median survival of 30 months. An objective response rate of 32% and median survival of 18 months were reported for the combination of HAI of cisplatin and epirubicin with the oral drug capcitabine (11).

More recently, HAI of gemcitabine has been studied in mostly pre-treated patients with biliary tract carcinoma (12-14). HAI of gemcitabine administered as a weekly infusion for three weeks in a four-week cycle was tolerated up to the dose of 1500 mg/m² administered at 10 mg/m² per minute (14). In another study, a higher dose of gemcitabine was administered in combination with degradable starch microspheres (12). Moreover, the median survival was longer in patients treated with HAI of gemcitabine with microspheres, compared to HAI of gemcitabine-alone (12). In a phase I/II trial of HAI of gemcitabine, the recommended dose for phase II was 1000 mg/m² administered weekly for three weeks in a four week cycle (13). The objective response rate and median survival were 12% and 11 months, respectively (13). In a pilot study in patients with intrahepatic cholangiocarcinoma, promising results were reported for the drug-eluting bead, irinotecan (DEBIRI) administered mostly in combination with systemic chemotherapy, with response rates using modified criteria reaching 80% and median survival of 18 months (34). 5-

Fluorouracil and cisplatin were used as an HAI chemotherapy backbone in the present cohort of patients who were treated at the time before the superiority of gemcitabine/cisplatin combination was reported. Consequently, in the present series gemcitabine was mostly used as a second-line treatment option.

An important proportion of the patients in the present series received only one course of HAI. In some of these patients, extrahepatic spread was found during the surgery to implant the permanent catheter. Thus, the effect of HAI may have been diluted in the present retrospective cohort of patients because of inclusion of patients who were subsequently found to harbor extrahepatic disease. Indeed, the median survival of patients treated with palliative surgery or no surgical procedure was significantly better after exclusion of patients who had only one course of treatment and/or patients in whom the preoperative findings precluded the insertion of a permanent intraarterial catheter. For obvious reasons, slightly better results were observed in more selected patient cohorts enrolled in prospective studies of HAI for biliary tract carcinoma, but after exclusion of the patients who had only one course of treatment or had extrahepatic disease, the survival data of the present cohort are comparable with data from most prospective trials of HAI (10-12). With the availability of positron-emission tomography/computed tomography (PET/CT), extrahepatic disease may be identified before the start of treatment, resulting in better patient selection, offering potential for even better results in the future.

HAI was, in general, well-tolerated in the present retrospective cohort, but in individual patients, serious toxicity linked to HAI was observed. The toxicities of systemic anticancer therapy, e.g. gastrointestinal toxicity induced by cytotoxic drugs (35), or side-effects accompanying the administration of targeted agents (36), have major impact on the quality of life. Some side-effects may be less expressed with HAI compared to systemic therapy. It has been demonstrated in patients with metastatic colorectal carcinoma that HAI is associated with improved quality of life (37). Theoretically, it could be hypothesized that HAI may result in increased hepatotoxicity, but, in clinical practice, liver toxicity of agents administered as HAI is, with few exceptions, limited. In patients with metastatic colorectal carcinoma, liver toxicities associated with the administration of agents used to treat this tumor, including non-alcoholic fatty liver disease after 5-fluorouracil, sinusoid obstruction syndrome after oxaliplatin, or steatohepatitis after irinotecan (38), do not seem to be increased in patients treated with HAI. Among serious adverse events observed in the present series, arterial thrombotic events were most prominent, being observed in 7% of the patients, including two patients (4%) with a fatal outcome. Other serious adverse events in the present series that had fatal outcome.
were probably more related to disease progression (symptomatic progression and pneumonia). Given the considerable frequency of arterial and venous thrombotic events in these patients, a prophylactic administration of low-molecular-weight heparin should be considered.

Even in the absence of radical surgery, some patients in the present cohort survived for several years. Specifically, in some patients with cholangiocarcinoma the disease may take an indolent course (39), and the prognosis of these patients may be further improved with therapy, including HAI. Unfortunately, there is currently no information on clinical, pathological or laboratory predictive factors or biomarkers that might help in identifying the patients with biliary tract carcinomas likely to benefit from HAI (40). Future studies should also investigate whether HAI suppresses the host immune response less than does systemic chemotherapy. It has been documented that systemic immune activation, that is commonly observed in patients with advanced cancer (41), is associated with depressed immune response (42, 43), and effective tumor control may enhance the host antitumor response.

In conclusion, the present data demonstrate the efficacy of HAI in patients with biliary tract carcinoma. HAI is a therapeutic method to be considered for patients with inoperable biliary tract carcinoma and no extrahepatic spread.

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References


Lorenz M and Muller HH: Randomized, multicenter trial of fluorouracil plus leucovorin administered either \textit{via} hepatic arterial or intravenous infusion \textit{versus} fluorodeoxyuridine administered \textit{via} hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma. J Clin Oncol \textbf{18}: 243-254, 2000.


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