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Hepatic Arterial or Celiac Trunk Infusion of Chemotherapy as Rescue Therapy in Pretreated Widespread Liver Metastases

(Running title: Locoregional rescue chemotherapy in liver metastases)

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Abstract

Background: *Liver is one of the most common sites of metastases from solid tumors. If it is the mainly metastatic site with widespread lesions unsuitable for local treatment, patients are at risk to develop liver failure as the result of loss of a critical mass of hepatocytes due to replacement with malignant cells, and also from ischemia and hepatic venous obstruction produced by tumor emboli or compression. Hepatic arterial or celiac trunk infusion of chemotherapy (HATI) may enhance the activity on tumor cells of some drugs that have a very high vascular extraction ratio on first pass removal.*

Materials and methods: *This is an observational, single-center, retrospective analysis of HATI in pretreated patients with liver metastases from biliary tract (BTC), breast (BC), and pancreatic cancer (PC) in which liver is the mainly life-threatening site of disease. Combination chemotherapy for HATI was 5-fluorouracil, epirubicin, and mitomycin-C in BC metastases, or cisplatin and epirubicin in BTC and PC metastases. HATI was associated to systemic low dose/dense chemotherapy in BTC and PC. Celiac trunk infusion was only for PC.*

Results: *From 2000 to 2018, 72 patients were treated. The median age was 62 (range 34-74). Liver metastases were from BTC, BC, and PC in 26 (36%), 23 (32%), and 23 (32%) cases respectively. Median lines of previous treatments for metastatic disease were 1, 4, and 1 in BTC, BC, and PC respectively. Overall, the HATI approach achieved a disease control rate (DCR) of 50% (with overall response rate, ORR, for BTC: 19%; BC: 26%; PC: 4%), and a clinical benefit rate (CBR) of 40% (BTC: 38.5%; BC: 47.8%; PC: 34.7%). An immediate disease progression occurred in 50% (BTC: 50%; BC: 43%; PC: 57%) of patients. The median progression-free survival (PFS) was 3.8, 6.4, 3.9 months in BTC, BC, and PC respectively.*

Conclusions: *In this series, patients with liver metastases from BTC, BC, and PC who failed standard previous treatments for metastatic disease, achieved with HATI a disease control in about one out of two cases, with a durable (equal or more than 6 months) benefit in 40% of treated patients (CBR). The activity of HATI on liver metastases from different cancers encourage the prospective evaluation of this treatment inside clinical trials like rescue therapy to preserve liver from visceral crisis/organ dysfunction.*

Keywords: *Liver metastases, rescue chemotherapy, arterial infusion, locoregional chemotherapy.*

List of Abbreviations:

HATI: hepatic arterial or celiac trunk infusion of chemotherapy
BTC: biliary tract cancer
BC: breast cancer
PC: pancreatic cancer
DCR: disease control rate
CBR: clinical benefit rate
ORR: overall response rate
PFS: progression-free survival

Introduction

As many as 50% of the patients with a primary malignancy will eventually develop metastases in the liver, a percentage greater than for any other organ, including the lung. Although primary tumors that drain principally into the portal circulation are more likely than others to develop hepatic metastases, many tumors arising in other sites, such as the breast and lung, also commonly develop hepatic metastases. Although the liver represents a common site of spread from many of these solid tumors, isolated hepatic metastases most commonly occur from colorectal and neuroendocrine tumors. For most other solid malignancies, the pattern of metastatic disease is most often that of generalized dissemination.

Life expectancy and prognosis for people with liver metastases are typically poor, as the cancer tends not to be curable. Death in these patients often occurs for liver failure as direct consequence of liver replacement by metastases, with loss of a critical mass of hepatocytes due to replacement with malignant cells, and also from ischemia and hepatic venous obstruction produced by tumor emboli or compression. Survival rates depend mainly on the cancer's origin and previous treatments. Other factors are patient-related (e.g.: age, comorbidity, etc.) [1].

The treatment of liver metastases and primary liver cancer is an important concern in oncology. The liver has a rich blood supply from both the hepatic artery and the portal vein. In the stepwise pattern of metastatic progression, haematogenous spread occurs via the portal vein to the liver [2]. However, after metastasizing, liver metastases are perfused almost exclusively via the hepatic artery, whereas normal hepatocytes derive most of their blood supply from the portal circulation [3,4].

Directing a high-dose infusion of chemotherapy into the hepatic artery therefore increases the concentration of drug to which the tumor is exposed, proportional to the hepatic parenchyma, as well as to the body as a whole, and should thereby improve the therapeutic index.

Several randomized trials have compared the results of continuous hepatic arterial infusion to systemic chemotherapy in patients with unresectable colorectal liver metastases. These have reported significantly higher response rates with local infusion (42% to 62% versus 10% to 21%) [5-10].

Moreover, also a meta-analysis comparing hepatic arterial infusion with systemic chemotherapy, confirmed a greater response rate with regional therapy, as well as suggesting a trend toward improved survival for those receiving regional therapy [11].

Based on these rationale and data, in patients at risk to develop a liver failure due to widespread metastases, regional infusion of chemotherapy in hepatic arterial or celiac trunk may enhance the possibility of tumor response even in chemotherapy-pretreated patients.

Materials and Methods

Patients

This is an observational, single-center, retrospective analysis of hepatic arterial or celiac trunk infusion of chemotherapy in pretreated patients with liver metastases from biliary tract (BTC), breast (BC), and pancreatic cancer (PC) in which liver is the mainly life-threatening site of disease (table 1).

Breast Cancer (BC)	
Number of patients	23
Male/Female	0/23
Median age (range): - diagnosis - treatment	 58 (range 38-71) 65 (range 40-77)
Median number of previous lines of anticancer treatments (range)	4 (range 2-6)
Patients with stage IV disease at diagnosis	4
Patients with extra-hepatic disease	17
Biliary Tract Cancer (BTC)	
Number of patients	26
Male/Female	14/12

Median age (range): - diagnosis	60 (range 34-73)
Median number of previous lines of anticancer treatments (range)	1 (range 1)
Patients with stage IV disease at diagnosis	20
Patients with extra-hepatic disease	7
Primary tumor: - intra-hepatic (cholangiocarcinoma) - extra-hepatic bile ducts - gallbladder	 23 2 1
Pancreatic Cancer (PC)	
Number of patients	23
Male/Female	15/8
Median age (range): - diagnosis	58 (range 47-71)
Median number of previous lines of anticancer treatments (range)	1 (range 1)
Patients with stage IV disease at diagnosis	20
Patients with extra-hepatic disease	20

Table 1: Summary of patients characteristics.

Patients were treated at Massa Carrara civil hospital by Oncology and Interventional Radiology units. The retrospective analysis was performed with data in medical records, and involves patients treated between the years 2000 and 2018 in clinical practice.

Massa Carrara civil hospital is a high-volume center for locoregional oncological treatments. This analysis involved only treated patients that met inclusion criteria established before retrospective data analysis.

To be evaluated for this retrospective observational analysis, patients had to have widespread liver metastases from BTC, BC, or PC unsuitable for surgery or any other local interventional locoregional treatment such as radiotherapy, radiofrequency, thermo-ablation, etc.

Standard systemic therapies must have been administered, with a number of previous lines based on evidence/guidelines for single disease.

Presence of extra-hepatic disease was also admitted, but the liver had to be the mainly life-threatening site of disease.

Treatment

Chemotherapy was administered after arterial catheter access via the femoral artery was obtained, and arteriography was performed to document the arterial supply to the single or multiple tumors. A C2 catheter (Cardinal Health, Dublin, Ohio, USA) was used to catheterize the origin of the superior mesenteric artery (SMA). Hand injection of contrast was performed to exclude the presence of a replaced right hepatic artery (RHA) or an accessory RHA originating from the SMA. This needs to be assessed, because missing such a replaced vessel can result in incomplete treatment. In many cases, this information can be determined from the arterial phase of the CT. The celiac axis was then cannulated and a celiac arteriogram was performed to obtain a general overview of the axis and to look for a replaced left hepatic artery (LHA) off the left gastric artery. If conventional hepatic arterial supply was present, this could be accomplished by catheter placement in the common hepatic artery (CHA) for hepatic arterial (BC and BTC) or celiac trunk (PC) infusion of chemotherapy. Tumor vascularity was assessed and compared with that seen on CT scan. As soon as all these data were collected, a decision was made with oncologists as to which vessels need to be treated. If the vessel to be treated is large enough and fairly straight, the 5-French catheter was negotiated out into it, usually with the aid of a 0.38-inch angled ZIPwire™ hydrophilic guide wire (Boston Scientific, Watertown MA). If the vessel was of a smaller caliber or if it was tortuous, microcatheters were used; in our institution the daily workhorse microcatheter choice is a 45° angled Direxion (Boston Scientific) [14]. Selective catheterization was performed at each cycle, without pumps, permanent catheters, or other devices implantation, to prevent potential device-related complications.

Combination chemotherapy for HATI was 5-fluorouracil, epirubicin, and mitomycin-C (FEM schedule) in BC metastases, or cisplatin and epirubicin (EC schedule) in BTC and PC metastases. HATI was associated to systemic low dose/dense chemotherapy in BTC and PC. Celiac trunk infusion was only for PC.

In particular, with the FEM schedule doses were flat: 5-fluorouracil 1000 mg, epirubicin 50 mg, and mitomycin-C 10 mg total dose each; with the EC schedule, in BTC and PC, doses were based on body surface for HATI and were cisplatin 60 mg/sqm and epirubicin 50 mg/sqm. All of the drugs were infused in arterial with slow boluses. Low

dose/dense chemotherapy in BTC and PC associated with HATI were gemcitabine (GEM) 1000 mg/sqm intravenously at day 1, and/or capecitabine (CAP) 1000 mg/sqm from day 1 to 14. Cycles were repeated generally every 21 days with EC associated with GEM and/or CAP, and every 28 days with FEM.
Patients underwent to clinical monitoring for the first 24 hours after HATI procedure in inpatient setting. After, they had periodical visits and weekly blood tests for the evaluation of safety profile.

Every 3 months patients underwent to CT scan of chest and abdomen, to check the trend of disease.

Patients underwent to treatment until unacceptable toxicities, disease progression, or for a maximum of 6 (FEM) or 8 (EC) cycles.

Study design and statistics

This is an 18-years monocentric and retrospective analysis of HATI in consecutive patients with predominant or exclusive liver metastases by BC, BTC, and PC, treated in clinical practice.

The objective of the study was to evaluate the role of HATI as rescue therapy in pretreated patients with widespread liver metastases at risk of liver failure in case of disease progression, who failed standard therapies for metastatic disease. To do this, the clinical benefit rate (CBR) was used like primary objective. In particular, CBR is defined by percentage of patients with a complete or partial response or with stable disease, for at least 6 months or more. This type of endpoint is useful to evaluate the activity of the treatment, excluding all cases of short benefit, insignificant for rescue treatments.

Secondary endpoints were other activity surrogates, like overall response rate (ORR), disease control rate (DCR), and progression-free survival (PFS). The evaluation of response was performed according to the Response Evaluation Criteria for Solid Tumors (RECIST), version 1.1. (table 2).

Clinical benefit rate (6 months) – (CBR)	
Overall	40%
Breast Cancer (BC)	47,8%
Biliary Tract Cancer (BTC)	38,5%
Pancreatic Cancer (PC)	34,7%
Disease control rate (DCR)	
Overall	50%
Breast Cancer (BC)	57%
Biliary Tract Cancer (BTC)	50%
Pancreatic Cancer (PC)	43%
Overall response rate (ORR)	
Breast Cancer (BC)	26%
Biliary Tract Cancer (BTC)	19%
Pancreatic Cancer (PC)	4%

Table 2: Summary of HATI activity in overall patients population and for each subgroups.

Correlation with toxicities was not in objectives of the study, because it has already well documented in literature.

Fisher's exact test was used to research significant relation between subgroups of patients. All tests were two-sided and $p < 0.05$ was considered as statistically significant. GraphPad Prism 6 (GraphPad Software, Inc.) was used for data analysis.

Results

From 2000 to 2018, 72 patients were treated. The median age was 62 (range 34-74). Liver metastases were from BTC, BC, and PC in 26 (36%), 23 (32%), and 23 (32%) cases respectively. Median lines of previous treatments for metastatic disease were 1, 4, and 1 in BTC, BC, and PC respectively.

Regarding BC patients, they were all female (23, 100%). The median age at BC diagnosis was 58 years (range 38-71), and the median age at HATI treatment was 65 years (range 40-77). Only 4 patients had metastatic disease “ab initio”. Regarding biology, most of patients (13) had hormone receptor (HR) positive and HER-2 negative disease. The others were triple positive (HR positive and HER-2 positive) in 3 cases, and triple negative (HR negative and HER-2 negative) in 2 cases. In 5 cases HR and HER-2 status were unknown. The median Ki-67 was 20% (range 15-90%). Extra-hepatic disease was present in 17 patients, with bone, nodes, and soft tissues like most frequent sites of metastases in addition to the liver (Figure 1 and 2).

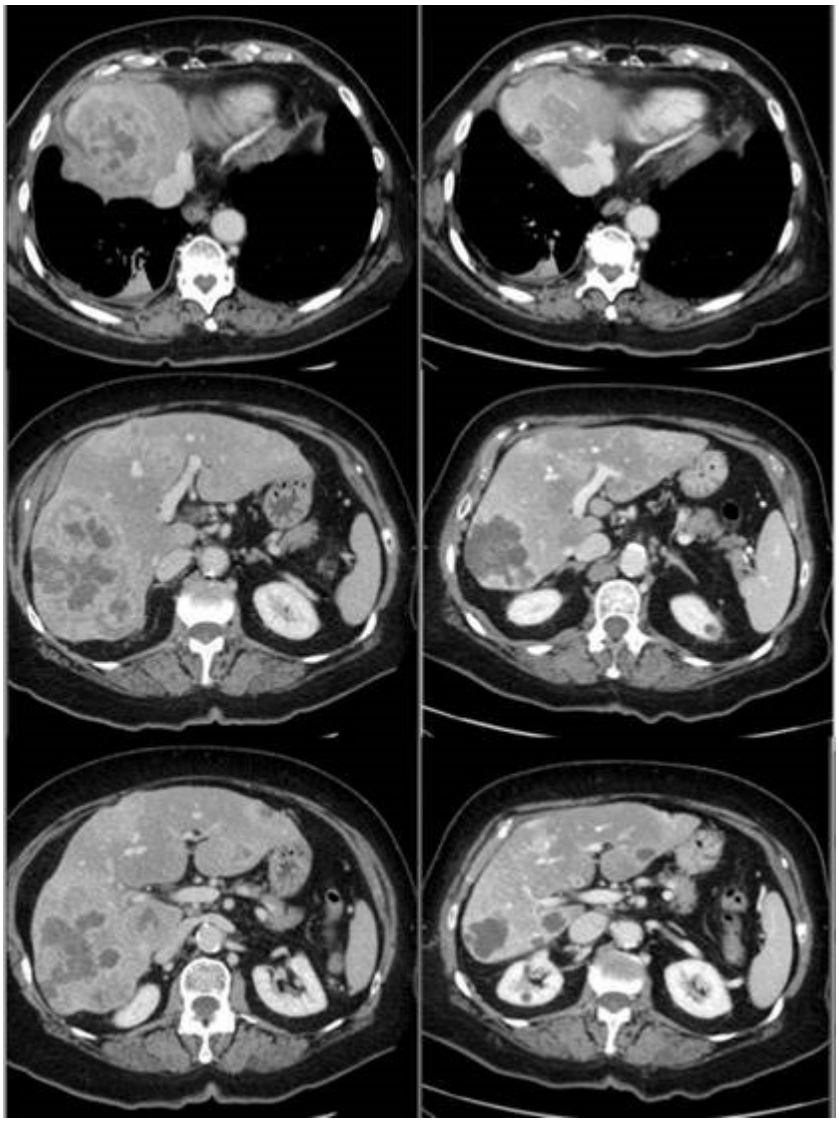

Figure 1: Response to HATI treatment in BC patient after 3 cycles. Basal CT-scan is on the left. On the right there is control CT-scan, performed after 3 cycles of FEM in hepatic arterial. On all represented lesions a significant tumor shrinkage was documented associated with reduction of the secondary hepatomegaly.

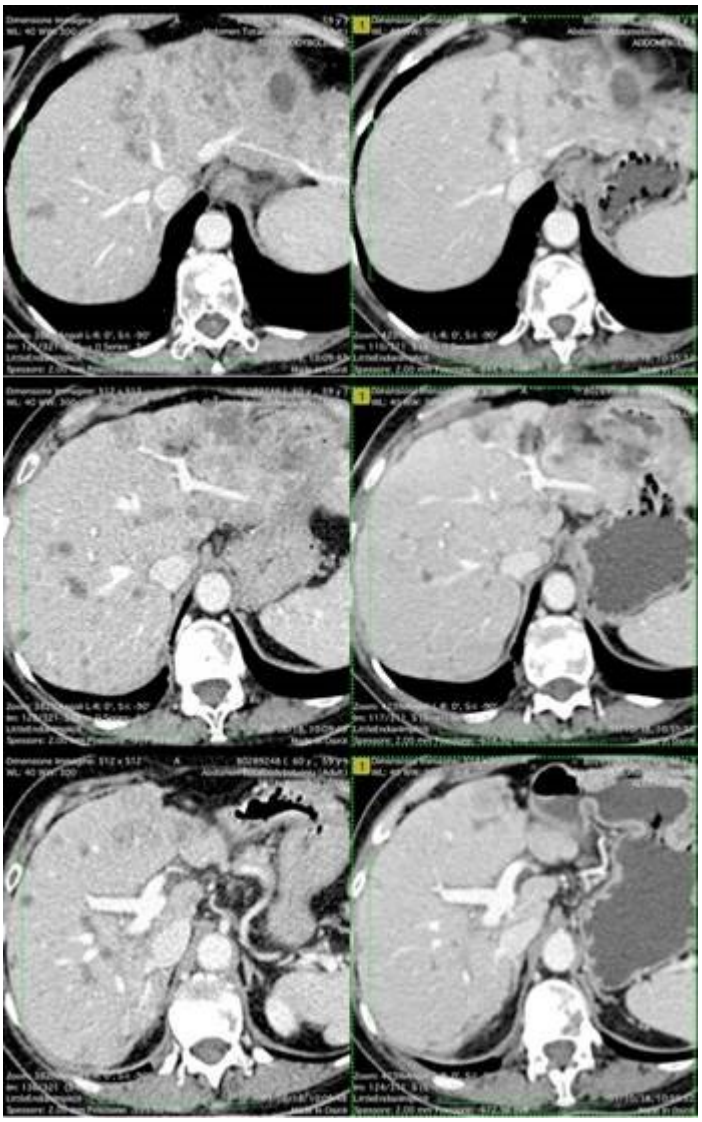

Figure 2: Response to HATI treatment in BC patient after 3 cycles. Basal CT-scan is on the left. On the right there is control CT-scan, performed after 3 cycles of FEM in hepatic arterial. In this case, different degree of response was documented in represented lesions, from complete response to stable disease.

Regarding BTC patients, they were 14 males (54%) and 12 females (46%). The median age at diagnosis was 60 years (range 34-73). Most of patients (23, 88%) had intra-hepatic primitive tumors (cholangiocarcinoma). Extra-hepatic bile ducts tumors were reported in other 2 cases, and a gallbladder tumor was reported in the other one. Extra-hepatic metastases were present in 7 patients, with abdominal lymph-nodes like main site. Majority of patients (20, 77%) had metastatic disease "ab initio".

Regarding PC patients, they were 15 males (65%) and 8 females (5%). The median age at diagnosis was 58 years (range 47-71). Most of patients in this series had primary pancreatic tumor associated with liver metastases (20, 87%); this is the reason why in PC patients the arterial infusions of chemotherapy were made in celiac trunk, instead hepatic arterial.

Overall, the HATI approach achieved a CBR of 40%. In particular CBR was 38,5% in BTC, 47,8% in BC, and 34,7% in PC.

The overall DCR was 50%, with ORR of 19% in BTC, 26% in BC, and 4% in PC. Consequently, an immediate diasease progression occurred in 50% of patients (50% of BTC, 43% of BC, and 57% of PC).

Median progression-free survival for HATI according to tumor types was 3,8 months in BTC, 6,4 months in BC, and 3,9 months in PC.

For BC patients there were no differences in response between subgroups of patients according to the number of previous lines (minor than 4 or major/equal 4, p value: 0,26). Moreover, no differences were detected in PFS for the same subgroups (p value: 0,56) or according presence or absence of extra-hepatic metastases (p value: 0,51). Median number of cycles was 3 (range 1-9).

Median overall survival (OS) for BTC and PC patients was 20,1 and 8,8, respectively.

Discussion

Generally widespread liver metastases are associated to poor outcome. When present, they lead to progressive deterioration of liver function, until organ failure. In these cases, the antitumoral activity of a treatment is critical to control tumor growth, limiting impact of liver function.

Not always chemotherapy and other antitumoral treatments achieve a disease control on liver and other sites of disease. When patients have failed standard lines of treatment (pretreated patients or in some cases heavy pretreated patients), the probability of disease control is even lower. The pharmacokinetics advantages of HATI approach could help to overcome resistance of pretreated and refractory tumor cells.

Being liver metastases perfused almost exclusively via the hepatic artery, directing infusion of chemotherapy into the hepatic artery therefore increases the concentration of drug to which the tumor is exposed, and should thereby improve the therapeutic index, overcoming resistances.

Moreover, certain drugs are extracted by the liver during the first pass through the hepatic arterial circulation, resulting in high local concentrations of drug and lower systemic toxicity. The area under the concentration versus time curve for regional therapy was a function not only of the clearance of the drug, but also of the hepatic arterial flow. Drugs with a high total body clearance and sites of delivery with low exchange rates are the most favourable for regional perfusion. Since the hepatic-arterial blood flow has a high regional exchange rate, drugs with a high clearance rate are needed. If a drug does not clear rapidly, it recirculates through the bloodstream many times and some of the advantage of the intra-arterial therapy over systemic therapy, in particular in term of safety, is lost. Moreover, drugs with a steep dose–response curve will be more useful, since large doses may be given regionally (with these drugs larger doses will produce a higher response). Chemotherapy agents like Floxuridine or 5-Fluorouracil, but also Mitomycin-C or Doxorubicin, have a high or medium single-pass extraction rate, and this makes them suitable for regional infusion [12,13].

In our series of 72 patients with widespread liver metastases from BC, BTC, and PC we had evaluated the role of HATI as rescue therapy, after failure of standard treatments. Almost all of patients with BTC and PC were treated in second line. Most of patients with BC were treated in the fourth line or following.

The overall CBR as primary endpoint of the analysis was 40%. This means that 40% of treated patients achieved a disease control for at least 6 months, in a poor prognosis setting. A trend of more activity has been documented in BC, how might expect, given the differences in natural prognosis of these disease (single CBR: 38,5% in BTC, 47,8% in BC, and 34,7% in PC). This durable disease control could prevent/significantly delay an immediate liver failure as result of high and evolutive burden of organ metastases.

Conclusion

This analysis suggests that HATI may have a role as rescue therapy for patients with widespread liver metastases from different tumors. Given the type of this analysis, this is an observation which must be validated in prospective controlled clinical trials that should provide homogeneous inclusion criteria, in particolar for the burden of liver disease, in order to evaluate efficacy with survival endpoints.

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